The role of beliefs in predicting adherence to nebulised therapy in adolescents with cystic fibrosis

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Submitted in accordance with the requirements for the degree of
Doctor of Clinical Psychology (D. Clin. Psychol.)

The University of Leeds
School of Medicine
Academic Unit of Psychiatry and Behavioural Sciences

May 2020

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

Acknowledgements

First, I would like to thank my research supervisor, Gary Latchford, for his enthusiasm, encouragement, positivity and guidance throughout this thesis project and course, and Alistair Duff and Elaine Edwards for their practical and clinical advice. I would also like to give a special thanks to Elaine Edwards, Hannah Day, Pamela McCormack, and Louisa Wallbridge for acting as field researchers for this project, and to everyone who kindly gave their time to take part, without whom this research would not have been possible.

I also want to say a big thank you to my tutors, Tracey Smith, Jan Hughes and Carol Martin for their guidance, time, and support throughout this course. Also, to Sara Matley and the rest of my colleagues, for their understanding and flexibility in allowing me time to write up my thesis. Finally, I want to thank my friends and family for their help and encouragement, and for always keeping me grounded.

Abstract

Introduction: Sub-optimal treatment adherence in Cystic Fibrosis (CF) is commonplace, and is known to deteriorate in adolescence, increasing risk of early morbidity and mortality. Although, in other chronic conditions, research focusing on psychological models of beliefs, and in particular the Necessity-Concerns Framework, has proved promising to understand this problem, comparatively little exists within CF. Importantly, the devices used to deliver nebulised treatments in CF provide objective recording of dose consumption, offering a singular opportunity to overcome the largest barrier in adherence research - subjective adherence measurement. However, the existing studies in CF which have examined this model in these treatments, have either relied on subjective measurement of adherence, and/or inadequately adapted the measure used to assess these beliefs.

Method: This thesis was completed in two parts. Study one developed a systematic process for adapting the BMQ-S into two versions, to separately capture necessity and concern beliefs of patients and their parents which may influence adherence behaviour to both categories of nebulised medications. This process included a modified two-round Delphi survey which elicited feedback from an expert panel on the value and clarity of the adapted questionnaires. Study two examined the relationship between beliefs elicited by the measures, and objectively-recorded adherence behaviour, to assess their relative utility in predicting adherence behaviour to nebulised treatments, from both patients', and their parents', beliefs.

Results: In study one, consensus on the value of items in both questionnaires was positive, but more variable for clarity, causing two original items to be removed, eight revised, and three created in each of the adapted measures. Study two found no significant relationships between patients' or parents' necessity and concern beliefs, and objectively-recorded adherence behaviour, in either medication category, in the original or adapted measures. Although analyses were underpowered by inadequate sample sizes, findings suggest that the Necessity-Concerns Framework may relate to adherence differently between nebulised medication categories and respondents, and, most importantly, that the original measure may be superior in capturing these relations.

Discussion: Although the results of this research are provisional, the novelty of design in both studies highlights several important considerations for future research, including the importance of assessing the psychometric properties of adapted belief measures, rather than assuming that refined versions will necessarily be superior to original versions. They also highlight the importance of considering parents beliefs when trying to understand adherence behaviour in adolescent populations.

Table of Contents

List of Figures

List of Tables

Chapter 1: Introduction

Overview of the introduction section

This introduction will begin by presenting a narrative review of the literature. First, the illness of cystic fibrosis and its medical management will be described, and definitions of medication adherence introduced. Following this, the extent and impact of non-adherence in the CF population will be examined, and difficulties in measuring and operationalising adherence explained. Relationships between sociodemographic, health, and treatment factors on adherence behaviour will then be outlined, after which practical, social and psychological barriers and facilitators to adherence will be considered. Finally, an overview of the predominant psychological health belief models, which attempt to understand and treat non-adherence in individuals with chronic health conditions, will be presented. This chapter will conclude by providing a context and rationale for the two empirical studies completed in this thesis.

Background on cystic fibrosis and adherence research

Cystic fibrosis and its medical management

Cystic fibrosis (CF) is the most common life-limiting genetic disease in Caucasian populations (O'Riordan, Robinson, Donaghue & Moran, 2008). The recessive gene carrier frequency is cited at 4% in the UK, and prevalence rates at 1: 2000/2,500 live births (Cystic Fibrosis Trust, 2015). CF is a multi-system disease which primarily impacts the respiratory and gastrointestinal tracts. It is caused by a dysfunctional protein, the *cystic fibrosis transmembrane conductance regulator*, which creates generalised abnormalities in the exocrine gland systems (Van Goor et al., 2009). Patients experience lung disease, pancreatic exocrine insufficiency, and symptoms such as meconium ileus and recurrent pulmonary infections. Respiratory disease is the main cause of morbidity, and respiratory failure the most cited cause of death (Yankaskas, Marshall, Sufian, Simon & Ridam, 2004).

Although no cure yet exists, advancements in the healthcare management and medical treatment of CF, have dramatically improved patients' quality of life and life expectancy. CF is no longer considered a fatal childhood genetic disorder, but a life-limiting disease of adulthood. Most patients are now of adult age, and in 2015, median life expectancy reached 45.1 years (Cystic Fibrosis Trust, 2015). These improved outcomes have, however, come with the cost of ever-increasingly complex, invasive, and time-consuming treatment regimens (Bell et al., 2020).

These multi-component regimens begin early in life, are life-long, and average two hours per day, every day. They aim to treat problematic symptoms, slow CF's progression (by preventing

pulmonary exacerbations and airway inflammation), and identify and treat common comorbidities such as diabetes, gastrointestinal conditions and mood disorders (Sawicki & Tiddens, 2012). At a minimum, they usually include vitamin and nutritional supplements, nebulised or oral antibiotics, nebulised mucolytics, pancreatic enzymes, and airway clearance (Sawicki, Sellers & Robinson, 2009). Unfortunately, symptom and treatment burden only increase as patients age, due to disease progression and age-related comorbidities (e.g. cardiovascular disease and renal failure), which themselves require further independent treatments (Brennan, Geddes, Gyi & Baker, 2004). Due to this high illness and treatment burden, CF teams are highly active in monitoring disease progression, adherence levels, and in providing support.

Defining adherence

Adherence has been defined as 'the extent to which a person's behaviour – taking medications, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider' (WHO, 2003, pg.3). Conversely, non-adherence has been defined as occasions 'where doses are missed, extra doses are taken, or doses are taken in the wrong quantity or at the wrong time' (Verbrugghe, Verhaeghe, Lauwaert, Beeckman & van Hecke, 2013, pg.610), and is widely considered to be either intentional (e.g. avoidance of side-effects) or unintentional (e.g. poor understanding) (Johnson, 1996).

Within this field, much research focuses on investigating adherence rates and the factors which influence them, in order to identify facilitators and barriers to optimal adherence. It is reasoned that this knowledge would allow patients at risk of sub-optimal adherence to be identified, and effective interventions developed for them (e.g. Owen & Jones, 2016). Interestingly, however, such research has historically focused on the adult population and on treatment regimens as a whole, and has assumed that findings can be generalised across treatments and populations. Recently, authors such as Owen and Jones (2016) have argued that such assumptions are erroneous, and that they underlie the limited effectiveness of current adherence interventions in chronic health conditions. As a result, more recent research has started to examine adherence across and within treatments in both adult and paediatric populations, with the aim of creating more targeted and effective interventions. This research will now be discussed with a focus on CF and nebulised treatments in the paediatric population, where possible.

Adherence to treatment in cystic fibrosis

Non-adherence to treatment is commonplace in CF and is viewed as the single largest barrier to treatment success, and the main challenge faced by CF care teams (Owen & Jones, 2016).

Adherence rates have been found to range between 35% and 75% depending on several factors, including treatment component, population characteristics, and data-collection methods (Eakin and Riekert, 2013). Sub-optimal adherence is problematic, as it limits the effectiveness of treatments, creating negative outcomes, both for patients (increased morbidity and mortality rates), and healthcare systems (increased consultations, admissions and wasted resources through unused medications and unnecessary treatment escalation). Such issues also constrain research by undermining treatment evaluation (Owen & Jones, 2016). For children and families, sub-optimal adherence also relates to increased time away from school, academic and social deficits, and enhanced stress and financial burden on families (Narayanan, Mainz, Gala, Tabori & Grossoehme, 2017). Consequently, adherence behaviour in CF has been positioned as a public health concern and research priority.

Measuring adherence

Within the adherence literature, non-adherence has been measured in a variety of ways, using both subjective and objective recording methods. However, almost all of these methods have been found to suffer from limitations, which undermine the validity and reliability of findings produced by studies which employ them.

Across treatments and illnesses, the most utilised method to assess adherence is self-report questionnaire; however, research has consistently shown that such subjective reports are inaccurate. For instance, within the CF population, patients and family members have been shown to overestimate adherence through recall biases including social desirability and retrospective memory bias (Quittner, Modi, Lemanek, Levers-Landis & Rapoff, 2008; Barker & Quittner, 2010), while health professionals have been found to underestimate adherence (Daniels, Goodacre, Sutton, Pollard, Conway & Peckham, 2011). Research has also shown that concordance rates between self-report and objective measures are low across treatments in the CF paediatric population. Modi, Lim, Yu, Gellar and Wagner (2006) found that objective adherence data (e.g. pharmacy refill history, and electronic monitors) was on average lower (<50% vs. 80%) and more variable (22%-71% vs. 67%-100%) than data collected through subjective methods (e.g. patient self-report, parent report). This highlights how subjective treatment adherence data can be significantly inaccurate and suggests that research should rely on objective measurement alone.

However, it is important to recognise that even seemingly objectively acquired data is also open to bias. For instance, frequently-used supposedly objective measures such as pill count data (i.e. a count of the number of pills remaining, compared with the number prescribed within a timeframe), pharmacy prescription refill records and electronic medication vial caps (which record the time of bottle opening) only indicate that a medication has been used or removed, with no guarantee that it was appropriately consumed. It is therefore impossible to know whether individuals have discarded

pills, consumed their prescribed dose, or taken their medications at the appropriate time. Such potential errors highlight how supposedly objective measures may also fail to provide a true representation of adherence data.

In recent years, however, new technologies have emerged to overcome such difficulties in measuring adherence for certain treatments. Within CF, technological advancements in the form of interactive nebuliser inhalation devices (trademarked as "I-nebulisers" / “I-nebs”) have allowed adherence to nebulised medications to be objectively recorded since 2006 (Profile Pharma, Zambon SpA, Chichester, UK). I-nebulisers use an electronic microchip to record the date and time medication is taken, and the dose inhaled. They also feature an adaptive aerosol delivery (AAD) system which ensures precise, reproducible doses are delivered to patients during the active inspiratory phase (inhalation) of their respiratory cycle, thereby minimising drug wastage from incorrect administration (Kesser & Geller, 2009). Together, this data recording and AAD technology allows accurate and highly reliable rates of treatment adherence to be calculated, leading many to promote the I-nebuliser as a ‘gold standard’ objective measure of inhaled medication adherence (McCormack, Southern & McNamara, 2012). Importantly, one study by Daniels et al. (2011) using I-neb data as an adherence measure has shown just how inaccurate self-report can be in nebulised CF therapy; adult self-report placed adherence at 80%, while downloaded I-neb data showed only 36%. Therefore, the remainder of this section will focus on objective measurement and, where possible, purely objective recording through such electronic monitoring devices.

Despite the availability of such accurate measures, it is important to recognise that further challenges exist in measuring adherence. First, adherence can be calculated in several ways using the same data. For instance, an overall measure of adherence can be determined by calculating the percentage of times that a medication is taken across the number of times it is prescribed, across a set period of time. Alternatively, one can measure how consistently a medication is taken, by calculating the percentage of days a patient fully adheres to their prescription. Finally, a minimum standard measure can be determined by calculating the percentage of days that the device was used at least once. Importantly, a study by Latchford, Duff, Quinn, Conway and Conner (2009) demonstrated that I-nebuliser adherence data calculated through these three different methods led to markedly different findings. Second, there is no established cut-off point for ‘poor’/‘insufficient’ adherence in these treatments, which makes adherence data difficult to interpret. The established clinical cut-offs for non-adherence which do exist typically rely on arbitrary thresholds proposed by expert clinicians, rather than values based on empirical evidence of treatment effectiveness (WHO, 2003). Third, most of these studies simply report an average percentage of adherence or non-adherence within a given sample. Such group-level data overlooks potential important individual differences, a flaw known as aggregation bias (Johnston & Johnston, 2013).

Objectively recorded adherence rates to nebulised treatments in cystic fibrosis

For nebulised therapies in adult populations, objective data collected through electronic medication monitors has shown that combined nebulised medication adherence can range between 36% and 50%, with large variability occurring between patients (i.e. IQR 5-84.5%, SD 39.7) (Daniels et al., 2011; Latchford et al., 2009). Within nebulised medication categories, average rates between 31% and 53% have been reported for antibiotics (Quinn, Latchford, Duff, Conner, Pollard & Morrison, 2004; Latchford et al, 2009), 24 to 82% for mucolytics (Burrows, Bunting, Masel & Bell, 2002), and between 41% and 72% for hypertonic saline (Elkins, Robinson, Rose, Harbour, Moriarty & Marks, 2006). However, only the studies examining nebulised antibiotic adherence used purely objective monitoring through electronic devices; the remainder relied instead on pharmacy refill data.

Interestingly, in the paediatric population, electronically-recorded adherence rates are higher and less variable than in the adult population. Ball et al. (2013) (N=24) found a mean adherence rate of 65% (SD 28%) for combined nebulised medications in adolescents, and a range of between 37% to 93%. They also found that patients on average took approximately 1.4 treatments a day, regardless of whether they were prescribed two or three treatments, and that adherence was higher on weekdays than weekends, and during school terms than holidays. For nebulised antibiotics alone, McNamara, McCormack, McDonald, Heaf and Southern (2009) (N=28) reported a similar average adherence rate of 67% (SD 31%) for children and adolescents. They also noted that adherence greatly varied both within and between patients', e.g. that adherence was higher in mornings than evenings. For mucolytic medications, however, no purely objective adherence data exists, although pharmacy refill data has placed average adherence rates at a higher level of between 67% and 84% (Modi, et al. 2006; Suri, Wallis, Bush, Thompson, Normand & Flather, 2002; Zindani, et al., 2006).

Overall, in the paediatric population, very little research exists which objectively examines adherence to nebulised medications, and that which does is limited by either small sample sizes, or a reliance on pharmacy refill data rather than objective recording. Importantly, while some studies suggest that mucolytic adherence may be higher than antibiotic adherence, no existing research provides a purely objective adherence rate for nebulised mucolytics. Nonetheless, it can be concluded that adherence rates to nebulised treatments are sub-optimal and variable in paediatric populations, and that adherence behaviour patterns appear to exist.

Evidence of poor adherence, alongside a paucity of research, is concerning due to the primary role that nebulised medications are argued to play in mucus clearance, and in preventing and treating lung infections – the key causes of morbidity and early mortality in CF (Eakin Bilderback, Boyle, Mogayzel & Riekert, 2011; Ryan, Singh & Dwan, 2011; Yang, Chilvers, Montgomery & Nolan, 2016). Supporting this, health outcome research across several studies has shown that increased

nebulised medication use relates to reduced use of intravenous antibiotic therapy, fewer pulmonary exacerbations and hospital admissions, reduced length of hospital stays, and better baseline lung function (Eakin et al., 2011; Briesacher, Quittner, Saiman, Sacco, Fouayzi & Quittell, 2011). This suggests that the negative consequences of non-adherence to nebulised medications alone can be significant, although it should be noted that the causal direction of these relationships is not always clear.

Correlates of treatment adherence

Adherence and demographic factors

Adherence is widely cited to decline with increasing age in CF populations (e.g. Masterson et al., 2011), with many studies across different treatments reporting adherence to be significantly poorer in adolescents than children (Zindani et al., 2006; Modi, Marciel, Slater, Drotar & Quitner, 2008; Lloente, Garcia & Martin, 2008; Bucks, Hawkins, Skinner, Horn, Seddon & Horne, 2009; Goodfellow, Hawwa, Reid, Horne, Shields & McElnay, 2015), or in older vs. younger adolescents (Bucks et al., 2009), suggesting that different barriers to adherence operate and possibly compound at different ages. Such adherence decline has been observed to start when individuals are approximately 10 years old, and to peak at roughly age 16 (Riekert, Mogayzel, Bilderback, Hale & Boyle, 2007; Quittner et al., 2014). At this point, sub-optimal adherence in adolescents has been reported to be almost three times more likely than in children (69% vs. 24%) (Llorente, et al., 2008).

It is not clear if this trend applies at similar levels, or at all, with nebulised medications, as relevant research is extremely limited. While some studies have found this same trend (Zindani, Streetman, Streetman & Nasr, 2006; McNamara, McCormack, McDonald, Heaf & Southern, 2009), others have found the converse (Modi, et al. 2008). If such a gradual but substantial decline does exist for nebulised medications in adolescence, it is important to understand and address it. A failure to adhere at this age may arguably allow the disease to progress at a faster rate, and create a poorer precedent for self-care in adulthood, since the transition from parent-led care to self-care usually occurs at this time.

Little research exists examining the impact of gender on treatment adherence in the paediatric CF population, and that which does is also inconsistent. While some research finds adolescent boys to be more adherent than girls (Miller, Willis & Wyn, 1993), others report the opposite (Patterson, Wall, Berge & Milla, 2008), or no difference (Llorente, et al, 2008; Bucks et al., 2008; Masterson et al., 2011). However, the former studies suffered from key methodological flaws, including assessing adherence with just a single question. Although the remaining studies gathered more robust adherence data, they only considered gender broadly, rather than within treatment subcomponents. Therefore,

the link between adherence and gender is unclear in the paediatric population, and unknown in relation to specific components of the treatment regimen, including nebulised medications.

Adherence and disease severity

Although the impact of disease severity on adherence rates in CF has been investigated, the research findings are mixed. While some studies report that treatment adherence is lower in children, adolescents, and adults when the disease is more severe (Conway, Pond, Hamnett & Watson, 1996; Hamutcu, Francis, Krakoc & Bush, 2002; Kettler, Sawyer, Winefield & Grenville, 2002, Llorente, et al., 2008), others report the opposite (Michaud, Frappier & Pless, 1991; Abbott, Dodd & Webb, 1996; Zindani et al., 2006; Hoo, Boote, Wildman, Campbell & Gardner., 2017), or find no association at all (Abbott et al., 1994; Daniels et al., 2011). For nebulised medications specifically, in the paediatric population, this relationship is unclear, as research is almost non-existent, and the studies which do exist (e.g. Modi et al., 2006) may be unreliable as they rely on medication vial data alone to examine adherence.

Adherence and treatment components

Differences exist between the treatment components in terms of their impact on symptoms, and in the time and effort they require. Higher rates of adherence have generally been found in simpler treatments which provide symptomatic benefit (e.g. pancreatic enzyme supplements and oral medications), with lower rates for more burdensome and/or prophylactic therapies (e.g. nebulised mucolytics and chest physiotherapy), in both adult and paediatric populations (Zindani et al, 2006; Modi et al., 2006; White, Stiller & Haensel, 2007; Sawicki, Heller, Demars & Robinson., 2015). For instance, in children with CF, objectively recorded adherence rates between treatment components have been found to range from 22% to 71% (Modi et al., 2006). These differences in adherence rates suggest that different factors mediate adherence behaviours between treatments, highlighting the importance of investigating them individually.

Summary

Overall, within paediatric populations in CF, adherence rates appear to differ based on certain demographic and clinical factors, and components of the treatment regimen, though the scarcity of research prevents firm conclusions. Research has attempted to investigate the reasons behind these adherence differences, identifying a multitude of barriers and facilitators. Although much early research was completed in the adult population, over the last decade, more studies have examined the

child and adolescent CF population. This research will now be discussed, with a focus on nebulised medications where possible.

Barriers and facilitators to treatment adherence

The influence of treatment burden and competing priorities on adherence

The time-consuming nature of treatments and competing life priorities, are often cited as barriers to adherence across treatments in children, adolescents and adults with CF (e.g., Conway et al., 1996; Modi & Quittner, 2006; Modi et al., 2006; Williams, Mukhopadhyay, Dowell & Coyle, 2007; Bucks et al., 2009; George, Rand-Giovannetti, Eakin, Borrelli, Zettler & Riekert, 2010; Bregnballe, Schiøtz, Boisen, Pressler & Thastum, 2011; Sawicki et al., 2015). Within nebulised treatments specifically, questionnaire-based and qualitative studies have shown that adults, children, adolescents, and/or their parents report time-burden (including preparation, administering treatment and cleaning equipment) and competing demands (balancing treatment with their social and occupational lives) to be a main, if not the primary, barrier in completing such treatments (Modi and Quittner, 2006; Llorente et al., 2008; Dziuban et al., 2010; Bregnballe et al., 2011; Hogan, Bonney, Brien & Karamy., 2014; Sawicki et al., 2015). The importance of time and convenience can also be seen in the recorded adherence rate differences between arguably easy-to-administer oral antibiotics (80%–95%) and more burdensome nebulised antibiotics (65%–80%) in adults (Abbott et al., 1994; Conway et al., 1996; Kettler et al., 2002).

However, despite such reports, adherence rates have not improved as nebulised treatment has become increasingly convenient and time-efficient; modern nebulisers do not require patients to reconstitute drugs, or engage in time-consuming preparation, cleaning and disinfecting procedures (Kesser & Geller, 2009). Patients also report new nebuliser devices as 'easy' or 'very easy' to use (Denyer, Black, Nikander, Dyche & Prince, 2010; Denyer, Prince, Dixon, Agent, Pryor & Hodson, 2010), which suggests that complexity of use is not a barrier. Finally, reducing prescribed daily doses has not been found to improve adherence in the long term (McNamara et al., 2009). Together, such findings suggest that the time and complexity of treatment preparation and administration does not act as a barrier in nebulised treatments. Contrary to self-report, 'competing demands' also do not appear to function as a barrier to adherence behaviour. As highlighted above, paediatric populations have been found to be significantly more adherent to nebulised therapy at times when free time is arguably sparser - for example, in mornings rather than evenings (McNamara et al., 2009), and during term-time rather than holidays (Ball et al., 2013). Such patterns of poor weekend adherence have also been found in young adults (George et al., 2010). Together, such findings suggest that time-burden and competing demands are not the originating factors of poor adherence.

The influence of forgetting on adherence

Recently, certain authors (e.g. George et al., 2010, McNamara et al., 2013) have suggested that routine change can cause individuals to simply forget to take medication, a factor they further promote as the general underlying barrier to adherence. Supporting this, interview- and questionnaire-based studies have shown that adults, children, adolescents, and/or parents report forgetting as a major, even primary, reason for non-adherence across treatments, including within nebulised therapy (Modi & Quittner, 2006; Dziuban et al., 2010; George, et al. 2010; Bregnballe et al., 2011; Llorente et al., 2011). Such studies equally highlight an established routine as a major, even primary, facilitator to adherence.

Despite such reports, it is surprising that forgetfulness arising from routine change would constitute such a fundamental barrier for CF treatments, considering the daily and life-long nature of the treatment regimes. Dziuban et al. (2010) suggest that what parents and patients label as 'forgetting' may represent a superficial explanation for deeper originating obstacles, e.g. beliefs within or outside of individuals' awareness. Supporting this, Sawicki et al. (2015) found that parents understood their child's 'forgetting' of treatments as a reflection of their denial around their need for therapy, or a failure to appreciate the long-term benefits, rather than an act of simple forgetfulness. They also noted that such lapses were often discussed in the context of competing priorities, suggesting that the process of 'forgetting', and beliefs driving it, may also underlie the barrier of 'competing demands'. It is also interesting to note that Modi and Quittner (2006) found that approximately half of parents were unable to identify the barriers to nebulised therapy for their children, possibly supporting the influence of less conscious processes.

Such findings suggest that improvements in treatment administration times, reminder systems, and setting routines alone would not significantly impact adherence levels, as it would not address the underlying factors driving such apparent forgetfulness: beliefs about the treatment itself.

The influence of family on adherence

The high treatment burden imposed by CF often causes individuals to rely on support from others, especially family members, to manage their treatments. Highlighting the importance of this, research has shown that strong family cohesion and support relates to improved treatment adherence in adults (McGuffie, Sellers, Sawicki & Robinson, 2008; Hogan et al., 2015) and children (Foster et al., 2001; DeLambo, Ievers-Landis, Drotar & Quittner, 2004; Hamutcu et al., 2002; White, Miller, Smith & McMahon 2009). Conversely, family dysfunction, including reduced parent-child attachments and psychological wellbeing, and increased conflict and stress, relate to lower adherence (Foster et al., 2001; DeLambo, Levers-Landis, Drotar & Quittner 2004; Badlan, 2006; Smith & Wood, 2007; Modi et al., 2008; Smith, Modi, Quittner & Wood., 2010; Szyndler, Towns, van

Asperen & McKay, 2005; Dziuban et al., 2010). Interestingly, Bregenbelle et al. (2011) found that adolescents who reported feeling less supported, and reported more family conflict, also described other treatment barriers more frequently, leading the authors to suggest that family dynamics not only act as a barrier or facilitator in themselves, but also create and remove other adherence barriers. Importantly, such dynamics undergo changes as children reach adolescence; autonomy and independence are increasingly promoted through alterations in roles and responsibilities, including a transfer of treatment responsibility from parents/guardians to the adolescent. Many authors, including Foster et al. (2001) and Modi et al. (2008) suggest that the decrease in adherence to CF medications between childhood and adolescence likely reflects this decrease in parental involvement.

Overall, these findings suggest that family dynamics and functioning impact adherence rates, and that families also have a strong role in both creating and mediating other adherence barriers.

The influence of developmental changes on adherence

Several developmental challenges (e.g. changes in education, vocation, independence, self-identity, cognition and peer relationships) occur in adolescence, which may help to explain the reduced adherence rates observed. Adolescents need to learn to navigate these changes alongside managing their health-needs and their transition to adult care teams, which requires them to form new relationships with healthcare professionals and take increasing responsibility for managing their own treatments (McLaughlin, Diener-West, Indurkhya, Rubin, Heckmann & Boyle, 2008; Sawicki et al., 2015). Unfortunately, alongside these challenges, the disease often suddenly worsens, with symptoms becoming more problematic, and the regimen, consequently, increasingly intensive and prevention-focused (Sawicki et al., 2015).

Unsurprisingly, considering such changes, research has identified differences in some self-reported treatment barriers between children and adolescents in CF. While younger children and their parents report barriers in oppositional behaviours, such as taste and swallowing dislikes (Modi & Quittner, 2006), adolescents/young adults and/or their parents report factors such as: fatigue (George, et al., 2010), privacy concerns (e.g. reluctance to disclose their diagnosis and/or take medications in front of others) (Bregnballe et al., 2011), increased social demands (e.g. preference for being with friends rather than adhering to scheduled treatment) (George et al., 2010), a wish to be 'normal' and experiences of embarrassment (Dziuban et al., 2007). These adolescent beliefs were found in relation to CF treatment broadly, though several were also reported in relation to nebulised treatments specifically. In the adult-focused literature, all of these beliefs have also been reported in relation to nebulised therapy alone (Hogan et al., 2015).

Although it is understandable that adherence would become more difficult for adolescents alongside so many changes and new barriers, it remains surprising that individuals would neglect their treatments at a time in their lives when disease progression would presumably make their health status more pertinent. Interestingly, Llorente et al. (2011) and Sawicki et al. (2015) suggest that illness- and treatment-related beliefs are likely to change at this time due to the number of developmental and situational changes highlighted above, and suggest that it is these belief changes that influence adherence behaviour.

The influence of illness and treatment beliefs on adherence

Arguably, certain characteristics of CF and nebulised medications may lead adolescents to develop beliefs that act as barriers to adherence. For instance, patients with CF can feel relatively healthy and asymptomatic, even when their organ functions are declining (Peckham & Whittaker, 2013). The preventive nature of nebulised mucolytics means that direct symptom relief is not experienced, and that immediate negative consequences from missed doses do not occur (Abbott et al., 1996). Also, the nature of the disease means that its progression is inevitable, even with optimal adherence. These observations and experiences may cause individuals to underestimate their disease severity, and to question their need for daily adherence, or even for nebulised treatments at all.

Supporting this, interview studies have found that adolescent patients can hold beliefs such as feeling they do not need to adhere to their medication (including nebulisers) if they feel fine (Sawicki et al., 2015; George et al., 2015), or during periods when they feel healthy more often (Dziuban et al., 2010), and may believe that a lack of immediate benefit means that preventive medications (including nebulised mucolytics) are not effective (Sawicki et al., 2015; George et al., 2015). Dziuban et al., (2010) found that a third of adolescents consider it acceptable to miss a treatment every few days, or when they are busy, with a minority of individuals further believing that taking extra doses later could counteract earlier non-adherence. A heightened awareness of disease trajectory has been found to lead adolescents to weigh up the importance of completing treatments in relation to their overall length and quality of life (Sawaicki et al., 2015), and specifically in relation to treatment sub-components, as they may vary by burden vs. perceived benefit (Llorente et al., 2008).

Similar beliefs regarding the lack of perceived need for daily nebulised medication, and the perceived low importance of this treatment relative to others, and life overall, have also been reported in the adult literature (Hogan et al., 2015; Hoo et al., 2017). In addition, adults have reported that nebulised medication is an exhausting activity, expressed concerns regarding short-term side-effects such as excessive coughing (Hogan et al., 2015), and have reported beliefs that it is boring and time-consuming (Hoo et al., 2017).

Interestingly, differences in beliefs have been reported between different nebulised medications. Dziuban et al. (2010) found that no adolescent in their study felt it acceptable to miss nebulised tobramycin, an antibiotic typically prescribed in 28-day on-and-off cycles. The authors speculate that the time-limited nature of this treatment, and its potential immediate symptomatic benefit, may have led to it being perceived as more useful and tolerable. Similarly, in the adult literature, Hoo et al. (2017) found that adults reported finding hypertonic saline easier to adhere to than dornase alfa, as the former causes an immediate effect by stimulating vigorous coughing and sputum expectoration. Importantly, such findings highlight the need to examine how barriers, including beliefs, can differ even within a treatment, depending on the medication being delivered.

Summary

In short, numerous psychological, social and practical barriers and facilitators influence adherence rates in adolescents with CF, several of which act specifically within nebulised therapy. These include treatment burden, competing demands, forgetting to adhere, decreased parental involvement, and perceptions of treatment necessity and value. Such findings highlight the complex and multifaceted nature of adherence, and the challenge of considering which factors to target for intervention, and/or which may be most amenable to change.

Importantly, it appears that some of these practical and psychosocial factors may originate from, influence, and/or be influenced by, individuals' underlying beliefs. However, the studies highlighted above investigating such beliefs have largely been conducted outside theoretical models, have been qualitative and exploratory in nature, or have used quantitative designs with inconsistent means of assessing beliefs. Crucially, frameworks and means to assess such beliefs have been developed, enabling cross-study comparisons and the relative importance of beliefs to be examined - these will be discussed next.

Health belief models of treatment adherence

Social cognitive models focus on individuals' motivations and intentions in order to understand the role of rational decision-making and planning processes in behaviour (Brawley & Culos-Reed, 2000). Such models have been used to provide theoretical frameworks to understand and study illness behaviour, including adherence, and are considered among the most effective in predicting and improving adherence behaviour in chronically-ill patients (Roter, Hall, Merisca, Nordstrom, Cretin & Svarstad, 1998). Several such models address how cognitive factors, including beliefs, determine how health information is understood, evaluated, and responded to (DiMatteo, Haskard-Zolnierek & Martin, 2012). So the challenge now is to identify which of these models are

useful for predicting adherence, so that targeted interventions can be developed to improve low adherence. Two of the most widely accepted belief models, and their relations to adherence behaviour will now be considered.

The self-regulatory model

Leventhal's self-regulatory model of illness representations (Leventhal, Zimmerman, & Gutmann, 1984) suggests that patients are active problem-solvers, who are motivated to construct cognitive and emotional representations about their illness and its treatment, in order to make sense of it. These representations, in turn, influence the formation of coping behaviours and expectations of physical and emotional outcomes, which help to guide an individual's behaviour towards managing it (Leventhal, Nerenz, & Steele, 1984). This model suggests that forming mental representations occurs through two partially-interacting parallel processes; cognitive and emotional (Diefenbach & Leventhal, 1996).

The first process is responsible for the development of cognitions, known as 'illness representations'. Cognitions are activated in response to internal or external cues about symptoms and health threats. They are argued to directly influence patients' awareness and interpretation of symptoms, and their expectations of treatment, which in turn influence their problem-based coping strategies, including adherence behaviour. It is argued that individuals' with more negative cognitive representations regarding their illness, therefore develop more negative coping styles and strategies, including poorer adherence to their treatments (Hagger & Orbell, 2003). Illness representations are argued to be structured around five separate dimensions: 1. cause (i.e. beliefs about what factor(s) underlie illness development); 2. illness identity and associated symptoms (i.e. beliefs about what is wrong); 3. illness consequences (i.e. beliefs about how the condition will impact physical, mental, and social functioning); 4. illness duration (i.e. whether it will be chronic, transient or cyclical); and 5. cure/control (i.e. beliefs about one's personal control over the illness, and treatment control: beliefs regarding the efficacy, necessity, and concerns of completing treatment) (Leventhal, Leventhal & Cameron, 2001).

The second process constructs emotional representations and feelings that can arise from the disease. These representations can be activated by illness representations, or by external and internal cues (e.g. bodily sensations). To attenuate or control these negative emotions, coping strategies are implemented which may be helpful or unhelpful. It is argued that this pathway interacts with the illness perception pathway, leading erroneous beliefs regarding illness, or unhelpful strategies for coping with associated emotions, to develop (Diefenbach & Leventhal, 1996).

These systems are argued to be built on information from sources such as personal and family experience, healthcare professionals, and the media. This model places the process of adapting to an illness into three inter-relating stages: i) 'interpretation', referring to the patient's attempt to make sense of their perceived symptoms; ii) 'coping', denoting maladaptive and adaptive of management of the problem, and iii) 'appraisal', a review process where patients evaluate how effective their coping has been. Therefore, illness representations are argued to be continuously evaluated and updated, as patients appraise the efficacy of their coping behaviours and acquire new illness- or health-threat-related information. This leads an individual to either persist with a coping behaviour, or to try alternatives. This model is presented in Figure 1 below:

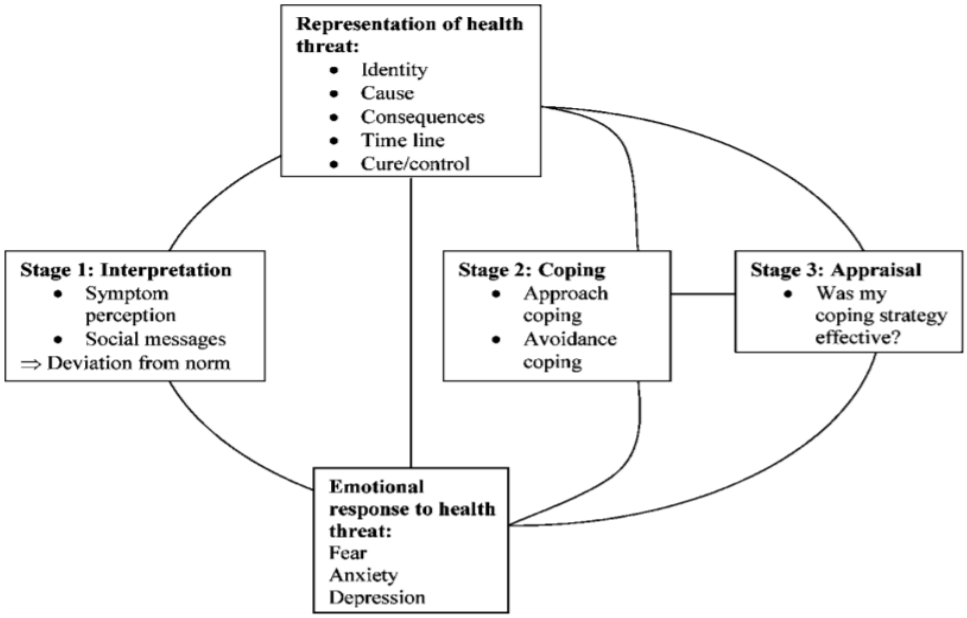

Figure 1: The self-regulation model (Diefenbach & Leventhal, 1996).

The Illness Perception Questionnaire (IPQ) (Weinman Petrie, Moss-Morris & Horne, 1996), the Illness Perception Questionnaire-Revised (IPQ-R) (Moss-Morris, Weinman, Petrie, Horne, Cameron & Buick, 2002) and the Brief Illness Perception Questionnaire (Brief IPQ) (Broadbent, Petrie, Main & Weinman 2006) were developed as means to assess the self-regulatory model. They are generic measures which aim to assess in varying levels of detail, illness perceptions that are commonly held across a range of acute and chronic illnesses. Each of these measures has been validated and has been found to have good psychometric properties across chronic conditions (Moss-Morris et al., 2002; Hagger & Orbell, 2005; Broadbent, Wilkes, Koschwanez, Weinman, Norton & Petrie, 2015).

The self-regulatory model and adherence behaviour

Within the literature, hundreds of studies across chronic conditions have used these IPQ questionnaires to examine relations between illness perceptions and a variety of outcomes, including treatment adherence in adult and paediatric populations. For instance, illness perceptions reported by children, adolescents, and parents, have been found to relate to treatment adherence across a range of conditions, including hypertension (Skinner, John, & Hampson, 2000), functional constipation (Koppen, van Wassenaer, Barendsen, Brand & Benninga, 2018), diabetes (Griva, Myers, & Newman, 2000; Skinner, Hampson & Fife-Schaw, 2002; Gaston, Cottrell and Fullen, 2011; Prikken et al., 2019), asthma (Horne & Weinman, 2002; Sonney, Insel, Segrin, Gerald & Moore, 2017; Kosse, Koster, Kaptein, de Vries & Bouvy, 2019) and CF (Bucks et al., 2009), supporting the utility of this model. However, it should be noted that other studies have found no such relationship (e.g. Klok, Kaptein, Duiverman & Brand, 2012). Interestingly, some recent studies (e.g. Gaston et al., 2011; Sonney et al., 2017; Koppen, et al., 2018; Prikken et al., 2019) have started to examine the influence of both patients' and parents' illness perceptions on adherence behaviour, as they argue that parents' illness and treatment beliefs are likely to influence the development of their children's illness representations, and that examining both sets of beliefs may therefore offer new insights into self-management behaviour in paediatric populations.

Within CF, just one study has assessed illness perceptions in the adult population (Sawicki et al., 2011), and one in the paediatric population (Bucks et al., 2009), although only the study by Bucks et al. (2009) did so in the context of treatment adherence. Bucks et al., (2009) found that perceptions that CF is not amenable to treatment control, and that CF is not permanent, related to poorer self-reported adherence to antibiotic treatments, but not to chest physiotherapy or enzyme supplements. Indeed, they found that no illness perceptions related to adherence for these treatments, suggesting that this model does not apply to all treatments, even within a single illness. They also found that age related to adherence for antibiotics, but that timeline chronicity beliefs appeared to be mediating this relationship, and that emotional representations became more adaptive with age. Such findings suggest that treatment control and timeline beliefs appear to relate to adherence in CF within antibiotic treatments, that beliefs may mediate relations between demographic variables and adherence, and that illness perceptions and emotion representations appear to change with age.

However, the paucity of research in this area prevents firm conclusions from being drawn - in fact, recent reviews examining the strength of such effects across treatments and illnesses suggest that they are weak and inconsistent. Brandes and Mullan (2014) completed a meta-analysis of twenty-three studies across chronic conditions to examine the predictive relationships between illness perceptions and adherence to medication, exercise, and diet recommendations in adults and adolescents. Findings showed that, although the illness perceptions of personal control, treatment control and coherence were found to be significant predictors, they only accounted for a small amount

of the variance in adherence outcomes, and effect sizes were very weak ranging from -.02 to .12. They also found variety in the illness perceptions that most strongly predicted adherence across studies. Such weak and inconsistent relationships were also found in a systematic review of fifteen studies by Law, Tolgyesi and Howard (2014) examining the relationship between illness perceptions and self-management in children and adults across conditions. Findings showed that, out of all beliefs, those relating to treatment control most consistently related to self-management. This led Law et al., (2014) to argue that this dimension should become the focus for research and the target for intervention.

Summary

Together, these findings show that illness beliefs relate to adherence behaviour in adult and paediatric populations, providing support for Leventhal's self-regulatory model. However, it remains unclear whether this model applies to all treatments and illnesses, and where it does apply, which specific beliefs relate to adherence behaviour. It appears that this relationship largely differs between conditions and treatments, with only treatment control beliefs showing some consistency across conditions and/or treatments. Only one study has examined these relationships in CF, and although this study found timeline and treatment control beliefs to predict adherence behaviour to antibiotic treatments, it found no such relations for chest physiotherapy and enzyme supplements. The weak relationships between illness perceptions and adherence outcomes suggest that this model is not the most appropriate for understanding adherence behaviour. Such findings have led researchers to attempt to identify improved cognitive predictors. As hoped, stronger and more consistent relationships have arisen from examining treatment beliefs in such a manner, discussed next

The Necessity-Concerns Framework

In the late 1990s, the cure/control dimension of Leventhal's self-regulatory model was extended, and the notion that beliefs about medications may be more potent predictors of adherence behaviour was developed (Horne, Cooper, Gellaitry, Date & Fisher, 2007). This model is known as the Necessity-Concerns Framework (Horne, Weinman & Hankins, 1999), and considers that primary common-sense evaluations people make about their medications fall into two categories. The first, necessity beliefs, refers to implicit judgements about personal need and benefits of the medication for current and future health (e.g. reduction of symptoms, improved quality of life). The second, concern beliefs, considers implicit views held about actual or potential adverse reactions or undesirable consequences of taking the medication (e.g. side-effects, disruption to daily life). The model proposes that the strength of these beliefs lies on a spectrum from low to high, and that their strength influences an individuals' decision to adhere to treatment recommendations. Necessity beliefs are argued to

promote adherence, while, conversely, concern beliefs hinder it. It is also theorised that an implicit cost-to-benefit analysis occurs between these belief types, in which patients judge their personal need for treatment, relative to concerns they hold about potential adverse effects. Individuals with high necessity beliefs relative to concerns are predicted to be most likely to adhere, while those with stronger concerns than necessity beliefs, less so.

The Beliefs about Medicines Questionnaire (BMQ) was developed as a generic measure to assess this model across conditions and treatments. It aims to provide direct quantification of commonly-held prescribed treatment beliefs, which are considered to fall into two categories: 'specific' and 'general' (Horne et al., 1999). The 'specific' category captures beliefs about specific medications prescribed for an illness, and is examined through two subscales; *necessity* and *concerns*. The 'general' category considers more beliefs about medication as a whole, through two subscales; *general harm*, which captures an individual's views on potential harm from medications, and *over-use*, reflecting views on how medications are used. This review and thesis will only concentrate on this specific scale, which is assessed by the BMQ-Specific (BMQ-S) questionnaire. Its constituent items (questions / statements with which responders may indicate a level of agreement/disagreement) were developed from the existing literature and interviews, and with six chronic illness groups (asthma, diabetes, renal, general medicine and psychiatric) to ensure that the developed questionnaire reflected a variety of disease and treatment characteristics.

Within this original study, the two-factor structure of this the BMQ-S was identified through exploratory principle component analysis, and verified across the five illness groups by confirmatory factor analysis. Subsequent evaluation of the psychometric properties of the BMQ-S was generally favourable, and included assessment of internal consistency, test-retest reliability, discriminant validity, criterion validity and predictive validity. Regarding internal consistency, almost all alpha values across the two subscales in each of the five diagnostic groups fell above 0.7, even with the small number of items in each subscale, leading the authors to conclude that it was adequate. Similarly, test-retest reliability was found to be acceptable for both necessity and concern subscales (r=0.77 and 0.76 respectively), although this was only examined in the asthmatic group. Discriminatory validity was examined through the ability of the BMQ-S subscale scores to distinguish between patients in different illness and treatment groupings, and findings showed that the measure was able to do so in accordance with predictions. Criterion validity was assessed through correlations with theoretically-related subscales from other illness and belief measures (including the IPQ), and was found to be lie in the predicted directions, and to be significant. Finally, expected correlations were obtained between BMQ-S scale scores and self-reported adherence to medication, and were found to be significant although weak in strength (necessity rs=0.19 and concerns -0.28). Overall, the authors conclude that the psychometric properties of the scale are encouraging, but also highlight how the scope of their evaluation of criterion validity and predictive validity were limited; the former due

to a paucity of existing validated measures, and the latter by only considering the outcome factor of adherence.

Since then, the BMQ-S has been validated further in adult populations in a variety of chronic conditions, including rheumatoid arthritis (e.g. Neame & Hammond, 2005; Treharne, Lyons & Kitas, 2004), hypertension (e.g. Ruppar, Dobbels & De Geest, 2012), diabetes (e.g. De Vries et al., 2014), CF (Bucks et al., 2008) and in mental health conditions (e.g. Cuevas, Rivero-Santana, Parestelo-Parez, Gonzalez-Lorenzo, Perez-Ramos & Sanz, 2011), and has been successfully translated into several languages (e.g. Fall, Gauchet, Izaute, Horne, & Chakroun, 2014; Gatt, West, Calleja, Briffa & Cordina, 2017). However, the thoroughness of such psychometric evaluation in these chronic illnesses has been limited. Although some studies have examined internal consistency and the predictive validity of the BMQ-S measure to various outcomes (e.g. Treharne, Lyons & Kitas, 2004; Bucks et al., 2008), others have only examined the predictive validity of the measure (e.g. Neame & Hammond, 2005; Ruppar, Dobbels & De Geest, 2012; De Vries et al., 2014). This minimal evaluation is problematic, since it could be the case that that the properties of this measure, do not generalise across all chronic illnesses.

The dynamic and self-regulatory nature of this model has also been increasingly shown through longitudinal studies, which have indicated that treatment beliefs and adherence behaviour change over time (e.g., Aikens, Nease, Nau, Klinkman & Schwenk, 2005; Horne, Cooper, Gellaitry, Date & Fisher, 2007; de Thurah, Norgaard, Harder, & Stengaard-Pedersen, 2010; Aikens & Klinkman, 2012). It is important to note that, although the BMQ-S was developed to represent a variety of chronic health conditions, it is relatively commonplace to tailor the questionnaire (i.e. modify wording, remove or add items) to allow idiosyncratic characteristics of the individual condition and medication(s) of interest to be captured. Without such adaptations, it is considered that key beliefs relevant to the specific condition of interest could be missed, and that certain items within the BMQ-S may simply not be applicable for certain treatments. Indeed, within Horne et al.'s (1999) original paper, during validation, they identified that the generated factor structure differed by one item in psychiatric conditions, and two items in diabetes. Since then, such observations have led to the development of several further condition-specific adapted BMQ-S measures, including the BMQ-AET-Specific for Adjuvant Endocrine therapy in cancer (Brett et al., 2018), and BMQ-HAART-Specific for HIV and aids (Horne, Buick, Fisher, Leake, Cooper & Weinman, 2004).

The psychometric properties of these adapted measures were examined. Of the two studies above, Brett et al. (2018) completed quite a thorough assessment, first examining the factor structure of the BMQ-AET-Specific through principal component analysis, and finding that their measure fitted the original two sub-scales model. They then examined several aspects of validity and reliability. They found the internal consistency of the adapted measure to be adequate for both necessity and

concern subscales (0.77 and 0.80 respectively) and, indeed, to reflect those found in Horne and Weinman's (1999) original study. Regarding convergent validity, they found that relations between the subscales and self-reported adherence behaviour fell in the expected directions, albeit only significantly so for necessity beliefs. Finally, they reported acceptability of the measure to be good, which they assessed through the rate of missing data, floor and ceiling effects, and face validity, which was examined through a discussion with both clinicians and service users. Although for the BMQ-HAART-Specific Horne et al., (2004) also examined internal consistency and found this to be high for both necessity and concern beliefs (0.80 and 0.82), and also examined convergent validity through self-reported adherence and found this to be as expected, they did not complete further psychometric evaluation. Various aspects of validity and reliability for this measure are therefore unknown, including whether the adapted items map onto the two-factor model of this measure and the strength of their loadings. This highlights the level of discrepancy between studies in such considerations.

The Necessity-concerns framework and adherence

Many studies using the BMQ (including adapted versions) in the adult population have supported the predictions of the Necessity-Concerns Framework by relating scores from the questionnaire to observed adherence behaviour. Such studies have been completed across a variety of healthcare settings, cultures, and chronic conditions, including asthma (e.g. Byer & Myers, 2000; Horne & Weinman, 2002; Menckeberg et al., 2008; Sofianou, et al., 2013; Foot et al., 2019), cardiovascular disease (e.g. Unni & Farris, 2011; Berglund, Lytsy & Westerling, 2013), mental illness (e.g. Russell & Kazantzis, 2008; Al Jumah, Hassali, Al Qhatani & El Tahir, 2014), HIV (e.g. Horne, Cooper, Gellaitry, Date, Fisher, 2007), diabetes (e.g. Aitkens & Piette, 2009), rheumatoid arthritis (e.g. Neame & Hammond, 2005), and cancer (e.g. Grunfeld, Hunter, Sikka & Mittal, 2005; Arriola et al., 2014; Brett et al., 2018). Interestingly, the relationship between the types of items (necessity or concern) and adherence has been found to vary between studies, with some studies only finding necessity beliefs to significantly relate to adherence behaviour (e.g. Byer & Myers, 2000; Berglund, Lytsy & Westerling, 2013; Van Steenis et al., 2014; Brett et al., 2018), while others only concern beliefs (e.g. Neame & Hammond, 2005; Russell & Kazantzis, 2008; Al Jumah, et al., 2014), or a combination (Foot, La Caze, Baker, Cotrell, 2019). Importantly, some studies have shown that the difference between necessity and concern belief subscales has a stronger relationship to adherence than the strength of either necessity or concern beliefs alone (e.g. Horne, Weinman & Hankins, 1999; Emilsson et al., 2011; Iudici, Russo, Mitidieri, Cuomo & Valentini, 2014). This calculation is known as the necessity-concerns differential, and accounts for the implicit cost-benefit analysis described in the Necessity-Concerns Framework.

Recently, two meta-analyses were completed to examine the explanatory value of this framework on a population level for predicting medication adherence in adults with long-term conditions. The first, by Horne, Chapman, Pargam, Freemantle, Forbes & Cooper (2013), examined ninety-four studies and found aggregate effect sizes to be moderately strong for both necessity (OR=1.74) and concern (OR=.50) beliefs. This effect stayed stable when data was stratified by condition, study design, sample size, adherence measurement method and country of origin. Overall, they conclude that this model is a potentially useful means to understand patients' evaluations of their prescribed medicines. However, in post-hoc analysis, they did not explicitly compare the differences in effect sizes between health conditions, and they only examined relationships in isolation (i.e. how necessity beliefs and concern beliefs separately related to adherence behaviour), despite recent studies increasingly considering how patients "weigh up" these beliefs by computing the necessity-concerns differential.

Foot, La Caze and Cottrell (2016) completed a second meta-analysis of ninety-four studies to overcome the former's limitations. Overall, on a population level, they found significant effects for necessity, concerns, and the differential, although these were all relatively weak, at 0.17, -0.18 and 0.24 respectively. Importantly, although these effects were present across almost all conditions, stratification by health condition revealed that the effect sizes for two of the conditions were very different from the aggregated results. A stronger overall effect size between necessity beliefs and medication adherence was found for asthma (r=0.33), while a very weak effect size was found for cardiovascular disease (r=0.07). Further analysis revealed that the asthma group's necessity beliefs were the most important correlate for adherence behaviour, regardless of concerns, while for the cardiovascular group, the opposite was true. From these findings, the authors argue that the relative importance of the belief scales in the Necessity-Concerns Framework, and their relation to adherence behaviour, is likely to vary between conditions, depending on the unique and varied symptoms, treatments and outcomes of different illnesses. They also argue that the necessity-concerns differential should be examined more in research studies, as it shows promising results, and allows the cost-benefit assumption of this model to be tested.

Overall, these findings suggest that both subscales, as well as the necessity-concerns differential, need to be examined separately for each illness and treatment. Ultimately, such understanding would allow interventions to be developed that appropriately target the beliefs that influence adherence in specific conditions and treatments. Both studies raised the need for future studies to employ objective measurement to overcome the limitation of subjective methods. Although Horne et al. (2013) did not find a difference in effect sizes between beliefs and adherence data collected through objective or subjective measures, Foot et al. (2016) found that concern beliefs had a lower mean effect size when assessed with objective adherence data. It is also important to note

that neither of these meta-analyses included the illness of CF, and that both were completed in adult populations alone.

Increasingly, the BMQ measure has been used in paediatric populations, and has been validated with parents and children of 7 years and above, allowing it to be completed by both patient and/or parents. These studies have reported findings supporting the predictions of the Necessity-Concerns Framework across conditions including CF (Bucks et al., 2009; Goodfellow et al., 2015), asthma (e.g. Conn, Halterman, Lynch & Cabana, 2007; Klok, Kaptein, Duiverman & Brand, 2012; Koster, Philbert, Winters & Bouvy, 2015; Sonney et al., 2017; Kosse et al., 2019), ADHD (e.g. Emilsson, Gustafsson, Öhnström & Marteinsdottir, 2017), haemophilia (e.g. van Os, Troop, Sullivan & Hart, 2017) and heart failure (e.g. Wray, Waters, Radley-Smith & Sensky, 2006). Like for the adult population, relationships between the subscales to adherence have been found to vary between studies; some report only necessity beliefs to significantly relate to adherence (Klok et al., 2012; Koster et al., 2015), while others studies only concerns (Wray, Waters, Radley-Smith & Sensky, 2006; Conn, et al., 2007), or only the necessity-concerns differential (Emilsson et al., 2017; Sonney et al., 2017), and yet others, a combination of these factors (van Os, Troop et al., 2017; Kosse et al., 2019). Interestingly, some studies have examined both patients' and parents' beliefs, as they recognise that the responsibility for medication management is often shared between children, particularly at school-age, and their parents (e.g. Yilmaz, Eroglu, Ozalp & Yuksel, 2012; Goodfellow et al., 2015; Sonney et al., 2017; Koppen et al., 2018). Such studies allow comparison of predictive validity between beliefs and adherence between parents and their children, and/or examination of the level of interdependence between parents' and children's treatment beliefs. In the next section, the paediatric studies which have considered CF specifically will be considered in further detail.

Importantly, although the relationships between medication-related beliefs and adherence behaviour are, on average, classified as weak-to-moderate, studies in this field have highlighted the superiority of this relationship over socio-demographic (education, gender, age), clinical variables (illness severity, number of medications) and other beliefs (e.g. illness perceptions) (Horne & Weinman, 2002; DiMatteo 2004; DiMatteo, Haskard & Williams, 2007). Treatment-related beliefs have even been found to mediate relationships between adherence and other demographic factors, including age (Bucks et al., 2009), gender (Ross, Walker & MacLeod, 2004), minority status (Tao et al., 2008), depression (Hilliard et al., 2015), health literacy (Federman et al., 2013), personality traits (Axelsson, Cliffordson, Lundbäck & Lötvall, 2013), medication burden (Phatak & Thomas, 2006), and even illness perceptions (Horne & Weinman, 2002).

Adaptations of the BMQ-S measure

As described, despite being intended as a generic measure, the BMQ-S has been adapted to individual treatments and conditions, in the hope of improving its psychometric properties. Several of the studies presented above, in both adult and paediatric populations, have tailored the wording and content of the BMQ-S with the aim of more effectively capturing beliefs that influence adherence behaviour. These modifications include minor revisions to the wording of existing items, removals of existing items and/or illness-specific additions. Without these adaptations, it is considered that certain unusual characteristics of the illness and treatment of interest could render items in BMQ-S irrelevant, and/or lead beliefs idiosyncratic to a particular illness and treatment to be missed entirely. Ultimately, this would reduce the utility of the BMQ-S, falsely reduce the predictive validity of the Necessity-Concerns Framework and in turn the foundation for developing interventions based on this model. Within this literature, great variability exists in the rigour of such adaptations. However, despite this, modified questionnaires have been found to generally have acceptable psychometric properties (i.e. internal consistency and construct validity). This lack of methodological rigour may nonetheless be limiting the development of such questionnaires, and, in turn, assessment of this model.

In several studies, details regarding the rationale and/or process of creating refined BMQ-S measures are minimal or simply omitted. For instance, some authors simply state which items were removed or added, but do not elaborate on the justification for these decisions (Bucks et al., 2009; Goodfellow et al., 2009), while others simply present the process for creating such changes as 'a discussion' (Bucks et al., 2009; Brett et al., 2018), or omit details of the procedure entirely and just state the changes made (Horne et al., 2004; Goodfellow et al., 2009). Also, where further details have been provided regarding the process of adaptation, methodological limitations have been noted. For instance, some studies have primarily relied on the knowledge of the research team alone to make modifications (Goodfellow et al., 2009), which existing research in questionnaire development suggests is likely to reduce the heterogeneity of opinion, and thereby the validity of the measure (Hardy et al., 2004). Also, none of the above studies provided an explanation for how, during said 'discussions', agreement was met on the changes to be made, and it is has been suggested within wider literature that without provision of a systematic agreement process, group dynamics may adversely impact such decision making processes (Rowe & Wright, 1999).

Perhaps more important than a less-than-ideal modification process, is the realisation that no study identified within this review appears to have directly assessed the superiority of such adaptations for predictive validity against the original measure. Instead, it appears that improved psychometric properties are simply assumed. Although validity and reliability assessments are often completed with these adapted measures as reported above, they are not, on the whole, compared to the

original measure for the same treatment in the same population. Overall, this lack of comparison appears to be a significant oversight.

Summary

Overall, although such findings provide support for the predictions of the Necessity-Concerns Framework, they suggest that the observed relationships are only of a weak-to-moderate strength. However, when these effects are examined alongside other correlates, they become a relatively strong predictor of adherence behaviour, and even a mediator for other correlates. Importantly, it appears that the strength of correlations between medication belief subscales and adherence behaviour does vary between conditions and treatments, suggesting that such beliefs may be of more importance to some conditions and treatments than others. Also, while the rationale for adapting the BMQ-S seems logical, the process of adapting the BMQ-S to treatments of interest across health conditions is often not well described or systematic within existing adherence literature, with some studies seemingly relying on the research team's knowledge alone, and/or simply describing the process as a 'discussion', if it is described at all. Crucially, the superiority of such adaptations compared to the original measure has not been directly assessed in most studies, just assumed. Ultimately, these oversights may be limiting assessment of the Necessity-Concerns Framework if these adapted questionnaires assess beliefs which are, in fact, less strongly related to adherence than those elicited in the original questionnaire. These assumptions could present a major unexplored methodological issue in this research area.

The existing research examining relations between medication beliefs and adherence in CF will now be considered in detail, in order to explore how such beliefs relate to adherence in this illness across different treatments. Alongside this, it will also be highlighted if, and how, the authors adapted the BMQ-S for this illness group and the treatments of interest, and the validation process they completed.

The necessity concerns framework and adherence in Cystic fibrosis

Bucks et al. (2009) examined the relationship between treatment beliefs, illness perceptions and emotional representations to self-reported adherence across three treatments – antibiotic medications, enzyme supplements and chest physiotherapy – in adolescents with CF (N=38, aged 11-17 years). The authors created modified versions of the BMQ-S for each treatment, and similarly modified the IPQ-R. These revisions sought to improve the pertinency of questions to CF, and/or specific CF treatments. They named the revised BMQ questionnaires the Belief about Treatment Questionnaires (BTQ). Alterations included the rewording, addition and replacement of certain questionnaire items. In the enzyme and antibiotics concern subscales, one item was added: *'My*

enzymes/antibiotics give me unpleasant side-effects', and for chest physiotherapy, two items: *'I sometimes worry about the long-term effects of my treatment'* and *'I sometimes worry about becoming too dependent on my treatment'*, were substituted for: *'My CPT is a hassle'* and *'My CPT is difficult because I need help from others to do it properly'*. The internal reliability of these measures was assessed, but was found to be poor for the concern subscales of the antibiotic and physiotherapy questionnaires (Cronbach's alpha = 0.55), so the authors chose not to examine the relationships between these subscales and adherence behaviour.

Findings showed that stronger necessity beliefs related to higher self-reported adherence for antibiotic medications (r = 0.38) and chest physiotherapy (r = 0.71), while increasing age related to poorer adherence to both treatments. Interestingly, a hierarchical multiple linear regression analysis revealed that, for chest physiotherapy, necessity beliefs appeared to mediate the relationship between age and adherence. Together, these findings support the utility of the necessity-concerns framework in understanding treatment adherence in adolescents with CF. They also highlight how relationships between age and adherence may be underpinned by differences in treatment-related beliefs between younger and older adolescents. However, it is important to note that this framework did not relate to adherence behaviour for enzyme supplements, supporting the notion that such beliefs may have higher pertinence to certain treatments over others, even within the same illness.

This study, however, had several limitations, including reliance on self-report (which is known to be unreliable), and inadequate concern subscales for antibiotic and physiotherapy treatments, which prevented consideration of relationships between these scales and adherence. The authors therefore highlight the importance of using objective measurement methods in future studies and of developing these subscales to ensure that they are relevant and useful to specific treatments. It is also noteworthy that the process through which these questionnaires were developed was simply referred to as "a discussion with the paediatric team", that the study did not consider parents' beliefs, and did not differentiate between antibiotic treatments administered through very different methods (i.e. oral vs. nebulised).

Goodfellow et al. (2015) examined the influence of treatment beliefs and parental depression on adherence to chest physiotherapy, enzyme supplements and vitamins in adolescents (N=100, aged 0-18 years). This study partially responded to the limitations highlighted above by: i) examining adherence through several methods (self-report, medication records, pharmacy prescription refill data and GP prescription issue data); ii) exploring both parents' and patients' beliefs; iii) further refining the medication belief questionnaires. These modifications were made after consulting the author of the BMQ-Specific, and included three additions to the chest physiotherapy concerns scale: *'I/My child finds chest physiotherapy tiring'*, *'I/My child finds it embarrassing to carry out chest physiotherapy'*, *'Chest physiotherapy makes me/my child feel worse'*, and one concern item to all

treatments: *'This treatment gives me/my child unpleasant side effects'*. Internal reliability was adequate across subscales, questionnaires and respondents.

Findings showed that weaker parental necessity beliefs, and increasing child age, were both significant predictors of non-adherence to enzyme supplements (OR: 0.79, 1.05) and chest physiotherapy (OR: 0.82, 1.05), while no significant predictors were found for vitamins. They also showed that the strength of beliefs held about treatments varied across treatments and respondents. While concern beliefs were low across all treatments, necessity beliefs were only high for enzymes and physiotherapy, and parents were found to have significantly stronger necessity beliefs than their children across all three treatments, and significantly stronger concerns about chest physiotherapy.

Together, these findings suggest that parents' beliefs can predict their child's adherence behaviour, and that parents' necessity beliefs are more pertinent to adherence behaviour for enzyme supplements and chest physiotherapy, than their concerns. For vitamin supplements neither of these beliefs offered a means to predict adherence behaviour. Therefore, these findings also support the notion that the Necessity-Concerns Framework does not apply equally across treatments, and that the belief subscales are not equally important within treatments. They also highlight how the strength of beliefs appear to differ by treatment and respondent (i.e. patient or parent). However, the findings of this study are, like most research in this field, limited by a lack of genuinely objective measurement.

An unpublished feasibility study by Maclean, Duff, Ball, Bowmer and Masterson (2015) responded to this problem of subjective adherence measurement when examining the influence of medication beliefs on adherence to nebulised medications (antibiotic and mucolytic) in children and adolescents with CF (N=18, aged 9-16). They used I-nebuliser technology to measure adherence, which, as previously described, is considered a 'gold standard' measure in terms of objectivity, and collected data retrospectively over an 8-week period. Medication beliefs were examined through the antibiotic-specific version of the Beliefs about Treatment Questionnaire, as developed by Bucks et al. (2009). Patients' or parents' beliefs were elicited with this measure, with parents completing a parent version of the measure for patients aged under 12 years (N=6).

Findings showed that concern beliefs alone significantly related to adherence, with participants who reported higher concerns having poorer adherence than those who expressed fewer concerns. Importantly, the results showed an interesting trend; participants with concern scores of ≥ 3 had adherence rates of <70%, while adherence rates of those with concerns score of <3 were >80%. These findings therefore suggest that concern beliefs could be the most important factor in predicting adherence behaviour to nebulised medications. The authors also highlight the clinical utility of the findings as a potential cut-off point to enable clinicians to quickly identify and respond to patients at risk of poor adherence from high concern beliefs, thereby allowing the BMQ-S to function as a screening measure.

However, several limitations exist in this study. The internal consistency of the BTQ measure was not assessed, which is problematic since the concern subscale of this measure was found to have inadequate internal consistency in Bucks et al.'s (2009) study, and it was not designed for mucolytic medications. Only 18 participants completed this study (12 patients and 6 parents), limiting the generalisability of its findings. Also, as only one BTQ was completed per patient-parent pair, differences between respondents could not be examined, and in its analysis, this study combined these reports, which is problematic as authors studies such as Goodfellow et al. (2015) suggest that beliefs are likely to differ between respondents. This study also combined all nebulised treatments into one category, rather than considering the different nebulised medications separately for the purposes of beliefs and adherence. Such a lack of differentiation is a significant limitation, when one considers the body of research showing that beliefs are likely to differ by treatment, as previously highlighted in this review. Finally, this study like much of the research in this field only examined adherence data retrospectively, so the predictive utility of the proposed cut-off for future adherence behaviour is unknown.

Summary

The chronic health research findings suggest that the Necessity-Concerns Framework is a useful model to understand adherence behaviour, and the BMQ-Specific an effective tool to elicit beliefs pertinent to this model, in patients and their parents.

Importantly, it appears that the importance of the two dimensions - necessity and concerns, both when assessed separately and in terms of the relative difference between them, can differ between therapies, even within the same medical condition. Interestingly, it also appears that, in the paediatric population, parents' medication beliefs are also a predictor of their children's adherence behaviour. However, these relationships remain acutely under-researched within CF, and especially within nebulised treatments, despite I-nebulisers' unique potential to allow purely objective measurement, thereby overcoming the major methodological limitation in existing adherence research.

As discussed, the existing research which does focus on nebulised medication adherence suffers from several methodological flaws. Bucks et al. (2009) combined data for orally-delivered and nebulised antibiotics, and used self-report adherence measures, and their revision of the BMQ for antibiotic medications was found to have inadequate internal consistency on the concerns subscale. While an unpublished feasibility study by Maclean et al. (2015) did examine the necessity-concerns framework in relation to nebulised treatments specifically, and objectively recorded adherence data, it used the measure that Bucks et al. (2009) had reported as having poor reliability and combined

analysis across nebulised medications and respondents. This study also suffered from general limitations, including a limited sample (N=18), reducing its validity and generalisability.

Overall summary and rationale for the project

Healthcare provision can only create optimal outcomes if treatments are completed. However, sub-optimal adherence is common across chronic conditions, particularly in adolescents and preventative therapies. Poor adherence has subsequently been positioned as the largest barrier to treatment success, and as a public health concern. To address this problem, research has sought to identify factors which influence this behaviour, and to create models of these factors in order to understand and improve adherence.

Increasingly, patients' beliefs about their illness and medications have been identified as factors that relate to adherence behaviour across chronic conditions, an observation which has led to the development of various models, including the Necessity-Concerns Framework of treatment beliefs. This framework has proved to be a particularly promising avenue in understanding adherence, with its predictions offering greater explanatory power than similar models.

Within CF, whilst most current research identifies practical barriers such as time constraints and forgetfulness, psychological barriers such as illness and treatment beliefs have increasingly been included in such assessment. Indeed, such research has led several authors to suggest that beliefs may be the underlying cause of more commonly referenced practical barriers. However, research examining such beliefs, and in particular the Necessity-Concerns Framework, is almost absent in the CF population, including within the paediatric population, despite adherence within CF rapidly declining during adolescence. Adherence to nebulised medications is often reported to be particularly problematic in this group, and the underlying factors appear acutely under-researched. This paucity of research is concerning when considering the primary role of such treatments in preventing lung infections, one of the key causes of morbidity and mortality in CF. It is also surprising when one takes into account the unique position that I-nebulisers, with their objective adherence recording, afford in overcoming the largest methodological barrier in adherence research: inaccurate self-report data. No other chronic condition or treatment has a purely objective measure available through which to record adherence behaviour.

Three studies have examined the influence of medication-related beliefs on adherence to treatments in the paediatric CF population using the Necessity-Concerns Framework (Bucks et al., 2009; Maclean et al., 2015, Goodfellow et al., 2015), and all supported the potential clinical utility of this framework. However, only the former two studies considered this model in relation to nebulised medications, and each suffered from several limitations. Most notably, the study by Bucks et al.

(2009) relied on self-report data, and conflated orally-delivered and nebulised antibiotics, rather than considering each in isolation. Maclean et al. (2015), while considering only nebulised medications, similarly conflated two separate treatments by examining nebulised antibiotics and mucolytics together. Also, the belief measure used in both studies was found by Bucks et al. (2009) to have inadequate reliability on the concern scale for antibiotic medications. As such, the BMQ-Specific has never been specifically tailored to nebulised medications in CF. More generally, within the wider literature, it is interesting to note that the rationale and processes for adapting the BMQ-Specific to specific treatments is often poorly described. For instance, Bucks et al. (2009) simply referred to this process as a "discussion with the research team", a level of detail which appears commonplace. The lack of a comprehensive process to adapt such measures is concerning, considering the relatively common nature of such practice, and since the psychometric properties of the developed measure depend on appropriate adaptation. Indeed, inadequate adaptation of this measure would in turn, adversely impact assessment of the Necessity Concern Framework.

Overall, there is a clear rationale for the necessity and value of research which can address the methodological limitations highlighted above, namely the lack of objective measurement and inadequate refinement of the existing BMQ-Specific measure to assess necessity and concern beliefs for both nebulised medication treatments (i.e. antibiotics and mucolytics, separately) in CF.

Introducing the studies

The proposed studies will replicate and extend the research reviewed above. Study one will, similarly to previous research, modify the BMQ-Specific to create versions specifically adapted to the treatment(s) of interest. Unlike much of this research, however, this study will undertake this refinement through an explicit and systematic process, and will create separate revised BMQ-Specific questionnaires for both categories of nebulised treatments in CF (mucolytics and antibiotics); thereby enabling this study to determine whether necessity and concern beliefs differ between these medication categories and if they relate to adherence differently. This decision was made and considered important for three reasons. First, the BMQ-Specific was created to be applied to individual treatments, not categories of treatment delivery. Secondly, the properties and purposes of these nebulised medication categories typically differ, including by their nature of action (prophylactic vs. symptomatic) and burden level (life-long vs. time-limited), which is very likely to lead to the development of different treatment beliefs. Thirdly, as highlighted above research has shown that the relations between treatments and adherence behaviour can change, even within the same illness, so amalgamation of these effects would obscure such differences.

A two-part process will be used to increase the rigour of these adaptations. First, the research and supervisory team will refine the original questionnaire to each medication category, using the

current literature and their clinical experience, to create initial draft versions. Second, a Delphi survey will be used to gain opinions from an expert group on the value and clarity of items in these questionnaires, as well as any recommendations for new items. These questionnaires will be named the CF-BMQ-Specifics and will consist of an antibiotic and mucolytic version. A second version of each questionnaire will also be created for completion by parents, to allow their medication beliefs to be examined, and the relationships between these and their child's adherence behaviour.

Study two will examine relations between nebulised medication beliefs and adherence behaviour to assess the predictive validity of the Necessity-Concerns Framework for these treatments, similarly to previous research reviewed above. Patients and their parents will be asked to complete a BMQ-S and CF-BMQ-S for each category of nebulised medication that the patient takes through an I-nebuliser device. This will allow examination of the relationship between necessity and concern beliefs, as assessed by the patient and parent versions of the BMQ-S and CF-BMQ-S, to objectively recorded adherence behaviour. This study will compare findings between the revised and original BMQ measures, between the categories of nebulised medications, and between patient and parent beliefs, comparisons which have not previously been explored for nebulised medications. Importantly, no other study using the BMQ-Specific, even outside of nebulised medications and CF, is known to have examined compared predictive validity between the original and revised measures.

Acquisition of 'gold-standard' objective adherence data in this study through the I-nebuliser will build upon previous studies, by responding to the main methodological difficulty faced by adherence studies generally. The use of prospective adherence data will allow the predictive validity of the developed questionnaires for future behaviour to be determined, unlike previous research which has relied on retrospective data. Like previous CF research, this study will explore the relationship between illness perceptions and adherence data, but through the B-IPQ rather than IPQ-R, and this relationship will be examined separately for patients and parents, which has not been completed before in CF. In turn, this will allow consideration of the strength of these relationships to adherence behaviour, compared with the BMQ-S. Finally, participants' sociodemographic and clinical properties will be recorded to allow adherence and belief data to be considered in relation to these factors.

This project therefore contains several novel elements which will extend the existing body of research which evaluates the utility of the Necessity-Concerns Framework in this patient group, and has the potential to inform both clinical and future research practice.

Research aims and hypotheses

Primary research aims

Study one:

1. To use a systematic process to create versions of the BMQ-Specific tailored to nebulised mucolytic and antibiotic nebulised medications in CF.

Study two:

1. To assess the utility of the Necessity Concerns Framework, assessed by the BMQ-S and CF-BMQ-S, to predict adherence behaviour to both categories of nebulised medications in adolescents with CF.

Secondary research aims

1. To examine whether adherence behaviour is influenced by medication type, sociodemographic and health factors.
2. To assess if medication beliefs differ between the two categories of nebulised medications (antibiotics or mucolytics) or by respondent (patient or parent).
3. To explore if illness perceptions differ by respondent, and if they relate to nebulised medication adherence in adolescents with CF.

Study hypotheses

Based on the primary aims of study two this project has three specific hypotheses in accordance with the predictions of the necessity-concerns framework.

1. Stronger necessity beliefs held by patients and parents will result in increased treatment adherence.
2. Stronger concern beliefs held by patients and parents will result in reduced treatment adherence.
3. Patients and parents with higher necessity and lower concern beliefs will have higher treatment adherence, than those with low necessity beliefs and high concern beliefs.

The first study within this two-part project will now be presented, with the method, results and discussion sections presented in turn. Following this, the same sections will also be described for the second study. Finally, a combined discussion will be presented which considers both studies together, and examines their clinical and research implications.

Chapter 2: Study One Method

Adapting the BMQ-Specific to nebulised medication categories

The CF-BMQ-Specific questionnaires were developed in two stages. The first stage involved the research team tailoring the existing BMQ-Specific separately to nebulised antibiotic and mucolytic medications, creating two adapted questionnaires: the CF-BMQ for Antibiotics (CF-BMQ-A) and the CF-BMQ for Mucolytics (CF-BMQ-M). The second stage evaluated and further refined these questionnaires using a two-stage Delphi survey.

Design

Initial development of the CF-BMQ-Specifics

To support initial adaptation of the BMQ-Specific for nebulised antibiotic and mucolytic medications, two sources of information were used. First, the qualified clinicians in the supervisory team used their clinical experience to evaluate the content and wording of the original BMQ-Specific for use with nebulised mucolytic and antibiotic medications in CF. Two are clinical psychologists with over 20 years of experience working in CF, and the other clinician is a physiotherapist with over 10 years of experience. These discussions led to items being modified, removed, or added based on complete agreement. Second, literature relating to adapting the BMQ-Specific to other treatments was examined, alongside research identifying necessity and concern beliefs in CF treatments. This process resulted in a list of potential items for inclusion in the two new CF-BMQ-Specifics. The supervisory team then rated these items for inclusion in the questionnaires on a 3-point Likert scale, ranging from ‘Very useful’ to ‘Not useful’. Only items that were considered ‘Very useful’ by all were included in the initial item set. Lastly, the team developed two variants for parents: the CF-BMQ-Specific-Antibiotic-Parent and CF-BMQ-Specific-Mucolytic-Parent. The subject of each of each item in the newly-developed questionnaires was simply modified for completion with parents (i.e. 'your child' instead of 'you').

Refinement and evaluation of the CF-BMQ-Specifics

The resulting CF-BMQ-Specific measures were then subject to further refinement from a larger number of clinicians with expertise in this field – physiotherapists in CF teams. The aim was to use a Delphi survey to evaluate and further refine the CF-BMQ-A and CF-BMQ-M, and to obtain consensus on the final item set for each questionnaire. The Delphi method is a structured process for collecting and organising judgements from a group of experts (Norcross, Pfund & Prochaska, 2013).

Although some authors within the research literature refer to Delphi as a methodology (Jairath and Weinstein, 1994; McKenna, 1994, Hasson et al., 2000), a variety of terms are used to describe it, the most notable of which include: 'process', 'approach', 'survey' and 'technique' (Suckley, 2012). These terms will also be used interchangeably here.

Delphi technique overview and application

The Delphi technique was developed by an intelligence think-tank named the RAND corporation in the 1950s, with the aim of developing a method that would provide an objective and reliable means of gaining consensus from expert groups for complex issues (McMillan, King, Tully, 2016). It was based on the premise that, and findings showing, that group decisions are more reliable than decisions made individually (e.g. Kaplan, Skogstad & Girshick, 1950). To accomplish this, this method structures group communication in a manner which aims to maximise helpful aspects of discussion and interaction (e.g. shared and developed knowledge and ideas), while minimising unhelpful group attributes (e.g. personal conflicts, unequal participation) (Rowe & Wright, 1999). This technique is often applied to support problem-solving and idea-generation, and its strength lies in its ability to facilitate decision-making through consensus where research evidence is inconclusive, or even absent (Mirtoff & Turoff, 2002).

The success of this method is clearly shown through its diverse applications across industries (McMillan, King, Tully, 2016). While early Delphi studies were limited to use in short- and long-range forecasting of future events, they are currently used within a variety of applications. Within healthcare research, this approach has been used to: identify research priorities (e.g. Ramelet & Gill, 2012), develop health quality indicators (e.g. Uphoff et al., 2012), clinical guidelines (e.g. Conway et al., 2013), education assessment tools (e.g. Sowter et al., 2011), as well as item generation for questionnaires (e.g. Eigenmann, Skinner & Colagiuri, 2011; Ski et al., 2019). The Delphi method therefore seemed like a natural fit for this study's research aim, i.e. the development and validation of the CF-BMQ-Specifics, especially considering the scarcity of research identifying necessity and concern beliefs in nebulised medications within CF.

Key features of the Delphi method

The Delphi method comprises four main features: i) anonymity, ii) iteration, iii) controlled feedback, and iv) statistical aggregation of group response. These features will now be described by considering the classic procedure of a Delphi survey. Delphi surveys are completed over several stages, which are referred to as rounds. Traditionally, the first round of a Delphi survey presents an open-ended questionnaire, which aims to identify pertinent issues for further exploration. After

completion of this round, panel members' responses are collated and analysed in order to develop a structured questionnaire (Rowe & Wright, 1999). In subsequent rounds, this questionnaire is presented, and panel members are asked to evaluate it. Typically, such evaluation is completed quantitively, with participants ranking each item individually (Jones & Hunter, 2000). Between each of these rounds, participants' responses are analysed, and each individual is normally presented with a statistical summary of the data. This summary allows panel members to consider their own responses and views in relation to group trends, and in the next round they have the option of retaining or altering their ratings in light of this. This process of iteration i.e. presenting questionnaires for evaluation, followed by anonymous group feedback, can allow convergence of opinion, or continued disagreement, and continues until predetermined stop-criteria are met, such as a set number of rounds, or level of stability in panel member responses (i.e. more than 70% of panel members consider an item useful (Rowe & Wright, 1999). Regardless of the criteria set, it is considered important to gain the balance between result accuracy and participant fatigue (Rowe & Wright, 1999).

Methodological considerations

In practice, over the years, the Delphi method has been implemented in a multitude of ways depending on several factors, including the research question and resources. Indeed, Hanson and Keeney (2011) lists over 10 variations of this technique, including classical, modified, decision, policy, real time, e-Delphi, technological, online, argument and disaggregative. Currently, no standardised definition of a Delphi survey exists, and no standardised guidelines exist for how it is conducted, including the meaning and measurement of consensus, and the criteria for defining an expert (Hasson & Keeney, 2011). Within the literature, the methodological rigour of different approaches is strongly debated, with attempts to establish guidelines remaining inconclusive, and strongly criticised (e.g. Rowe, Wright, & Bolger, 1991, Hasson & Keeney, 2011). Ultimately, it seems that while this technique can be applied flexibly, and guided by the research question and the situation, it remains important to consider methodological factors and to explicitly describe how this process is implemented, so that the study's rigour can be considered. A pragmatic stance was taken in applying the Delphi technique within this study.

Application of the Delphi method in this study

The Delphi method employed in this study differed from the classic design in several ways. Firstly, the initial round presented pre-existing, structured questionnaires for evaluation, rather than an unstructured list of items. An unstructured first round was not required in this study since it aimed to gain opinion on and refine an existing questionnaire, rather than generate a new one. This difference also partly underpinned the decision to complete the survey in just two rounds, alongside the fact that

the existing questionnaires had already been adapted by the supervisory team, as highlighted above. It was considered that panel members' evaluations would not significantly differ from the research team, and that an increased number of rounds would unnecessarily increase participant burden. This decision is in line with recommendations which suggest that a two-round survey is sufficient where a clear base exists and the survey simply aims to examine the temperature of opinion on a topic (Petry, Maes & Vlaskamp, 2007). Practical advantages of this two-round format include a reduced timescale, and lowered attrition rates (Cantrill, Sibbald, & Buetow, 1996). This is important since attrition rates in the Delphi method tend to be high, due to the relatively long-term commitment it can require, and potential distractions between rounds (Donohue & Needham, 2009). Such considerations were especially important in this study due to the time restrictions imposed on the project and the low target sample size.

Individualised or general statistical summaries were also not provided between the rounds in this survey; instead, feedback was provided by updating the second-round questionnaires in response to first-round feedback (i.e. majority opinion and clinician comments). This decision, too, was made for practical reasons; as already discussed, it was expected that participants' responses would be generally favourable, with little disparity between respondents. It was also considered that requiring busy NHS clinicians to examine both statistical and qualitative summaries for each item in the two questionnaires across both rounds would likely reduce participation and increase attrition rates. Therefore, in this instance, the advantage of asking practicing NHS clinicians to consider summaries between rounds was considered less clear. Finally, a mixed method approach was used to allow participants to also comment on individual items and suggest new items for consideration. It was considered that a purely quantitative approach would have reduced participants' role in shaping the questionnaires, as they would have been unable to provide comments which explained their ratings for individual items, and suggestions for improvements or additions. Equally, a purely qualitative approach using analyses, such as interpretative phenomenological analysis or grounded theory, would have been inappropriate, as such methods would seek to understand the personal meanings of items to participants, which was not the aim of this study.

Regarding methods of delivery, the Delphi method has traditionally been paper-based. In recent years, however, this method has increasingly been delivered electronically (Young & Jamieson, 2001). Importantly, although research has shown that no difference exists in the quality of data collected between paper and electronic means (e.g. Geist, 2010), research is less clear regarding response rates. While some studies find reduced response rates for electronically-presented Delphi methods compared to mail or telephone (Fan & Yan, 2010), others report high and sustained response rates for electronic methods (Gill, Leslie, Grech & Latour, 2014). Considering such findings, alongside an appreciation of enhancing convenience for busy NHS clinicians, the decision was made to deliver this survey electronically through a web-based software tool named 'Online Surveys'. This

software was selected as it is user-friendly, is supported by varied web browsers, and employs robust data-protection measures.

Alternative approaches

Other consensus methods were considered, the most notable of which is the nominal group technique (NGT; Delbecq & Van de Ven, 1971). It takes the form of a structured face-to-face meeting between experts and is typically completed in several stages. Initially, participants are requested to submit ideas independently and anonymously on paper. These ideas are then collated, and the group considers each in turn and ranks them. This process is supported by a facilitator who seeks to ensure equal participation and constructive consideration of all ideas. Like the Delphi method, this approach aims to overcome problematic group processes. The controlled feedback process in both approaches theoretically reduces unequal participation by ensuring that all panel member judgements and opinions are heard, regardless of personality and professional standing differences (Hsu & Sandford, 2007). However, the effectiveness of this process in practice is ultimately dependent on the skills of the facilitator.

Like the Delphi method, the NGT is also used to develop consensus where an evidence-base is absent or inconclusive (Cantroll, Sibbald & Bluetow, 1996). Despite these similarities, it was considered that the Delphi method's format offered several advantages for this study. Practically, the Delphi survey does not impose geographical constraints on participant selection, as it does not require participants to attend a meeting in person at a set date and time (Fink, Kosecoff, Chassin, & Brook, 1984). Such pragmatic considerations were important for this study, as CF is a very specialist area with limited physiotherapists locally, which meant nationwide recruitment was required. It was also considered that, even if an adequate number of clinicians could be recruited locally, or the method could be delivered online, they would likely find it problematic to meet together at a specified date and time due to clinical commitments. Further, although submission of ideas in the NGT can be anonymous, subsequent discussion is not. The increased anonymity in the Delphi method is considered to increase free communication and open critique by reducing social pressures to agree with others, especially more senior individuals (Skulmoski, Hartman & Krahn, 2007). Equally, it reduces fear of critique, allowing lower-'status' individuals to introduce ideas without fear of outright rejection (Turoff & Hiltz, 1996). Again, it was considered that these qualities of the Delphi method would better lend themselves to this study, as it aimed to recruit clinicians with a range of clinical experience, and required systematic consideration and critique to be produced for each item. Unlike the NGT, the Delphi method also allows a mixed statistical methodology, which was considered a better fit for the research aims.

Participants

Recruitment

Purposeful sampling was used to recruit 'expert participants' for the study. It is important in the Delphi method to ensure that the individuals recruited have the required knowledge and skills to consider the topic under investigation, so that their level of expertise are unlikely to be challenged (Hasson & Keeney, 2011). The decision was made to define experts for this study as both clinicians with experience of supporting adherence to nebulised medications in CF, and adolescents and parents with experience of using or supporting use of these medications. The decision was made to recruit experts by profession and experience to increase the heterogeneity of the sample and thereby validity, in line with research recommendations (e.g. Hardy et al., 2004). It was planned that five expert clinicians and one expert patient and parent would be recruited for the study, which would meet the minimum recommended Delphi method recruitment figure of seven (Linstone, 1978).

Clinicians were recruited for the survey by an invitation email, which was circulated to a nationwide special-interest group for physiotherapists working in CF, by a member of the supervisory team who is an administrator for this group (Appendix A). The email provided a summary of this study and contained a participant information sheet (Appendix B) and an eligibility form (Appendix C). Clinicians who wished to participate in the study were asked to express interest by emailing the researcher and returning their completed eligibility form. Clinicians had two weeks in which to respond to the invitation email before the study began, a timeframe selected due to the time constraints placed on this project. However, only four clinicians had replied within the first two weeks, which was considered insufficient, so a reminder email was sent, and the recruitment deadline extended by one month.

Patients and parents were approached regarding the study during their outpatient appointments in their local paediatric CF clinic. After their eligibility had been assessed by their physiotherapist, they were provided with an information sheet during their appointment and were asked to email the researcher to express interest (Appendix D.1 to D.2). A voucher incentive of the value of ten pounds was offered to patients and parents to take part. Although four patients and four parents were approached regarding the study, no patient or parent contacted the researcher to take part. Unfortunately, due to time constraints, further recruitment was impossible.

Inclusion criteria

In regard to defining experts by profession, it was decided that physiotherapists would be best-placed to support development of the questionnaires, as their job roles involve considering patients' adherence to nebulisers. Although other healthcare professions were considered, it was decided that their expertise and knowledge would be weaker due to the very specific nature of the

area of investigation (i.e. beliefs regarding specific medication categories within nebulised treatments). Equally, it was considered that input from academics, due to the lack of research in this field, would be less useful, and could reduce the real-world applicability of the measure. The eligibility criteria requirements for experts by profession was set to: clinicians who i) hold a professional qualification in the discipline of physiotherapy, ii) have worked clinically within the area of CF for at least one year. This timespan was chosen to ensure that clinicians were experienced enough in their field to have developed an adequate level of knowledge and experience.

For patients to be eligible for this study, they needed to: i) be aged 16-17 years, ii) attend outpatient clinics at Leeds Regional CF centre, iii) have used an I-neb device for both mucolytics and antibiotics within the last two years, for at least two months. These criteria were chosen to fit with the questionnaires' target audience, and to ensure that the individuals recruited had the experience, knowledge and maturity needed to understand and complete the survey. For the parent, the criteria were that they must i) have a child who satisfies the above criteria, ii) have capacity to consent to the study.

Ethical approval and considerations

Ethical approval was gained from the Proportionate Review Sub-committee of the NRES Committee York and Humber - Leeds West, in December 2018 (Appendix E). Consent was gained implicitly by participants choosing to complete the two survey rounds after reading the information sheet. Data was stored securely and confidentially in accordance with the Data Protection Act (1998).

Measures

The Beliefs about Medicines Questionnaire (BMQ)

The original BMQ has two sections: BMQ-General and BMQ-Specific (Horne et al., 1999). The BMQ-General examines individuals' perceptions of medications in general through two subscales: The General-Harm subscale, which assesses beliefs about how harmful medicines are, and the General-Overuse subscale which examines the concept of over-prescription. On the other hand, the BMQ-Specific section assesses perceptions of specific medications that have been prescribed for an individuals' personal use. It is composed of two sub-scales: the Specific-Necessity scale examines patients' perceptions of their personal need to adhere to their prescribed medication to control symptoms and maintain health, while the Specific-Concerns scale assesses patients' beliefs concerning the likelihood of adverse reactions and consequences from taking their prescribed medication. Although these measures can be used in combination or separately, the BMQ-Specific questionnaire is often used alone to test the predictions of the Necessity-Concerns Framework; since

findings have shown that specific, rather than general, medication beliefs relate more closely to adherence behaviour (Horne et al., 1999). As such, only the BMQ-Specific was employed in this study.

The BMQ-Specific consists of ten items, five of which examine patients' beliefs regarding the necessity of their medication to maintain their health (items: 1, 3, 5, 7, 10), and five, concerns about the potential negative consequences of taking their prescribed medication to their health (items: 2, 4, 6, 8, 9) (Horne et al., 1999). These statements lie on a 5-point Likert Scale, from 1: 'strongly disagree' to 5: 'strongly agree'. Responses are summed to produce separate sub-scale scores for the two dimensions (i.e. necessity and concerns), with total scores ranging from 5 to 25. Higher scores in either domain represent stronger necessity or concern beliefs regarding the medication in question. Scores that fall above the midpoint (i.e. 16 or above) are categorised as strong beliefs, as stated in the original paper by Horne et al. (1999). The necessity-concern differential represents the difference in scores (i.e. benefit-to-risk ratio) between the necessity and concern subscales. Higher necessity scores, relative to concern, produce a positive total, while a relatively higher concern to necessity score, a negative total. These total scores can range from -20 to +20. The BMQ is originally worded for completion by patients, but the statements have been edited for completion by parents (i.e. 'my medicine disrupts my life' becomes 'my *child's* medicine disrupts *their* life') in a number of studies (e.g. Klok et al., 2012; Goodfellow et al., 2015; Sonney et al., 2017). The BMQ-Specific has been validated in adults (Horne et al., 1999), and in children as young as 7 years of age and their parents (Yilmaz, et al., 2012). The literacy level of the original BMQ-Specific is reported to be at the reading ability of 11- to 12-year-olds (Sonney et al., 2017), which is appropriate for this study's sample.

Delphi Survey: Round One Questionnaires

Clinician's demographic questionnaire

A brief online demographics questionnaire was developed for clinicians for the Delphi survey and delivered in the first round. It collected the following information: clinicians' gender, age, full name, email address and years of experience working in CF. Full names and email addresses were collected to allow data tracking and correspondence, while years working in CF was used to determine 'expert' status.

CF-BMQ Specifics

The initial CF-BMQ-Specific-Antibiotic and CF-BMQ-Specific-Mucolytic measures were presented in round one, which together consist of 21 items (Appendix F.1 to F.2). The CF-BMQ-A consisted of eleven items (four necessity beliefs, and seven concern), while the CF-BMQ-M ten items

(four necessity, six concern). The decision was made to not include the parent versions of either CF-BMQ-Specifics in the Delphi survey, as the items are identical except for the change in subject ('me' to 'my child'). It was therefore considered that presenting all four questionnaires would increase participant burden, for little benefit. Instead, participants were informed of the existence of these questionnaires and asked to consider whether they could identify any necessity or concern beliefs which might apply to parents but not to their children.

In the process of developing these questionnaires from the original BMQ-Specific, several changes were made by the research team. Modifications were made to item wording and/or items were removed or added, to increase the clarity and/or relevance of items, and thereby the validity of the questionnaires. The following items were re-worded to increase clarity: 'My health, at present, depends on my medicines' became 'My health at present depends on *me taking my* nebulised medicines'; 'My medicines are a mystery to me' became 'I don't understand why I need to take my nebulised medication', and 'My medicines protect me from becoming worse' became 'My nebulised medication stops me from becoming worse'. The following item: 'My medicines disrupt my life' was made more specific: '*Taking my* nebulised medication disrup*ts* my life'. It was considered by the clinicians within the research team that it is the act of taking nebulised medications that causes patients most disruption, and that the generic wording of the original item weakened its relevance. The following necessity item was removed from both questionnaires: 'My life would be impossible without my nebulised medication'. This item was considered too strong for nebulised treatment, especially since mucolytics operate preventively, and these medications work within a treatment regimen to maintain health, rather than to cure symptoms. The following concern item was added to both questionnaires: 'My nebulised medication causes unpleasant short-term side effects', as nebuliser patients are known to report such concerns. Similarly, 'Taking my nebulised medication is unpleasant' was added to the antibiotics questionnaire alone, based on patient reports that nebulised antibiotics taste unpleasant. All items, like in the original BMQ-Specific, were placed on a 5-point Likert Scale, from 1: 'strongly disagree' to 5: 'strongly agree'.

Round one aim and format

The overall aim of this round was to validate the initial CF-BMQ-Specific questionnaires by gaining further expert opinion on the importance of each item for assessing necessity or concern beliefs in antibiotic and mucolytic nebulised medication categories, and their views on the comprehensibility of each item. To this end, value and clarity ratings were requested for each item in both questionnaires. Ratings were placed on a 7-point Likert scale, from 1 'strongly disagree' to 7 'strongly agree'. A wide scale was selected to allow greater data granularity but was limited to 7 points, as research suggests that individuals find discrimination difficult beyond this (Streiner,

Norman & Cairney, 2015). After each item, a free text box was provided to allow participants to explain their rating and/or provide suggestions for rewording/rephrasing. A text box was also provided at the end of each questionnaire to allow panel members to provide suggestions for new necessity and/or concern belief items. Finally, it was considered that parents and adolescent patients may hold different necessity and concern beliefs. Therefore, the last section of the survey asked panel members to consider this and report such differences.

Piloting round one

This survey was piloted in line with good practice recommendations (e.g. Latour et al., 2009). Two academics and one member of the research team piloted the survey, and each was asked to give feedback regarding; i) their understanding of the individual items in the survey, ii) their view on the readability of instructions and functionality of the survey (i.e. ease-of-use), and iii) the time taken to complete it. All participants found the format easy to follow and the questionnaire items clear, and reported completing the survey within 15-20 minutes, which is below the recommended round time of 30 minutes (Okoli & Pawlowski, 2004). Participants recommended few changes, with just minor re-wording and grammatical errors highlighted within participant instructions, with minor suggestions made as a result.

Delphi Survey: Round Two Questionnaires

Demographic questionnaire

In this round, the demographic form only requested participants' full names. Names were gathered in both rounds to allow tracking of data, with contact details already elicited in the first round.

CF-BMQ-Specifics

Like round one, round two presented the CF-BMQ-A and CF-BMQ-M (Appendix G.1 to G.2). However, in this round, they had been modified based on the data elicited in round one. Together, they comprised 23 items: 12 items in the CF-BMQ-A, and 11 in the CF-BMQ-M. Both questionnaires consisted of 5 necessity statements, with the remainder being concern items.

Round two aim and format

The aim of the survey and format remained the same, though the section regarding parent beliefs was not included.

Procedure for both Delphi survey rounds

The Delphi survey was completed in two iterative rounds using the web-based platform 'Online Surveys'. Participants who met the study's eligibility criteria were emailed a link to access round one of the survey, and were informed of the survey's closing date.

The opening page of the round-one survey contained the participant information sheet and made participants aware that their consent would be taken implicitly through their completion of the survey. The following page requested basic demographic and career information, as previously described, after which brief instructions were provided. The CF-BMQ-A items were presented after this, and on the next page, the CF-BMQ-M items. For each item, in both questionnaires, participants were required to provide an importance and comprehensibility rating to maximise data collection, and, where they wished, comments to explain their rating and/or provide suggestions for re-wording. At the end of each questionnaire, participants were also asked to use free-text boxes to report any necessity and concern beliefs regarding the target nebulised medication category, which they considered important but which had not been addressed by the existing items. Following this, they were asked to provide their thoughts on any necessity and/or concern beliefs regarding nebulised medications that might be held by parents but not their children. Finally, the survey's last page thanked participants for taking part and reminded them that the researcher would email them a link to the second-round survey within the next four weeks. This data was then analysed to allow the two CF-BMQ-Specifics to be revised ready for further evaluation in round two.

Within a week of the first round's completion by all participants, participants were sent an email containing the link for round two, whose structure was largely identical to round one. The only change was the removal of the section requesting differences between parents and adolescents' beliefs, as it was considered that little further benefit would be gained from repeating this question. The structure of both rounds of this Delphi survey can be viewed in Figure 2.

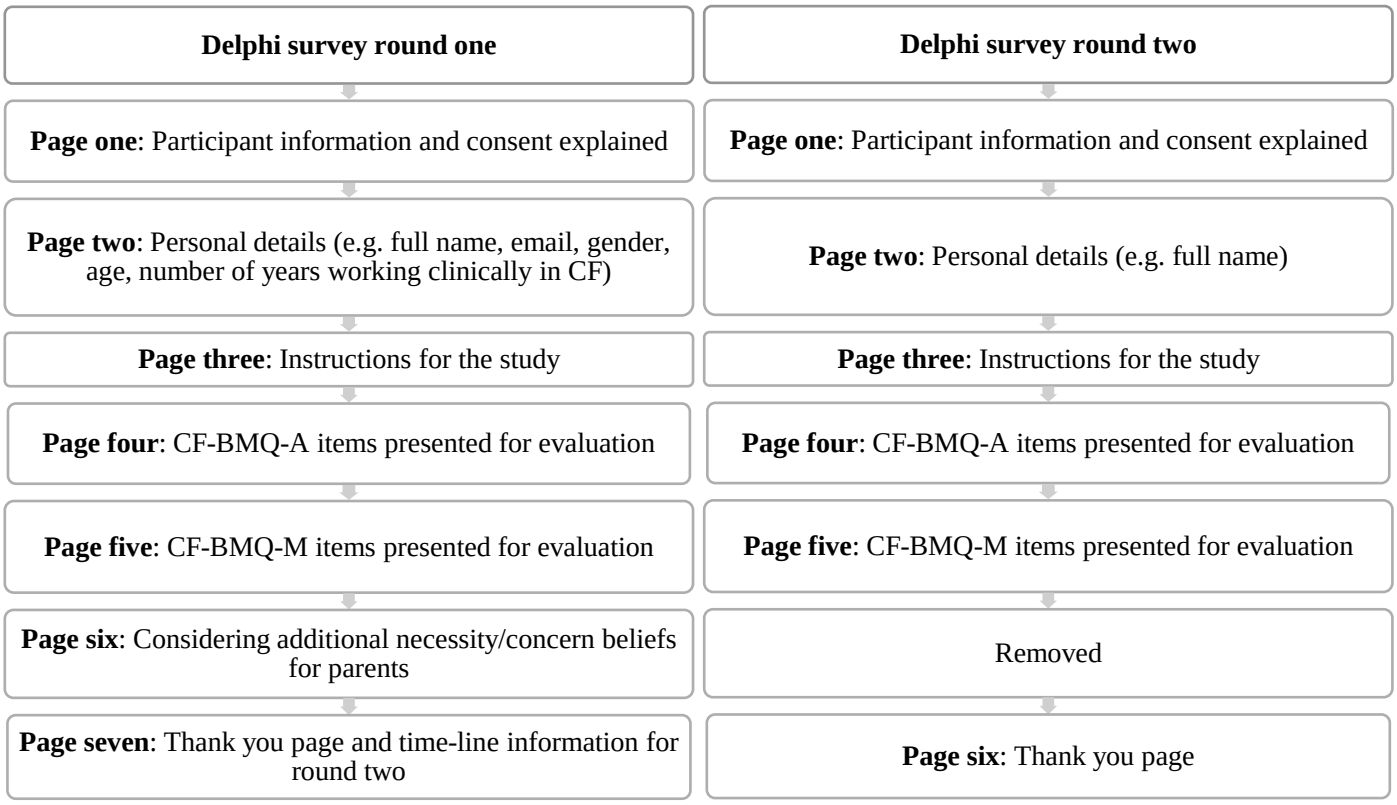

Figure 2*: Flow diagram detailing the broad structure of the Delphi survey in round one (left) and round two (right).*

Each survey round remained open for a maximum of three weeks, and email reminders were sent on a weekly basis during this time to increase response rates, in line with research recommendations (Fan & Yan, 2010). The process of creating the final CF-BMQ-Specifics for patients and parents, and the steps of the Delphi survey, can be viewed in Figure 3.

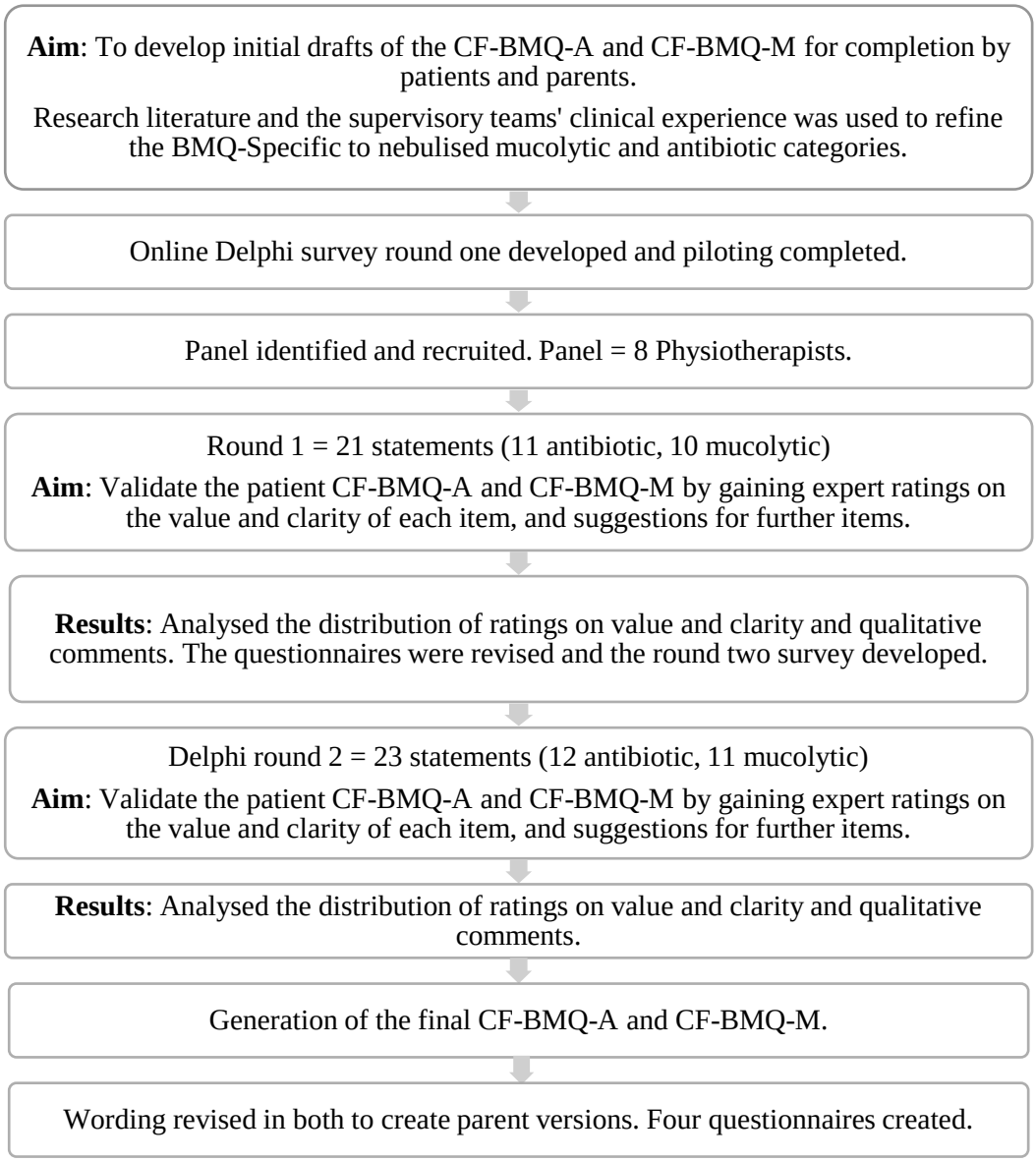

Figure 3: Steps of the process used to develop the CF-BMQ Specifics.

Data analysis

Response, attrition rates and sample characteristics (e.g. age, gender, years working in CF) were examined across survey rounds.

Measuring and assessing statistical consensus in Delphi surveys

Currently, there is no universally accepted criterion for measuring or determining consensus in Delphi studies, and great contention exists in the literature regarding the best means to assess this (Landeta, 2006). For instance, while some authors attempt to increase the validity of results by proposing set analytical processes (e.g. Holey, Feeley, Dixon, Whittaker, 2007), others argue that the best means to measure and determine consensus is dependent on the purpose and design of each study, and that authors need to present rationales for their decisions (e.g. Jorm, 2015). Some also attempt to clarify what consensus is, and how it can be measured; Holey et al., (2007) describe how consensus is considered to be the same as agreement, and how it can be determined by: an aggregate of judgements; a move to a subjective level of central tendency, or by confirming stability in responses (i.e. the consistency of answers between a study's successive rounds).

Within the literature, percentage agreement levels, measures of central tendency and dispersion statistics, applied both individually and in combination, have been most commonly used to examine consensus (Diamond et al., 2014). However, the rationale for selection of these measures is often not reported. In recent years, reliance on one measure alone has been heavily criticised (e.g. Giannarou & Zervas, 2014), leading some authors to advocate the use of several complementary measures to improve the validity of results in Delphi surveys. Holey et al., (2007) for instance, consider consensus reached when the following occurs: an increase in percentage agreements; convergence of importance rankings; increase in Kappa values; a decrease in comments as rounds progressed; a smaller range of responses, and smaller standard deviation values.

Delphi studies often use predetermined threshold values to gauge consensus, as these are considered to reduce response bias (Williams & Webb, 1994). However, these values are subjective and vary greatly; for instance, a review by Hasson, Keeney, McKenna (2000) found that accepted percentage of agreement values ranged from 51% to 80%. This has led some to argue that quantifying the degree of consensus is more important than reaching these values (Linstone & Turoff, 2011; von der Gracht, 2012).

Measuring and assessing statistical consensus in this study

Several descriptive statistics were calculated after each round for the items in both questionnaires in this study, to examine agreement levels. The accepted level of consensus was set at

a high level across these statistics, as the measures presented in this study had already been adapted by clinicians from CF services, and the sample consisted of a homogeneous panel, which led to the assumption that the panel would rate the questionnaire items favourably. It was therefore judged that a lower threshold would create difficulty in differentiating less-favoured items.

i) Median, interquartile range and range

The median, a measure of central tendency which represents the central value of a set of ordered data, was selected instead of the mean to assess the level of group agreement. The agreement data is ordinal in nature, and it was expected that the data would be negatively skewed (i.e. responses would be strongly positive across participants) rather than normally distributed across the range of responses, factors which contraindicate use of the mean. An increase in this value across rounds was considered to indicate increasing consensus, and the median consensus level was set at a threshold of 6 'agree' for both usefulness and clarity ratings.

The range, and interquartile range (IQR) were used as measures of dispersion. The variance was not used, as it is considered less robust than the IQR in Delphi surveys (von der Gracht, 2012). The IQR represents the range in which the middle 50% of ratings occur, and provides a description of the average distribution of agreement, while the range indicates the degree of divergence. A decrease in the IQR and range across rounds was deemed indicative of increasing group consensus. The IQR consensus level was set at 2, rather than 1, as a value of 1 is only considered appropriate for 4- or 5-point Likert scales (von der Gracht, 2012). Thresholds were not specified for the range, as it was used to complement the IQR.

ii) Percentage of agreement

The percentage of agreement values was used to complement the mean, it assessed the percentage of responses that met or exceeded the mean consensus cut-off value of 6. An increase in this value across rounds was considered to indicate increasing consensus, with the consensus threshold set as ≥70%.

iii) Number of comments

The total comments made for each item were summed. A decrease in constructive comments across round was considered indicative of increasing group consensus, as reported in Holey et al.'s (2007) study.

Item-specific comment analysis

Following each round, the item-specific comments were collated for each item and examined individually. A basic content analysis was completed on these data, as outlined in Graneheim and Lundman (2004).

Additional item comment analysis

Comments regarding additional necessity or concern beliefs were collated after each round, and, again, a basic content analysis was completed on this data, as outlined in Graneheim and Lundman (2004).

Decision making from item-specific feedback

Decisions on whether to retain, revise or remove items were made on a case-by-case basis after both rounds, using both the statistical rating summaries (for both usefulness and comprehensibility) and item-specific comments. Qualitative data was prioritised in the analysis and was used to guide and provide context for item amendments or removals. It was considered for every item regardless of whether consensus had been met statistically. Indeed, in instances where statistical summaries and item-specific comments were discrepant (i.e. high values, but negative feedback), comments were prioritised. Item-specific comments were, however, not implemented where contradictions existed, or where changes could reduce an item's clarity or modify its nature without strong justification. For items to meet consensus, high scores needed to be paired with comments that supported or did not strongly question their value or clarity. Throughout the process of refining and removing items from the original questionnaire, significant caution was applied, as this study sought simply to tailor the questionnaire to nebulised medications, rather than reinvent it. To support this process, all amendments and item removals were discussed with a member of the supervisory team.

Decision making from additional item feedback

The addition of new items for round two was driven by the additional item comments in round one, while additions to the final questionnaire were based on comments and statistical summaries from round two. The same procedures were applied.

Chapter 3: Study One Results

Participants

Response rates

In total, 8 physiotherapists registered interest in this Delphi survey from a potential pool of 240. All of these clinicians completed the survey's first round, while 7 completed the second, producing a 100% response rate for round one and an 87.5% response rate for round two. This meets the minimal recommended participant level of 7 (Linstone, 1978), and exceeds the minimal accepted attrition rate of 70% (Keeney et al., 2010).

Sample demographics

Demographic information for rounds one and two is summarised in Table 1. This table shows that although all participants were female, varied age ranges and geographical locations were represented. All participants reported working within CF for at least two years, with a large majority working for at least 10 years (e.g. round 1: 75%, round 2: 71.4%); confirming the strong clinical expertise of this sample.

Table 1*: Participant demographics across the two rounds.*

Demographics		Round One	Round Two
Gender		Female: 8 (100%)	Female: 7 (100%)
Age	22-32	1 (12.5%)	1 (14.3%)
	33-43	2 (25%)	1 (14.3%)
	44-54	3 (37.5%)	3 (42.9%)
	55-65	2 (25%)	2 (28.6%)
	65+	-	-
Region of work	Scotland	2 (25%)	2 (28.6%)
	Yorkshire	2 (25%)	2 (28.6%)
	East of England	1 (12.5%)	1 (14.3%)
	North West	1 (12.5%)	1 (14.3%)
	Greater London	1 (12.5%)	1 (14.3%)
	South East	1 (12.5%)	-
Years of experience	1-2	-	-
	2-5	1 (12.5%)	1 (14.3%)
	5-10	1 (12.5%)	1 (14.3%)
	10+	6 (75%)	5 (71.4%)

Note: Years of experience represents the number of years spent working clinically within Cystic Fibrosis.

Delphi survey: round one results

Aim of round one

Round one aimed to gain the opinion of an expert group on the value and clarity of items in the CF-BMQ-A and CF-BMQ-M, and their recommendations for new items.

Statistical summary item-specific

Participants rated 21 statements, 11 items in the CF-BMQ-A and 10 in the CF-BMQ-M, on two dimensions: usefulness and comprehensibility. Descriptive statistical summaries for both ratings were produced for every item, and can be viewed in Table 2. These include: the percentage of agreement score and median, which represent the level of group agreement, the IQR which reflect the degree of group consensus, and the range which highlights dispersion of opinion.

Table 2*: Round one importance and comprehensibility ratings for the CF-BMQ-A and CF-BMQ-M.*

CF-BMQ-A	**Importance ratings**			**Comprehensibility ratings**		
Item	Median (IQR)	Range	% Agreement	Median (IQR)	Range	% Agreement
1. My health at present depends on me taking my nebulised antibiotics (N)	6 (1.25)	2	75%	5.5 (1.25)	4	50%
2. Having to take nebulised antibiotics worries me (C)	6 (1)	5	87.5%	6.5 (1.25)	3	75%
3. I sometimes worry about long-term effects of taking my nebulised antibiotics (C)	6 (1)	2	87.5%	6 (1)	2	87.5%
4. Without my nebulised antibiotics I would be very ill (N)	6 (1.5)	5	62.5%	6 (1.25)	4	75%
5. I don't understand why I need to take my nebulised antibiotics (C)	7 (0.25)	1	100%	7 (0.25)	1	100%
6. My health in the future will depend on my nebulised antibiotics (N)	6 (1)	2	87.5%	6 (0.25)	2	87.5%
7. Taking my nebulised antibiotics disrupts my life (C)	7 (0.25)	1	100%	7 (0)	1	100%
8. I sometimes worry about becoming too dependent on my nebulised antibiotics (C)	6 (2.25)	4	62.5%	5.5 (1.25)	3	50%
9. My nebulised antibiotics stop me from becoming worse (N)	7 (1.25)	3	75%	6 (1.25)	3	75%
10. Taking my nebulised antibiotics is unpleasant (C)	6 (1.25)	2	75%	6 (2.25)	3	62.5%
11. My nebulised antibiotics cause unpleasant short-term side-effects (C)	6 (1.25)	3	75%	5.5 (2.25)	4	50%
CF-BMQ-M						
1. My health at present depends on me taking my nebulised mucolytics (N)	6.5 (1.25)	2	75%	5.5 (2)	4	50%
2. Having to take nebulised mucolytics worries me (C)	6 (1.25)	4	75%	6 (1.25)	3	62.5%
3. I sometimes worry about long-term effects of taking my nebulised mucolytics (C)	6 (1)	1	62.5%	6 (1)	2	62.5%
4. Without my nebulised mucolytics I would be very ill (N)	6 (0.25)	2	75%	6 (0.25)	2	100%
5. I don't understand why I need to take my nebulised mucolytics (C)	7 (0)	4	87.5%	7 (0)	3	87.5%
6. My health in the future will depend on my nebulised mucolytics (N)	6.5 (1)	2	87.5%	6 (0.5)	3	75%
7. Taking my nebulised mucolytics disrupts my life (C)	7 (0.25)	2	87.5%	7 (0)	4	87.5%
8. I sometimes worry about becoming too dependent on my nebulised mucolytics (C)	5 (1.25)	2	25%	5 (1.25)	2	37.5%
9. My nebulised mucolytics stop me from becoming worse (N)	7 (1)	1	100%	6 (1)	2	87.5%
10. My nebulised mucolytics cause unpleasant short-term side-effects (C)	6 (1.25)	2	75%	5.5 (1.5)	3	50%

In general, usefulness ratings suggested that participants considered items in both questionnaires important. Only 19% (4/21) of items (CF-BMQ-A necessity item 4 and concern item 8, and CF-BMQ-M concern items 3 and 8) failed to reach consensus across the three statistical measures Within median ratings, all items scored between 6 and 7, with only item 8 in the CF-BMQ-M failing to reach consensus by scoring 5. Regarding percentage of agreement, although all four items did not reach the consensus threshold, all but item 8 in the CF-BMQ-M (which scored just 25%) came close, with 62.5% of respondents rating these items as useful. Little deviation occurred within item usefulness ratings across the questionnaires. In the CF-BMQ-A, IQR item ratings ranged from 0.25 to 2.25, with the range itself averaging just 2.7 across items. Six items (1, 4, 9, 8, 10, 11) exceeded an IQR value of one, of which item 8 also exceeded the consensus threshold of two. In the CF-BMQ-M, IQR ratings were less variable, ranging between 0 and 1.25 across items, with the range itself averaging just 2.2. Only four of these items (1, 2, 8, 10) exceeded an IQR value of one, and none met or exceeded a value of two.

Overall, item clarity ratings were lower and more variable than usefulness ratings across both questionnaires. In total, 43% (9/21) of items (CF-BMQ-A necessity item: 1 and concern items: 8, 10, 11, and CF-BMQ-M necessity item 1 and concern items: 2, 3, 8, 10) failed to reach consensus across the three statistical measures. Median ratings ranged between 5.5 to 7 for the CF-BMQ-A items, and 5 to 7 for the CF-BMQ-M items, with 3 items in each questionnaire failing to reach the median consensus threshold of 6. All 9 items failed to reach the percentage of agreement threshold. Most notably, five were rated as clear by just 50% of respondents (CF-BMQ-A items 1, 8, 11, and CF-BMQ-M items 1, 10), and item 8 in the CF-BMQ-M was rated clear by just 37.5%. IQR values across items for the CF-BMQ-A ranged between 0 and 2.25, with the range itself averaging 2.7. Seven items (1, 2, 4, 8, 9, 10, 11) exceeded an IQR value of one, of which items 10 and 11 exceeded a value of two. CF-BMQ-M IQR values ranged between 0 and 2 across items, with the range itself averaging 2.8. Four items (1, 2, 8, 10) exceeded a value of one, of which only item 1 met an IQR value of two.

Round one: item-specific qualitative feedback

During the first round, 49 item-specific comments were made by participants across both questionnaires. However, three of these comments were not considered relevant to the value or clarity of these items. The first explained why a patient may not hold a certain belief, while the remaining statements highlighted that if patients completed the questionnaires they would not understand the reference to medication categories in the items, since they are only aware of their medication's names. Of the remaining 46 items, 27 were reported in the CF-BMQ-A (13 within necessity-belief items, and 14 within concern), and 19 in the CF-BMQ-M (7 necessity, 12 concern). These comments were placed within four categories: constructive feedback on item relevance, meaning, wording, or positive

feedback. The frequency of these comments across items within both questionnaires can be seen in Table 3.

Table 3: *Item-specific qualitative feedback for round one.*

CF-BMQ-A		Comment categories				
Item and belief type: Necessity (N) or Concern (C)		Item relevancy	Item wording	Item meaning	Positive feedback	Total
1.	My health at present depends on me taking my nebulised antibiotics (N)	-	2	2	-	4
2.	Having to take nebulised antibiotics worries me (C)	-	-	2	-	2
3.	I sometimes worry about long-term effects of taking my nebulised antibiotics (C)	-	1	-	-	1
4.	Without my nebulised antibiotics I would be very ill (N)	-	4	-	-	4
5.	I don't understand why I need to take my nebulised antibiotics (C)	-	-	-	1	1
6.	My health in the future will depend on my nebulised antibiotics (N)	-	1	2	-	3
7.	Taking my nebulised antibiotics disrupts my life (C)	-	1	-	-	1
8.	I sometimes worry about becoming too dependent on my nebulised antibiotics (C)	1	1	-	-	2
9.	My nebulised antibiotics stop me from becoming worse (N)	-	2	-	-	2
10.	Taking my nebulised antibiotics is unpleasant (C)	-	1	2	-	3
11.	My nebulised antibiotics cause unpleasant short-term side-effects (C)	-	4	-	-	4
	Total:	1	17	8	1	27
CF-BMQ-M						
1.	My health at present depends on me taking my nebulised mucolytics (N)	-	2	1	-	3
2.	Having to take nebulised mucolytics worries me (C)	1	-	-	-	1
3.	I sometimes worry about long-term effects of taking my nebulised mucolytics (C)	1	1	-	1	3
4.	Without my nebulised mucolytics I would be very ill (N)	-	1	-	-	1
5.	I don't understand why I need to take my nebulised mucolytics (C)	-	-	-	1	1
6.	My health in the future will depend on my nebulised mucolytics (N)	-	1	1	-	2
7.	Taking my nebulised mucolytics disrupts my life (C)	-	-	-	-	0
8.	I sometimes worry about becoming too dependent on my nebulised mucolytics (C)	2	1	-	-	3
9.	My nebulised mucolytics stop me from becoming worse (N)	-	1	-	-	1
10.	My nebulised mucolytics cause unpleasant short-term side-effects (C)	1	3	-	-	4
	Total:	5	10	2	2	19

Table 3 shows that while the relevance of just one item (item 8) was questioned in the CF-BMQ-A in one comment, the relevance of four items (items: 2, 3, 8 and 10) were questioned in 5 comments in the CF-BMQ-M. Importantly, item 3 in the CF-BMQ-M, and item 8 in both questionnaires had also failed to reach consensus on usefulness ratings.

In total, 27 comments were made regarding *item wording* across both questionnaires; 17 across 9/11 items (82% of items) in the CF-BMQ-A, and 10 across 7/10 items (70% of items) in the CF-BMQ-M. Most notably, within the CF-BMQ-A, 47% of these comments were made regarding items 4 and 11, and for the CF-BMQ-M, 30% for item 10 (which is the equivalent of item 11 in the CF-BMQ-A). This category included comments which questioned item wording explicitly, and/or which presented rewording suggestions which did not change item meaning. Ten comments were made in relation to *item meaning* across both questionnaires; four items (1, 2, 6, 10) were questioned by 8 comments in the CF-BMQ-A, and two items (1, 6) by two comments in the CF-BMQ-M. This category included comments which explicitly reported problems with item meaning, suggested statements which changed item meaning, or which made an item more specific. Positive comments were made for item 5 in both questionnaires, and item 3 in the CF-BMQ-M. Although item 5 only received this comment, item 3 also received comments which questioned the relevance and wording of this item. Comments related to item wording, meaning and positive feedback did not clearly relate to quantitative measures.

It is important to note that significantly more wording and meaning comments were made regarding the CF-BMQ-A, despite the questionnaires being identical in wording. It was considered that this resulted from participants not wishing to repeat themselves across the questionnaires, since all participants assessed the CF-BMQ-A before the CF-BMQ-M. It was therefore considered that comments regarding item wording and meaning in either questionnaire applied to the other.

Item changes from item-specific feedback in round one

As a result of the item-specific statistical and qualitative feedback, 8 items were revised in each questionnaire (representing 73% of CF-BMQ-A items, and 80% of CF-BMQ-M items), and three items removed entirely across both questionnaires.

Item revisions

Revisions ranged from minor wording adjustments to language changes which increased clarity or altered meaning. These changes and their rationale will now be presented. The most substantial amendments were made to item 1: '*My health at present depends on me taking my nebulised medications'*, and its future equivalent, item 6 *'My health in the future will depend on my*

nebulised medications'. For item 1, dissatisfaction arose in clarity ratings and comments across both questionnaires, while for item 6, dissatisfaction was only represented within comments. Importantly, several of the comments regarding item 1 highlighted how nebulised medications are just one component of maintaining health in CF, causing disagreement with this item to reflect either: a patients' belief that nebulised medication is not important for their current health, or a recognition that their health depends on several complementary treatments. To overcome this, the item was modified to: '*To be healthy now, I need to take my nebulised medications'*. This statement continues to reflect the core meaning of the original statement (i.e. personal need for a treatment to maintain current health), with the word 'need' used to place a strong but non-exclusive focus on this treatment. Similar issues also arose regarding item 6, alongside further ambiguity concerns, i.e. that this item could be understood as meaning: 'taking nebulised medications *in the future* will improve my future health', rather than: 'taking my medication now will improve my *future* health' (the intended meaning). The former interpretation is problematic since it would bear no theoretical relation with present-day adherence behaviours. To remedy both problems, item 6 was modified to: '*To be healthy in the future, I need to take my nebulised medications now'*.

As a result of dissatisfaction in clarity ratings and comments, the following two items: *'Without my nebulised medications I would be very ill'* and *'My nebulised medications cause unpleasant short-term side-effects'* underwent moderate revisions. Reports for the first item expressed unease with the phrase *'very ill'* and its impact on patients. This was amended to: *'Without my nebulised medications, my health would be much worse'*. The strength of the original statement was retained through inclusion of the word 'much'. Comments on the second item suggested that patients would struggle to understand the phrases *'short-term'* and *'side-effects'*. To support understanding, examples were added, and the item was modified to: *'My nebulised medications can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick)'.*

Minor changes were made to four items in response to clarity ratings and/or comments:

i) '*Having to take nebulised medications worries me'* became *'Having to take <u>my</u> nebulised medications worries me'*

ii) *'I sometimes worry about long-term effects of taking my nebulised medications'* became '*I sometimes worry about <u>the</u> long-term effects of taking my nebulised medications'*

iii) *'My nebulised medications stop me from becoming worse'* became *'My nebulised medications stop <u>my health</u> from becoming worse'*

vi) *'Taking my nebulised antibiotics disrupts my life'* was modified to *'Taking my nebulised antibiotics <u>gets in the way of</u> my life'.*

Finally, one item was not modified, despite receiving clarity-related feedback: 'Having to take my nebulised medications worries me'. Participants' comments queried whether this item could be made more specific. However, it was considered that this would change the question's nature which is intentionally broad.

Item removal

Two items were removed from the CF-BMQ-A, and one from the CF-BMQ-M, after examination of usefulness ratings and related comments. Table 4 presents these items alongside a summary of the reasons for their removal.

Table 4: *Items removed across the CF-BMQ-A and CF-BMQ-M following round one feedback*

	Item	Reason for removal
Both questionnaires	Item 8 – 'I sometimes worry about becoming too dependent on my nebulised medications' – an original concern belief	Item failed to achieve statistical consensus for value and clarity on both questionnaires and 50% of relevancy comments made across the questionnaires critiqued this item.
CF-BMQ-A only	Item 10 – 'Taking my nebulised antibiotics is unpleasant' – a concern belief generated from the research team.	Item failed to achieve statistical consensus for clarity and comments critiqued the items vagueness. Most importantly, once item 11 (side-effects) was revised from round one feedback, substantial overlap existed with these items.

Several items were, however, retained despite statistical and/or qualitative feedback questioning their relevance. Table 5 presents these items alongside the rationale for why they were retained.

Table 5*: Items retained from the CF-BMQ-M despite feedback questioning item relevance.*

	Item	Reason retained
CF-BMQ-M	Item 3 – 'I sometimes worry about the long-term effects of taking my nebulised mucolytics' – an original concern belief.	Although this item did not reach statistical consensus, it only received one comment. Although this belief may be less probable within this medication than antibiotics, where it is held it was considered that it would be highly likely to influence adherence behaviour.
	Item 2 – 'Having to take nebulised mucolytics worries me' – an original concern belief.	This item received one comment. Again, although clinicians may not perceive that individuals worry about these medications. It is likely that if they do, such worries will influence adherence behaviour.
	Item 10 – 'My nebulised mucolytics cause unpleasant short-term side-effects' – an original concern belief.	This item received one comment. Although mucolytics are less likely to cause side-effects, where side-effects do occur or where it is considered that they could occur, they are no less likely to influence adherence behaviour than antibiotics.
CF-BMQ-A	Item 4 – 'Without my nebulised antibiotics I would be very ill' – an original concern belief.	This item did not reach statistical consensus and received four qualitative comments. They however, suggested that it was the wording of the item that dissatisfied clinicians, rather than item usefulness.

Round one: additional item qualitative feedback

Addition of belief items to the CF-BMQ-A and CF-BMQ-M

At the end of the questionnaires, participants were asked to report any necessity or concern beliefs for nebulised medications which they considered to be missing from the existing questionnaire items. In total, 11 comments were made across both questionnaires, although four of these were general beliefs related to completing treatments, rather than necessity or concern beliefs regarding medications. From these comments, three new items were developed, two of which were included in both questionnaires, and one in the CF-BMQ-A alone. These comments, and their categorisation and development into items for the round 2 questionnaires, can be viewed in Table 6.

Table 6*: Round one categorisation of patient feedback for new items.*

Version	Necessity item suggestions	Round 2 inclusion?	Concern item suggestions	Round 2 inclusion?	More general beliefs	Round 2 inclusion?
CF-BMQ-A	I don't believe my nebulised antibiotics work for me.	**No**. Overlap with existing item: 'To be healthy now, I need to take my nebulised Antibiotics'	Increasing resistance to antibiotics.	**Yes**. 'I sometimes worry that taking my nebulised antibiotics now will mean that they won't work as well in future'	Time taken to take nebulised antibiotics.	No.
	I only need to take my nebulised antibiotics regularly if I feel unwell.	**Yes**. 'I only need to take my nebulised Antibiotics when I feel unwell'			Fitting in with other treatments.	No.
	Something around the frequency of use e.g. I think taking some of treatment is better than none at all.					
CF-BMQ-M	I don't need to take my nebulised mucolytics regularly if I feel well.	**Yes**. 'I only need to take my nebulised Mucolytics when I feel unwell'			Time taken to take nebulisers.	No.
	I only need to take my nebulised mucolytic if I am going to do my physiotherapy.					
	Something around the frequency of use e.g. I think taking some of treatment is better than none at all.					
					Visibility of nebulisers in front of friends.	**Yes, for both questionnaires.** 'Taking my nebulised medications is embarrassing'.

Importantly, the inclusion of the items: ‘I only need to take my nebulised medications regularly if I feel unwell’ and ‘Taking my nebulised medications is embarrassing’, extends the nature of this questionnaire beyond the BMQ-Specific. The first item broadens the original definition of necessity beliefs, as it considers not only if a medication is needed to maintain or improve current health, but also when it is taken. Such timing-related beliefs are an important consideration in medications that can be prophylactic in nature within a health condition that can be asymptomatic. The second item is considered to extend the definition of concern by moving from concerns regarding the medication itself, to the medication delivery system. This was considered important, as the I-nebuliser delivery system is clearly visible when in use and requires steady breathing to work.

The decision was made to not include the other more general beliefs related to completing nebulised treatments i.e. time and fitting in with other treatments, as time is not a belief specific to medication categories, and does not in itself offer an explanation for poor adherence, while prioritisation of different treatments was too broad for this study’s focus.

Addition of belief items to the parent questionnaire versions

Participants were asked to report necessity and concern beliefs for nebulised medications that they considered only a parent would hold. Although 10 comments were made, the majority were general concerns regarding health and treatment, with just 4 comments relating specifically to nebulised medications. These comments and their categorisation can be viewed in Table 7.

Table 7*: Round one suggestions for new items in the parent versions of the CF-BMQ-A and CF-BMQ-M.*

Necessity and concern beliefs for nebulised medications	Beliefs regarding using nebulisers	General health and treatment beliefs
'Will the nebulised medication cause resistance' (concern).	'That the equipment takes a long time to clean and may be a source of infection'.	'In my experience, the main concern from parents is their child's adherence'.
'Will I as the parent develop resistance' (concern).	'My child would not take their nebulised medication if I did not prepare it for them'.	'Parents are more likely to have long term implication concern beliefs regarding lung function, transplantation etc that patients may not yet be aware of'.
'My child does not understand why they need to take nebulised …' (necessity).	'Perhaps concerns relating to the child's ability to do the treatment alone / dependency on the parent to do the treatment'.	'What happens if my child can't take all or any of the medications?'
'That antibiotic nebulisers may make the child wheezy or their wheeze worse' (concern).		

Within the items concerning nebulised medications, only the item '*Will I, as the parent, develop resistance*?' was considered potentially exclusive to parents, but it was also considered unlikely to be held in the first place. The number of general comments resulting from this question suggests that participants had difficulty answering it, which in turn suggests that the patient questionnaires would sufficiently capture parents' necessity and concern beliefs regarding these medications, once re-worded.

Delphi survey: round two results

Aim of round two

Round two aimed to gain opinion on the new items and to gain increased consensus on the value and clarity of revised items in the CF-BMQ-A and CF-BMQ-M, from the same expert group, and any further recommendations for new items.

Statistical summary item-specific

Participants rated 23 statements, 12 in the CF-BMQ-A and 11 in the CF-BMQ-M, on the same dimensions of importance and comprehensibility. Descriptive statistical summaries for both ratings were produced for every item, and can be viewed in Table 8.

Table 8*: Round two importance and comprehensibility ratings for the CF-BMQ-A and CF-BMQ-M.*

CF-BMQ-A		Importance ratings			Comprehensibility ratings		
Item and belief type: Necessity (N) or Concern (C)		Agreement %	Median (IQR)	Range	Agreement %	Median (IQR)	Range
1.	To be healthy now, I need to take my nebulised antibiotics (N)	85.8	7 (1)	2	85.8	6 (0.5)	2
2.	Having to take my nebulised antibiotics worries me (C)	71.5	6 (0.5)	4	71.5	6 (1.5)	4
3.	I sometimes worry about the long-term effects of taking my nebulised antibiotics (C)	85.8	6 (1)	2	85.8	6 (0.5)	2
4.	Without my nebulised antibiotics my health would be much worse (N)	85.8	6 (1)	2	85.8	6 (1)	2
5.	I don't understand why I need to take my nebulised antibiotics (C)	100	7 (0.5)	1	100	7 (0.5)	1
6.	To be healthy in future, I need to take my nebulised antibiotics now (N)	71.5	7 (1.5)	2	71.5	6 (1.5)	2
7.	Taking my nebulised antibiotics gets in the way of my life (C)	100	7 (0)	1	100	7 (0)	1
8.	I sometimes worry that taking my nebulised antibiotics now will mean that they won't work as well in future (C)	85.8	7 (0.5)	2	85.8	6 (1)	2
9.	My nebulised antibiotics stop my health from becoming worse (N)	100	7 (1)	1	100	7 (1)	1
10.	My nebulised antibiotics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick) (C)	100	7 (0.5)	1	100	7 (0.5)	1
11.	Taking my nebulised antibiotics is embarrassing (C)	57.2	6 (2)	5	85.8	6 (1)	2
12.	I only need to take my nebulised antibiotics when I feel unwell (N)	85.8	7 (1)	2	100	6 (1)	1
CF-BMQ-M							
1.	To be healthy now, I need to take my nebulised mucolytics (N)	85.8	7 (1)	2	71.5	7 (1.5)	2
2.	Having to take my nebulised mucolytics worries me (C)	85.8	6 (0.5)	4	71.5	6 (1.5)	3
3.	I sometimes worry about the long-term effects of taking my nebulised mucolytics (C)	57.2	6 (2)	2	71.5	6 (1)	2
4.	Without my nebulised mucolytics my health would be much worse (N)	85.8	7 (1)	2	71.5	6 (1)	2
5.	I don't understand why I need to take my nebulised mucolytics (C)	85.8	7 (0)	2	100	7 (0)	1
6.	To be healthy in future, I need to take my nebulised mucolytics now (N)	85.8	7 (1)	2	71.5	6 (1.5)	2
7.	Taking my nebulised mucolytics gets in the way of my life (C)	100	7 (0)	1	100	7 (0)	1
8.	My nebulised mucolytics stop my health from becoming worse (N)	100	7 (1)	1	100	6 (1)	1
9.	My nebulised mucolytics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick) (C)	85.8	7 (0.5)	2	100	7 (0.5)	1
10.	Taking my nebulised mucolytics is embarrassing (C)	71.5	6 (1.5)	5	100	6 (1)	1
11.	I only need to take my nebulised mucolytics regularly when I feel unwell (N)	85.8	6 (1)	3	85.8	6 (1)	3

In round two, item usefulness ratings had improved from round one across both questionnaires. Only 8% (2/23) of items (CF-BMQ-A concern item 11 and CF-BMQ-M concern item 3) failed to reach consensus across the three statistical measures. Importantly, CF-BMQ-M item 3 had also failed to reach consensus in round one, while CF-BMQ-A item 11 had only been introduced in this round. All items' median ratings were between 6 and 7 across both questionnaires, and in percentage of agreement, all scored above 70%, apart from the two failed items above, which each scored 57.2%; highlighting that only a small majority rated these items as useful. Overall, less deviation occurred within item usefulness ratings than in round one. In the CF-BMQ-A, IQR values ranged from 0 to 2, with the range itself averaging just 2. Just two items: 6 and 11, exceeded an IQR value of one, with item 11 meeting the consensus threshold value of two. Similarly, the CF-BMQ-M IQRs ranged between 0 and 2, with the range itself averaging 2. Again, just two items (3 and 10) exceeded a value of one, with item 3 meeting the consensus threshold value of two.

Item clarity ratings were significantly improved from round one; all items reached consensus across all three statistical measures. Greater consistency within ratings was also achieved; IQR item ratings across both questionnaires ranged from just 0 to 1.5, with the range averaging 1.8 for the CF-BMQ-A, and 1.7 for the CF-BMQ-M. Also, only 5 items (CF-BMQ-A items 2, 6; CF-BMQ-M items 1, 2, 6) exceeded an IQR value of one.

Round two: item-specific qualitative feedback

During the second round, 27 item-specific comments were made by participants across both questionnaires. However, eight of these comments were not considered relevant to the value or clarity of the items, as they provided general feedback or reflected participant misunderstandings of the items' or questionnaires' purpose. For instance, general feedback raised the problem of using medication categories rather than names as highlighted in round one, while another raised an ethical concern: '*Could asking about potential concerns cause increased concern in patients*?'. Regarding misunderstandings, one participant reported that the following item: '*I only need to take my nebulised antibiotics when I feel unwell'*, is not applicable to patients who take antibiotics on a continuous basis regardless of their infection status. It is possible that this participant interpreted this item as: '*I only need to take my nebulised antibiotics when <u>I am</u> unwell*'. Surprisingly, other comments suggested declaring adherence behaviour within belief statements; for instance, one participant suggested adding: '...and this is why I don't take them regularly' to an item.

Of the remaining 19 comments, 8 related to the CF-BMQ-A (6 for necessity items, 2 for concerns), and 11 for the CF-BMQ-M (7 necessity, 4 concern). Again, these comments were placed within four categories: constructive feedback on item relevance, meaning, wording, or positive

feedback. The frequency of these comments across items within both questionnaires can be seen in Table 9.

Table 9*: Item-specific qualitative feedback for round two items.*

CF-BMQ-A		Comment categories				
Item and belief type: Necessity (N) or Concern (C)		Item relevancy	Item wording	Item meaning	Positive feedback	Total
1.	To be healthy now, I need to take my nebulised antibiotics (N)	-	1	1	-	2
2.	Having to take my nebulised antibiotics worries me (C)	1	-	-	-	1
3.	I sometimes worry about the long-term effects of taking my nebulised antibiotic (C)	-	-	-	-	0
4.	Without my nebulised antibiotics my health would be much worse (N)	-	1	-	-	1
5.	I don't understand why I need to take my nebulised antibiotics (C)	-	-	-	-	0
6.	To be healthy in future, I need to take my nebulised antibiotics now (N)	-	-	1	1	2
7.	Taking my nebulised antibiotics gets in the way of my life (C)	-	-	-	-	0
8.	I sometimes worry that taking my nebulised antibiotics now will mean that they won't work as well in future (C)	-	-	-	-	0
9.	My nebulised antibiotics stop my health from becoming worse (N)	-	1	-	-	1
10.	My nebulised antibiotics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick) (C)	-	-	-	-	0
11.	Taking my nebulised antibiotics is embarrassing (C)	-	-	1	-	1
12.	I only need to take my nebulised antibiotics when I feel unwell (N)	-	-	-	-	0
	Total:	1	3	3	1	8
CF-BMQ-M						
1.	To be healthy now, I need to take my nebulised mucolytics (N)	-	2	-	-	2
2.	Having to take my nebulised mucolytics worries me (C)	1	-	-	-	1
3.	I sometimes worry about the long-term effects of taking my nebulised mucolytics (C)	-	-	-	-	0
4.	Without my nebulised mucolytics my health would be much worse (N)	-	2	-	-	2
5.	I don't understand why I need to take my nebulised mucolytics (C)	-	-	-	-	0
6.	To be healthy in future, I need to take my nebulised mucolytics now (N)	-	-	-	1	1
7.	Taking my nebulised mucolytics gets in the way of my life (C)	-	-	-	-	0
8.	My nebulised mucolytics stop my health from becoming worse (N)	-	2	-	-	2
9.	My nebulised mucolytics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick) (C)	1	-	1	-	2
10.	Taking my nebulised mucolytics is embarrassing (C)	1	-	-	-	1
11.	I only need to take my nebulised mucolytics when I feel unwell (N)	-	-	-	-	0
	Total:	3	6	1	1	11

Overall, Table 9 shows the substantial reduction in comments between rounds one and two, from a constructive comment total of 43 in round one, to just 17 in round two. Regarding *item relevance*, one concern item (item 2) was questioned in the CF-BMQ-A by one comment, and three concern items (2, 9, 10) by 3 comments for the CF-BMQ-M. Interestingly, despite this feedback all of these items had achieved statistical consensus.

In total, only 9 comments were made regarding *item wording* across both questionnaires. In the CF-BMQ-A, 3 comments were made across 3 necessity items (1, 4, 9), and in the CF-BMQ-M, 6 comments were made across the equivalent 3 necessity items (1, 4, 8). Regarding *item meaning*, 3 items (1, 6, 11) attracted 3 comments in the CF-BMQ-A, while only one comment questioned one item (item 9) in the CF-BMQ-M. Positive comments were made for item 6 in both questionnaires, despite item 6 in the CF-BMQ-A also receiving a comment which questioned item meaning. Comments related to item wording, meaning and positive feedback did not clearly relate to quantitative measures.

Item changes from item-specific feedback in round two

In this round, item-specific statistical and qualitative feedback led to no revisions or removals for any item.

Item revisions

As previously described, all items met statistical consensus for clarity, and just 13 comments were made regarding item meaning or wording over both questionnaires. Although these comments were examined, it was considered from this feedback that no further revisions were needed. For instance, 'Without my nebulised medications, my health would be much worse' received comments questioning the need for language as strong as 'much worse'. However, it was recognised that weakening the language of this item would likely reduce the variability of responses to it, on the continuum of 'strongly disagree' to 'strongly agree'. Similarly, for the item 'My nebulised medications can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick)', one comment highlighted that the wording did not differentiate between whether an individual has experienced side-effects first-hand, or simply has knowledge that they could occur. However, for the purposes of this item, such a distinction makes no difference, as both possibilities could be considered valid concerns about a treatment

Item removal

Despite statistical and/or qualitative feedback questioning the usefulness of several items, none were removed. Table 10 presents these items alongside a brief rationale for why they were retained.

Table 10: *Items removed across the CF-BMQ-A and CF-BMQ-M following round one feedback.*

	Item	Reason retained
Both	Item 11 in the CF-BMQ-A and item 10 in the CF-BMQ-M – 'Taking my nebulised medications is embarrassing' – a concern item generated from round one.	Although the item failed to reach statistical consensus in the CF-BMQ-A, it achieved statistical consensus on the CF-BMQ-M, and only received one comment which questioned its relevance across both questionnaires.
	Item 2 – Having to take my nebulised medications worries me – an original concern item.	Only one comment in each questionnaire questioned the relevance of this item
CF-BMQ-M	Item 3 – 'I sometimes worry about long-term effects of taking my nebulised mucolytics' – an original concern item.	Again, this item did not reach consensus statistically. The rationale for retaining this item despite this was explained in round one.
	Item 9 – 'My nebulised mucolytics cause unpleasant short-term side-effects' – an original concern item.	Only one comment questioned the relevance of this item. The rationale for retaining this item was explained in round one.

Round two: additional item qualitative feedback

Addition of belief items to the CF-BMQ-A and CF-BMQ-M

Again, at the end of the questionnaires, participants were asked to report any necessity or concern beliefs for nebulised medications that they considered to be missing from the existing items. Only one comment was made in this round; 'Ask questions about time taken to take nebulised antibiotics', however this item was not considered for inclusion due to reasons previously discussed. The lack of comments in this section suggests that the panel were satisfied with the questionnaire items by round two.

Final questionnaire

The final CF-BMQ-A and CF-BMQ-M are identical in item content, with each containing 5 necessity and 7 concern beliefs (see Appendix H.1 to H.2).

Importantly, it was decided that item 8 developed after round one for the CF-BMQ-A alone: '*I sometimes worry that taking my nebulised medications now will mean that they won't work as well in future'* should also be included in the mucolytic questionnaire. It was considered reasonable that this belief could be held regarding mucolytics, even if the development of such tolerance is not medically founded.

Assessment of reading level

The Flesch-Kincaid Grade level was used to calculate the reading level of the questionnaires. The original BMQ-Specific scored 4.8, while the CF-BMQ-Specific a slightly increased score of 5.1. Nonetheless this tool placed the reading level of both questionnaires at the US 5th grade, suggesting that 10- and 11-year olds would be able to understand the language used in the questionnaires.

To further ensure the readability of the final questionnaires, they were piloted with 8 children (3 = male and 5 = female) aged between 11 and 12 years. They were asked to indicate whether there were any words or sentences that they found harder or impossible to understand in the CF-BMQ-Specific. The first two children to consider the questionnaires indicated that they found item 8 ('*I sometimes worry that taking my nebulised medication now will mean that they won't work as well in future'*) more difficult to understand. They reported experiencing difficulty with the phrasing *'now will'* and the length of the sentence. In response, the item was amended to: '*I sometimes worry that if I take my nebulised medications now, they won't work as well in future*'. This item was then included in the questionnaire and individuals were asked to choose their preferred phrasing; 4 of the 6 of these children chose the revised wording.

Item content of the original and final questionnaires

The original BMQ-S items and the final adapted items for the CF-BMQ-S can be viewed in Table 11 below.

Table 11: *Original BMQ-S items and final adapted items for the CF-BMQ-S.*

	Original BMQ-S		**Final CF-BMQ-S items**
	Item and belief type: Necessity (N) or Concern (C)		
1.	My health, at present, depends on my medications (N)	1.	To be healthy now, I need to take my nebulised medications (N)
2.	Having to take medications worries me (C)	2.	Having to take my nebulised medications worries me (C)
3.	My life would be impossible without my medications (N)	3.	I sometimes worry about the long-term effects of my nebulised medications (C)
4.	I sometimes worry about the long-term effects of my medications (C)	4.	Without my nebulised medications my health would be much worse (N)
5.	Without my medications I would be very ill (N)	5.	I don't understand why I need to take my nebulised medications (C)
6.	My medications are a mystery to me (C)	6.	To be healthy in future, I need to take my nebulised medications now (N)
7.	My health in the future will depend on my medications (N)	7.	Taking my nebulised medications gets in the way of my life (C)
8.	My medications disrupt my life (C)	8.	I sometimes worry that taking my nebulised medications now, means that they won't work as well in future (C)
9.	I sometimes worry about becoming too dependent on my medications (C)	9.	My nebulised medications stop my health from becoming worse (N)
10.	My medications protect me from becoming worse (N)	10.	My nebulised medications can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick) (C)
		11.	Taking my nebulised medications is embarrassing (C)
		12.	I only need to take my nebulised medications when I feel unwell (N)

Chapter 4: Study One Discussion

Review of study one

This study adapted the BMQ-Specific – a generic measure used to assess necessity and concern beliefs in medications across health conditions – for use specifically with nebulised antibiotic and mucolytic medications in CF. It consisted of two phases. First, two draft questionnaires were developed from the BMQ-Specific by the researcher and supervisory team: one for nebulised antibiotics and the other for nebulised mucolytics. Following this, a modified Delphi survey was used to gain consensus from a panel of experts regarding the usefulness and clarity of items in both questionnaires, and to elicit recommendations for new items, over two rounds. The findings from the first round were used to revise the content of the questionnaires for round two, and the findings from round two were used to inform the content of the final form of the questionnaires.

Summary of findings

As previously discussed in Chapter 3, the draft questionnaires were constructed by the research team from the original BMQ-S, with several changes made to increase the clarity and/or relevance of items to nebulised antibiotics and mucolytics specifically. This included four items being reworded, one necessity item being removed from each questionnaire, and two new concern items being developed, both of which were added to the antibiotics questionnaire, and one to the mucolytics questionnaire. These changes were made as a result of discussion based on the team's clinical experience, and after consideration of the relevant research literature, with full consensus gained within the team before alterations were made.

In relation to the Delphi survey, positive consensus on the value and clarity of items in both questionnaires was gained by round two. In round one, although initial consensus was positive regarding the value of items in both questionnaires, findings regarding clarity were more variable. Only 19% (4/21) of items failed to achieve statistical consensus for value, but almost half of items (43%) did not attain this for clarity, and six times more item-specific feedback comments were given for clarity than value (6 vs. 37). As a result, for the second round, three concern items (two from the CF-BMQ-A and one from the CF-BMQ-M) were removed, and eight items (four necessity and four concern) were identically revised in each questionnaire, leaving just one unaltered item in each. Although these revisions were widespread, most were minimal in scope, and just one original BMQ-Specific item was removed entirely from each questionnaire. Seven suggestions were given for new items, leading to one necessity item and two concern items being generated; one of each was added to the CF-BMQ-M, and all three to the CF-BMQ-A.

As hoped, these changes led to improved consensus after round two; only two items failed to reach statistical consensus for value (one on each questionnaire, including a newly-added concern item), and all items attained consensus for clarity. Additionally, only four item-specific comments were made regarding value, and thirteen for clarity. Only one suggestion for a new item was made in this round, suggesting increased satisfaction with the items available. Importantly, no removals, additions or even minor revisions were made in either questionnaire as a result of round-two feedback. This decision was made due to the already strong positive consensus after round two; it was determined that any changes made at this point might be equally likely to reduce consensus, with no further Delphi survey round available to examine this. Also, most of these comments were considered minor or to represent dissenting views, so did not provide strong justification to make further changes. Possible reasons for such a quantity of comments despite high quantitative consensus, will be considered later in the discussion. Additionally, the two items which had failed to reach consensus were also retained, for reasons which will also be discussed later.

The lack of consensus regarding item clarity after the first round was surprising. It had been expected that a high level of positive agreement would be gained immediately from the panel regarding both the value and clarity of items, since the BMQ-Specific is a well-developed and validated measure and the research team had already adapted it to nebulised CF medication categories. Consequently, most of the changes highlighted above were made as a result of such less favourable feedback to improve item clarity. It was expected that the majority of these comments and subsequent item changes would focus on problems in relation to their adaptation to nebulised medications and/or CF – however, most related to the general wording of items, including grammatical errors, ambiguity, and concerns regarding language complexity. This suggested that the panel was actually highlighting clarity problems in the original wording of items in the BMQ-Specific, independent of the illness and medications of interest. Importantly, the improved quantitative and qualitative results for several items in the second round following these changes, support this view.

Interestingly, perceived value was rated less favourably overall for concern than necessity items in both rounds. Indeed, three of the four items which failed to achieve consensus for value in round one were concerns, as were both such items in round two. Qualitative findings showed a similar pattern; all comments which critiqued item relevance were for concern items, across both rounds. These findings suggest that concern items were considered by the panel to be of less value than necessity items. Most of these comments were reported for the CF-BMQ-M, which shows that the panel's views of the value of concern beliefs differed between the two medication categories.

Importantly, this finding supports this study's novel decision to create two questionnaires to differentially assess beliefs between the nebulised medication categories

In the second round, more item-specific comments were made that were not relevant to the survey questions, than in the first round (8 vs. 3). In round one, such comments were mostly relevant, but related to the questionnaires generally, rather than to specific items. However, those from round two seemed instead to indicate that specific items, as well as the questionnaires' purpose, were being misunderstood in places. Arguably, if this was due to misunderstanding the survey itself, such issues would have arisen similarly in both rounds. Instead, it may simply be that participants felt a continued wish to suggest helpful changes as they had done in the first round, but had greater difficulty generating relevant comments due to the improved questionnaire items. This hypothesis seems reasonable, considering the large number of otherwise useful comments in both rounds, and the fact that piloting was favourable.

Developing the final questionnaires

It was originally planned that any item failing to reach consensus in either questionnaire would be removed from it – however, it was recognised that entirely omitting certain items from one questionnaire alone would prevent direct examination of differences in beliefs between the two medication categories in the second study. The two final questionnaire items were therefore made identical in content, a decision which also partially underpinned the lack of changes to the questionnaires following round two. In practice, this meant that the two items which had failed to reach statistical consensus for value following round two in either questionnaire, were retained in both. This decision also led to one item being added to the final version of the CF-BMQ-M which had originally been developed by the research team for the CF-BMQ-A alone. The reasons for retaining these items, rather than simply removing them from both questionnaires, will now be examined in detail.

The first item which had failed to achieve consensus on value: "Taking my nebulised medications is embarrassing" was a new item suggested in round-one feedback by a panel member. It was expected to perform well in round two since both published research (see Dziuban et al., 2007; Hogan et al., 2015 as discussed in the introduction), and the supervisory team's clinical experience, had highlighted the relevance of embarrassment as a barrier to adherence in nebulised medications. Surprisingly, however, it failed statistical consensus for value on the CF-BMQ-A, and only marginally reached consensus on the CF-BMQ-M. One possible explanation for the poorer performance of this item is a design flaw in the survey instructions. When this item was developed, it

was recognised that it extended the nature of the BMQ-Specific, by potentially allowing consideration of both the medication itself, and its delivery method. However, the survey instructions asked the panel to consider the value and clarity of beliefs relating to the medications in isolation, arguably potentially leading panel members to discount the delivery device. Another potential explanation is that the panel members were all physiotherapists, to whom concerns relating to emotions surrounding medications arguably have reduced pertinence compared to other professionals such as psychologists. In view of these considerations, the decision was made to retain the item for both questionnaires.

The second, an original BMQ-Specific item, "I sometimes worry about the long-term effects of taking my nebulised medications", failed on the CF-BMQ-M, an outcome which could be easily justified by the fact that mucolytics are less likely than antibiotics to cause long-term detrimental effects to health. However, as considered in the introduction, patients often hold scientifically incorrect beliefs regarding their medications, the frequency of which healthcare professionals can underestimate, so, as described above, it was considered of interest to retain this item in both questionnaires. The same rationale also underpinned the decision to include the following item which had been developed for the CF-BMQ-A alone "I sometimes worry that taking my nebulised medications now will mean that they won't work as well in future" in the CF-BMQ-M, despite such beliefs about resistance not being reported by patients in regards to mucolytics.

Finally, it is also important to note that some of the item additions and/or rephrasing of original items for the final questionnaires extended their nature beyond the original BMQ-Specific. The necessity item – "I only need to take my nebulised medications regularly if I feel unwell" – was developed from round-one feedback, and broadens the original definition of *necessity* by considering not only if a medication is needed to maintain or improve current health, but also *when* it needs to be taken. Timing-related beliefs are an important consideration with CF medications, as they are generally only effective when taken regularly. Both concern items – "Taking my nebulised medications gets in the way of my life" (an original but modified BMQ-Specific item), and "Taking my nebulised medications is embarrassing" (generated from round-one feedback, as discussed above) – extend the original focus of *concerns* by now including the word 'taking', which, as discussed above, includes not only the medication, but its delivery system. These changes were considered important as, theoretically, the nature of the I-nebuliser device itself is highly likely to impact adherence behaviour, especially as it can be highly visible and time-consuming to use and clean. In other treatments in CF, and indeed in other illnesses, where the BMQ has been used, the delivery mechanism of a treatment may not have been as pertinent an issue. However, examination of delivery devices could be an interesting extension for this model and subsequent research.

Study one strengths and limitations

Several strengths and limitations exist in this study, the most significant of which will now be considered. The first key strength of this study lies in its originality; it presents the first known attempt to adapt the BMQ-Specific to both nebulised medication categories in CF, and to complete such adaptations through a process driven by gaining consensus from a group of experts. Importantly, this represents a more systematic means of tailoring the BMQ-S to specific medications, than those undertaken in several previous studies; for instance, that of Bucks et al. (2009), who simply describe the method for refining questionnaires as a 'discussion with the team'. This study not only potentially provides the foundation for a measure to assess beliefs in nebulised medication categories in CF, but also suggests a method for future researchers to use when tailoring the BMQ-Specific to other treatments.

Participants

Response numbers for this study were surprisingly low. No 'experts by experience' (CF patients using these medications, or their parents) were successfully recruited, despite four patients and parents being approached; also, only eight clinicians agreed to participate. This lack of interest was unexpected, especially considering that the clinicians approached were all members of a nationwide CF special-interest group. Despite this, at least 7 participants took part in both rounds. This is the minimal level required for Delphi surveys (Linestone, 1978), but falls below the range of 10-15, more recently advocated by several authors as optimal in ensuring the reliability of group judgements (e.g. Skulmoski et al., 2007). The panel itself was also limited to just one group (physiotherapists); such homogeneity is considered by several authors to limit the range of elicited viewpoints, and thereby the validity and generalisability of developed questionnaires (e.g. Linstone & Turoff, 2002). However, this panel represented physiotherapists of various ages, levels of clinical experience, and national locations. Clinical psychologists from the supervisory team were also involved in supporting the initial development and revisions of these questionnaires. These factors, taken together, will have widened perspectives. A further strength of this study lies in the clinical experience of the panel, supervisors, and wider research team; most panel members had at least 10 years of clinical experience in CF, the wider research team at least 5 years' experience each, and the supervisory team of clinicians over 20 years' experience each. This suggests that all individuals involved in this research were well-placed to give their clinical opinion on the questionnaires.

Despite the small sample, attrition between the rounds was minimal (N=1) and participants provided a high volume of feedback, suggesting that those who participated were knowledgeable and interested, factors considered to increase the content validity of Delphi surveys (Goodman, 1987). The use of quasi-anonymity in this study is likely to have contributed to this strong retention and

participant input. Research has shown that quasi-anonymity supports retention compared to full anonymity, by allowing the use of personalised correspondence, including reminder emails (e.g. Sánchez-Fernández, Muñoz-Leiva, & Montoro-Ríos, 2012), and that it increases accountability, and therefore, participants' motivation and due consideration (Goodman, 1987). Although this can, in turn, lead participants to be more cautious and rate items more favourably (McKenna, 1994), this did not appear to occur in this study; item-specific constructive feedback was commonplace, even where ratings were already favourable. Importantly, quasi-anonymity also allowed examination of the feedback of the individual who left the study after the first round. This feedback was very favourable, showing that the increased consensus in round two was not attributable to their dropping out.

Ultimately, regardless of specific limitations, it is important to recognise that Delphi surveys are, by their nature, limited in reliability – they simply represent the views of a subset of individuals at a single point in time, so it would be scientifically untenable and overstated to claim that one group can represent generalisable expert opinion. In recent years, some Delphi surveys in the literature have begun to address this by correlating findings between independent expert groups (e.g. Garnett, Crane, West, Brown & Michie, 2015). This study did not have the capacity to do this, so the generalisability of findings to another group is unknown.

Survey design

Although certain features of the survey design may have been advantageous in promoting retention, these same features may arguably have limited it. For instance, within this Delphi survey, rather than being presented with a summary of their individual and group responses for each item after the first round, panel members were instead given updated questionnaires developed from the group feedback. While this will have reduced the time-burden, it also prevented participants from considering the specific ratings and comments of other members in relation to their own responses, potentially limiting opportunities to understand others' perspectives, and/or change their own views as a result. Without such feedback, it is likely that some respondents had difficulty in understanding why their suggestions had, or had not, been implemented between rounds, and in recalling what their previous responses had been. This may explain why certain comments were repeated across rounds, and why dissenting opinions were still reported. Overall, this is likely to explain why comments appeared less useful and/or relevant in round two.

It is also important to note more general difficulties with the surveys themselves; the questionnaires were presented to all panel members in the same order across both rounds (CF-BMQ-A first, CF-BMQ-M second). As discussed in the results section, this order-effect is assumed to have underpinned the significantly higher number of clarity-related comments made for the CF-BMQ-A than the identically-worded CF-BMQ-M in round one. However, this discrepancy did not occur in

round two, or in value-related comments in either round (since the value of items requires a fresh appraisal between medications while clarity does not). This suggests that such effects were likely minimal, since genuine order-effects (e.g. fatigue) would have affected both kinds of comments equally. Also, a proportion of irrelevant comments provided in both rounds can be attributed to participants finding the survey format constraining; although participants were able to comment on individual questionnaire items, a space for more general comments regarding the questionnaire as a whole was not provided, leading some respondents to place them within item-specific spaces. This factor is also likely to have limited respondents' ability to provide overall impressions of the questionnaires, some of which feedback did indeed prove useful when provided.

Conclusion

Overall, despite the limitations arising from the application of the Delphi method, both in this study specifically, and more generally, it provided an effective means to draw together the opinion of a group of experts, and gain consensus on the developed questionnaires, in a more robust way than many similar previous studies. Ultimately, the adaptation of the BMQ-Specific to assess necessity and concern beliefs within nebulised medication categories in CF was completed in order to examine whether these questionnaires can predict adherence behaviour to these medications more effectively than the original measure. This is examined through study two.

Chapter 5: Study Two Method

Predicting adherence behaviour from medication beliefs

Design

A longitudinal design was used to examine the relationship between medication beliefs and adherence behaviour to nebulised medications in CF. Participants were provided with a series of questionnaires by their physiotherapist, which collected information regarding their beliefs about their nebulised medication(s), illness perceptions, and sociodemographic and health factors. Although other data-collection methods and designs were considered, they were deemed less suitable. For instance, while postal or online questionnaires might have reduced the time burden placed upon the physiotherapy teams, they often lend themselves to small and biased samples, especially when sample sizes are limited (Sax, Gilmartin & Bryant, 2003). Also, although a longer longitudinal design would have allowed examination of the stability of beliefs and adherence behaviour over a period of time, and thereby of the self-regulatory aspect of the Necessity Concerns Framework, this was not deemed possible due to the project's time constraints.

The specific version(s) of the medication-belief questionnaires (i.e. BMQ-Specifics and CF-BMQ-Specifics) that participants (i.e. patients and parents) completed were determined by the patients' I-nebuliser prescription. This created three possible groups; those prescribed only mucolytics or antibiotics through the I-nebuliser device, and those prescribed both. The first groups were named 'antibiotic-only' or 'mucolytic-only', while the dual group was named the 'combined group'. It is important to note that some individuals were prescribed more than one medication within a medication category through the I-nebuliser device. In these instances, one medication was nominated, rather than participants completing a BMQ-Specific and CF-BMQ-Specific questionnaire for each individual medication within a category, as it was considered that this would lead to high repetition and burden for certain participants. Equally, asking participants to complete just one questionnaire for multiple medications was thought to be inappropriate, since there is no reason to assume that participants would hold the same necessity and concern beliefs about different medications, even within the same medication category. In all such cases, selection of which medication to nominate was based on which would afford the most reliable adherence data. Where no clear advantage existed, participants chose the medication. Also, as the questionnaires are very similar in nature, their order of completion was counterbalanced within the groups, to reduce order effects.

Objective adherence data was collected from patients' I-nebuliser devices at their next clinic appointment, which usually occurred six to eight weeks after questionnaire completion. Adherence data was collected prospectively, rather than retrospectively, as assessing the predictive validity of the belief measures in this study for future behaviour was of higher interest to clinicians. This timeframe was considered sufficient to provide a stable and representative measure of a patient's adherence

while fitting within the time constraints of this study. Although it could be argued theoretically that participation in this study (i.e. completion of questionnaires and knowledge about I-neb data being collected) could influence subsequent adherence behaviour, when it is considered that I-neb data is routinely monitored in these services, and the importance of adherence routinely advocated, such effects were considered unlikely.

Participants

Recruitment

Convenience sampling was used to recruit adolescent patients and their parent or guardian (hereafter referred to simply as 'parents') to the study. Patients and parents were approached at their local paediatric CF centre, during either routine outpatient appointments or inpatient discharge appointments, after the patient's eligibility had been assessed by their physiotherapist. If eligible, patients and parents were informed of the study's purpose and procedure by their physiotherapist, provided with an information sheet each (see Appendix I.1 to I.2), and given the opportunity to ask questions. They were informed that they could make their decision on whether to take part within that appointment, or at their next outpatient routine appointment, but that the study would close after this.

Based on the theoretical and empirical literature, a moderate effect size was anticipated for this study (e.g. Horne et al., 1999; Bucks et al., 2009). A power analysis using G*power (Erdfelder, Faul & Buchner, 1996) calculated that to complete a multiple linear regression analysis with 2 to 4 predictors, a moderate effect size, and an alpha level of 0.05, a minimum sample of 23 would be needed to achieve a power of .80, and for correlations, a minimum sample size of 34. Clinician review of caseloads at the three paediatric CF centres suggested that each site would be able to recruit at a minimum 10 patients and 10 parents over a three-month period, equating to 30 patients and 30 parents. Therefore, this minimum sample size would allow reliable statistical analysis to be completed for regression analysis, and potentially for correlational analysis if this minimum sample size was exceeded.

Inclusion and exclusion criteria

For patients to be eligible for this study, they needed to: i) be aged between 12 to 17 years, ii) attend outpatient clinics at Leeds, Sheffield or Liverpool Paediatric CF centres, and iii) be taking nebulised mucolytic and/or antibiotic medications on a set-prescription basis through a I-nebuliser device. A set-prescription basis was required, since these medications can, on occasion, be prescribed on a PRN basis (i.e. as-needed), which would prevent calculation of adherence. Patients were excluded from the study if they: i) completed an inpatient stay during the data collection period, as

research has shown that hospital stays increase nebuliser adherence rates (Abbot & Gee, 1998), ii) were due to transition to adult care, as this would prevent follow-up, iii) were due to stop their I-neb treatment imminently, iv) appeared distressed in clinic, v) could not provide consent, vi) had a learning disability, as the measures have not been validated in this population, or vii) if they had a recorded lung function of FVB1 < 30% and were awaiting transplant. For parents to participate, they needed: i) a child who satisfies the above criteria, ii) capacity to consent to the study.

Ethical approval and considerations

Ethical approval was gained from the Proportionate Review Sub-committee of the NRES Committee York and Humber - Leeds West, in December 2018. Potential ethical issues of note will now be described. Firstly, while all participants provided informed consent to take part in the study, they were able to begin the study soon after being informed of it. Although this could theoretically have prevented participants from fully considering their participation, it was considered that the low risk and routine nature of this study, alongside the fact that outpatient appointments are 6-8 weeks apart, made this a practical option. Though adherence is a sensitive topic, it was not considered that this research would cause increased distress to participants or increased risk, since these discussions, and responding to risks that arise from low adherence, represent routine practice in outpatient clinics in these services. Finally, although data was stored securely and confidentially in accordance with the Data Protection Act (1998), it was only pseudo-anonymised rather than fully anonymised, through clinicians creating patient identifiers at their CF centres. It was considered that this would be important to allow data-checks, due to the potential complexity of some patients' adherence data.

One amendment was made following completion of study one, as a result of the CF-BMQ-Specific questionnaires being adapted. Ethical approval was gained from the Proportionate Review Sub-committee of the NRES Committee York and Humber - Leeds West, on 03/06/19 (see Appendix J).

Site recruitment and management

The researcher made contact with clinicians at the Liverpool and Sheffield sites, and site visits were completed to discuss the study's feasibility, including data-collection strategies and data-storage facilities. Once research and development approval were gained, study documentation was provided to all three sites, and communication was maintained throughout the study's recruitment phase.

Measures

Sociodemographic questionnaire

A brief sociodemographic questionnaire for parents was developed for the study. It collected the following details: parents' gender, age, ethnicity, religion, marital status, family composition (i.e. number of adults / children in the household), home postcode, occupation, and education level (see Appendix K). The final three items were collected as a means to determine socioeconomic status.

Patient demographic and health status questionnaire

A demographic and health status questionnaire was developed for completion by clinicians. This included the following patient information: age, gender, current FEV1%, number of inpatient admissions within the last year, and their nebulised medication prescription during the data collection period (see Appendix L).

The Beliefs about Medicines Questionnaire-Specific (BMQ-Specific)

The original BMQ-Specific has been described within the method chapter for Study 1 (see Chapter 2). In Study 2, four versions of this standard questionnaire were developed, one for each medication category (i.e. antibiotics and mucolytics) for completion by both participant types (i.e. patients and parents). First, the wording of the items was adapted by substituting 'nebulised antibiotic' or 'nebulised mucolytic' for the word 'medication' (e.g. the original BMQ item: 'my *medicine* disrupts my life' became either 'my *nebulised antibiotics* disrupt my life', or my *nebulised mucolytics* disrupt my life') (see Appendix M.1 to M.2). The BMQ-Specific is designed to be adapted in this manner for the specific medication of interest. To accommodate the change in respondent, items were altered from first person (patient perspective) to third person (parent perspective). For example, 'my nebulised antibiotics disrupts my life' became 'my *child's* nebulised antibiotics disrupts *their* life') (see Appendix N.1 to N.2).

The Cystic Fibrosis Beliefs about Medicines Questionnaire-Specific (CF-BMQ-Specific)

The CF-BMQ-Specific refers to two questionnaires that were developed in Study 1 to assess necessity and concern beliefs for nebulised medication categories in CF. The first, the CF-BMQ-A, was tailored to antibiotics, while the second, the CF-BMQ-M, to mucolytics. Importantly, although these questionnaires were developed separately for each nebulised medication category, the content of the final items were made identical (except for the substitution of 'antibiotics' vs. 'mucolytics'). These questionnaires were also adapted to be completed by parents in the same manner as for the

BMQ-Specific, described above. The four versions of the BMQ-Specific and CF-BMQ-Specific for this study can be seen in Table 12 below:

Table 12: *The BMQ-Specific and CF BMQ-Specific divided into four versions by nebulised medication category and respondent.*

		Respondent	
		Child	**Parent**
BMQ-Specific	**Mucolytic**	BMQ-Specific child mucolytic	BMQ-Specific parent mucolytic
	Antibiotic	BMQ-Specific child antibiotic	BMQ-Specific parent antibiotic
CF BMQ-Specific	**Mucolytic**	CF BMQ-Specific child mucolytic	CF BMQ-Specific parent mucolytic
	Antibiotic	CF BMQ-Specific child antibiotic	CF BMQ-Specific parent antibiotic

Brief Illness Perception Questionnaire (B-IPQ)

The Brief Illness Perception Questionnaire (B-IPQ) is a 9-item measure that has been designed to quickly assess cognitive and emotional representations of illness (Broadbent et al., 2006). It was developed from the Illness Perception Questionnaire-Revised, which has over 80 items and 9 subscales, by reducing each of these sub-scales to just one item. Five of the B-IPQ items assess cognitive representations of illness perceptions: consequences, timeline, personal control, treatment control, and identity; while two items assess emotional representations: concerns and emotional impact. These cognitive and emotional perceptions are measured on a single scale of 0-10, with higher scores indicating increased negative impact of the illness on that domain of an individual's life. The final two items examine their degree of understanding and perceived causal factors of the illness. The B-IPQ has been validated for use in adults (Broadbent et al., 2006) and has been adapted for use with parents and children (Sonney et al., 2017). The literacy level of this measure has been reported to be at the reading ability of 9- to 10-year-olds (Sonney et al., 2017), which is appropriate for this study's target sample.

For this study, the questionnaire was edited in several ways. First, the wording of the items was adapted to the participant group, by substituting 'CF' for the word 'illness' (i.e. 'How much does

your *illness* affect your life?' became 'How much does your *CF* affect your life?). This measure is designed to be adapted in this manner (see Appendix O.1 to O.2). The phrasing of the items was again altered for completion by parents as well as patients (i.e. 'How much does *your* CF affect *your* life?' became 'How much does *your child's* CF affect *their* life?). Finally, the decision was made to remove the final item from this questionnaire which considers cause, since it is considered of little relevance to genetic illnesses (Olsen, Berg & Wieb, 2008).

Measuring and calculating medication adherence

Adherence data for this study was collected through I-nebuliser devices. As described in detail in the introduction, these devices provide a 'gold standard' means to record adherence behaviour, through adaptive aerosol delivery and data-recording technology. These devices record both the date and time that medication is taken, and the dose inhaled, allowing information on how and when the device was used to be compared with prescription data, and adherence behaviour to be objectively calculated.

The richness of data provided by the I-nebuliser device allows adherence to be defined and calculated in several ways. First, an overall measure of adherence can be determined by calculating the percentage of times that the nebuliser was taken over the number of times it was prescribed over a set period of time. This calculation can lead to a value above 100% if the patient uses the dose more than prescribed. Second, one can determine how *consistently* the medication was taken, by calculating the percentage of days that each patient fully adhered to their medication. Third, a minimum standard measure can be determined by calculating the percentage of days that the device was used at least once. Most studies relating to the I-nebuliser device have defined and calculated adherence using the first measure alone (e.g. McNamara, 2009; Daniels et al., 2011; Ball et al., 2013), though others have used a combination of these measures (e.g. Latchford et al., 2008). To allow comparison to previous research adherence was calculated using the first measure in this study.

It is important to note that I-nebuliser devices code the dose successfully completed into three tiered categories: full, partial and none. 'Full' indicates that ≥75% of the dose has been successfully taken, while 'partial' indicates between 25% and 75%, and 'none' < 12.5%. For this study, the binary measure 'medication adhered to' was chosen to include such 'partial' recordings. This decision was made as clinicians report that a partial dose often represents a problem or malfunction with the device rather than a failure to adhere by the patient, while 'none' is considered to represent non-adherence, where patients activate the device, but do not complete it appropriately.

Unfortunately, I-nebuliser recordings do not discriminate between different medications taken with the same device, preventing adherence behaviour from being calculated for individual

medications. To overcome this difficulty, where patients took more than one medication through the same I-nebuliser device, clinicians elicited patients' typical patterns of medication use for each medication and used these to retrospectively identify which activations belonged to which medication. For instance, nebulised mucolytics are usually taken by patients at the start and end of each day, while nebulised antibiotics are typically taken in the afternoon. In instances where patterns were harder to discriminate, or varied over time, clinicians examined this data with patients to manually match it to the medication of interest. Importantly, this method of manually examining adherence data is routinely used in clinical practice, and while it is unlikely to be fully accurate, is the best method currently available for such cases. Also, some patients' prescriptions changed during the data-collection period (e.g. the dose frequency was modified, or treatment paused or ended). To accommodate this, prescription changes within the data-collection period were recorded, and adherence calculated accordingly.

Procedure

After being informed of the study, patients and parents who wished to participate were asked to complete the appropriate consent or assent form (see Appendix P.1 to P.3). Patients aged less than 16 years old completed the assent form, and required the consent of their parents to take part. Participants were given the option to start the study at the appointment where the study was introduced, or at their following outpatient appointment. In the appointment where participants started the study, hereafter referred to as *baseline*, both patients and parents were asked to complete several questionnaires. Physiotherapists acted as field researchers for this study and administered these questionnaires at a time convenient to the running of the clinics. They provided participants with an overview of the different questionnaires, explained that they needed to be completed independently (i.e. without parents' help in selecting answers, though they could clarify meaning), and encouraged questions. First, participants were asked to complete their appropriate version of the BMQ-Specifics and CF-BMQ-Specifics. Patients and parents within the 'antibiotic-only' or 'mucolytic-only' groups were given one BMQ-S questionnaire and one CF-BMQ-S questionnaire for their medication category, while those in the 'combined' group completed two BMQ-S questionnaires, and two CF-BMQ-S questionnaires, one each for each medication category. Before completing these questionnaires, patients and parents were made aware of which specific medication they were completing each medication belief questionnaire for, if appropriate. For each item in these questionnaires, participants were asked to rate how much they agreed with each belief statement (on a scale from 1: strongly agree to 5: strongly disagree). All participants were then asked to complete the patient or parent version of the B-IPQ, which again asked them to rate their agreement with the illness perception items (on a scale of 0 to 10). Finally, patients were asked to complete a questionnaire seeking to assess the accessibility and usability of the CF-BMQ-Specific questionnaire (see Appendix

Q). They were asked to rate how well they understood the questionnaire items, and how well they liked them, and to report any items that they did not understand or like. Parents were asked to complete a short sociodemographic questionnaire for themselves. On average, each questionnaire took approximately 5 minutes to complete. Therefore, patients and their parents in the 'mucolytics-only' or 'antibiotics-only' groups spent approximately 20 minutes completing these questionnaires, while those in the 'combined' group took approximately 30 minutes. Participants were thanked for their participation and reminded that the next part of the study would require access to their I-nebuliser device at their next outpatient appointment.

At patients' next routine outpatient appointment, named the *follow-up session*, which occur on average at 6- to 8-week intervals at the sites, patients' I-nebuliser data was downloaded by their physiotherapist. This data was then visually displayed through Insight software (Philips, Chichester, UK) and reviewed with patients and parents, to consider adherence levels and patterns, and data anomalies. Importantly, this method of examining the data represents routine practice at all three centres. Participants were then debriefed, thanked for their participation, and asked if they would like to receive a summary of the study's findings. Following this, clinicians reviewed patients' medical notes to complete the patient health and demographics form (see Appendix R). All data collection for this study took place between July 2019 and November 2019.

A visual representation of the procedure for phase 2 across the three nebulised medication categories can be seen in Table 13.

Table 13*: The procedure in phase 2 for baseline and follow-up for each medication group, for patients, parents and clinician.*

		Mucolytics-only		**Antibiotics-only**		**Combined**		
		Patient	Parent	Patient	Parent	Patient	Parent	Clinician
Baseline	Consent forms	✓	✓	✓	✓	✓	✓	
	BMQ-Specific (Child version)	✓		✓		✓✓		
	BMQ-Specific (Parent version)		✓		✓		✓✓	
	CF-BMQ-Specific (Child version)	✓		✓		✓✓		
	CF-BMQ-Specific (Parent version)		✓		✓		✓✓	
	B-IPQ (Child version)	✓		✓			✓	
	B-IPQ (Parent version)		✓		✓		✓	
	Questionnaire evaluating the CF-BMQ-Specific	✓		✓		✓		
	Sociodemographic questionnaire		✓		✓		✓	
Follow-up	I-Nebuliser data							✓
	Health questionnaire							✓

Note: The BMQ-Specifics and CF-BMQ-Specifics are identical in item contents, with only the item subject changing depending on the medication category of interest. The symbol '✓✓' denotes that this questionnaire was completed twice, once for each nebulised medication category.

Data analysis

All data analysis was completed using IBM Statistical Package for the Social Sciences (SPSS, version 26, 2018) with statistical significance set at $p<0.05$ throughout.

Before data analysis was completed, data was verified and cleaned, allowing identification of outliers, missing values and other irregularities. These items, and the subsequent actions taken, are

discussed in the appropriate sections. Although prior to inferential statistics all variables were assessed for parametric test assumptions, including normality and homogeneity, it was recognised that the very limited sample sizes reduced the validity of these tests. Therefore, the decision was made to be conservative and use non-parametric statistics in inferential analysis.

Descriptive statistics were used to summarise the samples' demographic and clinical characteristics, belief subscale scores and adherence behaviour. Categorical data was expressed as frequencies and percentages, while most non-categorical data was represented by means and standard deviations. It was reasoned that on balance the mean and standard deviation would offer the fairest representation of the data, since unlike the median and interquartile range they consider all the collected data, and were computable for all the groups, unlike the interquartile range which could not be calculated for the smallest group. In addition, the internal reliability of the BMQ-S and CF-BMQ-S necessity and concern subscales were examined using Cronbach alpha. This was not examined for the B-IPQ, since this measure only has one question for each illness representation. However, due to the limited sample conclusions from this analysis were limited, this will be discussed further in the relevant section.

Inferential statistics used included correlational analysis and tests of difference. The former was used to identify significant relationships between continuous and/or ordinal variables and was completed through Spearman's rank correlation (ρ). Correlation coefficients between 0-0.39 were interpreted as weak, those of 0.4-0.69 moderate, and those above 0.7 strong, in accordance with general opinion (e.g. Mukaka, 2012). Tests of difference were used to examine whether belief subscales and adherence scores significantly differed between categorical variables and were completed through Mann-Whitney U tests. Several of these tests were however, not computed due to the limited sample and this is highlighted in the relevant sections. Similarly, although multiple comparisons were completed in this study, no adjustments were made for mass significance, since this study was examined as a pilot.

Finally, the planned multiple linear regression analysis to examine whether subscales from the medication questionnaires could predict adherence behaviour was not completed, since the study's sample size was much smaller than expected, which would have led to inadequate power, increasing the chance of type-II error.

Chapter 6: Study Two Results

Overview

This results section will firstly describe this sample's demographic and clinical characteristics before considering patients' adherence behaviour to nebulised medications overall, by medication category, and by demographic and clinical characteristics. Following this, the medication beliefs of adolescent patients and their parents will be presented by questionnaire version (i.e. original or modified) and nebulised medication category (i.e. antibiotics or mucolytics). The bivariate relationships between belief subscales will then be assessed, followed by their relationship to objectively recorded medication adherence. Finally, patients' and parents' illness perceptions will be reported, and their relationship to adherence behaviour.

Descriptive statistics

Sample characteristics

Between June 2019 and November 2019, 27 patients (Leeds = 14, Sheffield = 8, Liverpool = 5) and 25 of their parents were approached regarding the study across the three sites. Fewer parents than patients were approached, as two older adolescent patients attended their clinics alone. In total, 16 patients (Leeds = 7, Sheffield = 6, Liverpool = 3), and 14 parents (Leeds = 5, Sheffield = 6, Liverpool = 3) agreed to participate, equating to an average response rate of 58%. Reasons provided by patient-and-parent pairs for not wishing to take part included not being interested in research and not having the time.

Unfortunately, data for four of the patient-and-parent pairs who started the study is not included in this analysis. For three of these pairs, a significant delay in data collection occurred, as they either did not attend follow-up clinic appointment(s) or attended but forgot to bring I-nebuliser device, preventing their adherence data from being downloaded. Due to the timescale of this project, it was not possible to delay data acquisition further. In addition, one patient's I-nebuliser device malfunctioned in the data collection period, making their adherence data irretrievable. The demographic and clinical characteristics of participants is summarised in Table 14 below.

Table 14: Demographic and clinical characteristics of each patient and their parent.

No	**Patient**							**Parent**		
	Gender	Age	FEV1%	Inpatient stays in the last year	Pseudomonas growths in the last year	Abscess growths in the last year	I-nebuliser medication prescription	Gender	Age	Relationship
1	Female	13y 0m	67	0	1	0	DNase, Promixin	Female	44	Mother
2	Male	12y 2m	100	0	0	0	DNase	Female	47	Mother
3	Female	16y 8m	95	0	2	0	DNase, Promixin	Female	40	Mother
4	Female	16y 1m	57	2	0	0	DNase			
5	Female	14y 11m	96	1	0	0	DNase	Male	46	Father
6	Male	12y 8m	74	1	0	0	DNase	Female	52	Mother
7	Female	12y 2m	56	5	13	0	DNase, Promixin, Hypertonic Saline	Female	30	Mother
8	Female	16y 0m	62	5	0	12	DNase			
9	Female	13y 8m	77	2	0	0	DNase, Promixin, Hypertonic Saline	Female	43	Mother
10	Male	14y 2m	76	0	0	0	DNase	Male	45	Father
11	Female	13y 7m	113	4	0	0	DNase	Female	32	Mother
12	Female	15y 0m	71	4	0	0	DNase	Female	48	Mother

Table 14 shows that most patients (75%, n=9) and parents (80%, n=8) who participated in the study were female, that the average age of patients was 14.17 years (S.D 1.56), and parents 42.7 years (S.D. 6.94). Patients' mean FEV1% was 78.7%, although large variability was found between participants (SD=18.31%). These FEV1% ratings were equally divided between normal lung function (n=4; >90%), and mild (n=4; 70-89%) and moderate lung disease (n=4; 40-69%). Most patients (n=8; 66%) had at least one inpatient stay over the previous year. Of these patients, half (n=4) had two or fewer inpatient stays, while the other half (n=4) had four to five inpatient stays. Most of the patients in this sample did not acquire a *pseudomonas aeruginosa* infection (75%, n=9) or grow abscesses within the last year (91.6%, n=11), although large variability existed between patients. While two of the three patients who did develop a *pseudomonas aeruginosa* infection did so on two occasions or fewer, the third developed this infection 13 times. Similarly, the one individual who developed abscesses within the last year developed them 12 times. Since only one individual experienced abscess growths within this sample, this clinical characteristic was not examined further.

In total, across all 12 patients 18 medication prescriptions were delivered through I-nebuliser devices, consisting of 12 prescriptions of DNase, 4 of Promixin, and 2 of Hypertonic Saline. Most patients were prescribed DNase alone (66%; n=8), with the remaining patients taking either DNase and Promixin (16.6%; n=2) or DNase, Promixin and Hypertonic Saline (16.6%; n=2). Patients prescribed DNase alone were required to use their I-nebuliser once a day; those also taking Promixin were required to use it three times, and those who also took Hypertonic Saline, four times.

Adherence data characteristics

It is important to note that while 18 medications were delivered through the I-nebuliser devices, adherence data was only calculated for 17 of these, since one patient's hypertonic saline was prescribed on an as-required rather than regular basis, preventing calculation of an overall adherence percentage. The mean number of days over which the I-nebuliser adherence data was collected was 53.41 (7.63 weeks), although large variability occurred between individuals (S.D. 23.57, range 11 – 88 days). Further inspection revealed that the mean length of time between the baseline and follow-up appointment was much lower at the Sheffield site (29 days), than at the Liverpool (56 days) or Leeds (69 days) sites. Importantly, the timespan over which adherence data was collected was similar between the medication categories; it was only slightly lower and more variable for mucolytics (M = 52.54, SD = 24.79, range 11-88) than antibiotics (M = 56.25, SD = 22.17, range 25-73).

Adherence to nebulised medication in adolescent patients with CF

Overall adherence

The overall mean adherence percentage for both categories of nebulised medications across patients was 69.55% (median 77.09), although large variability was found between patients (S.D. 28.75, range 2.13-100). Figure 4 highlights this variability by displaying each patient's adherence percentage to their nebulised medication(s).

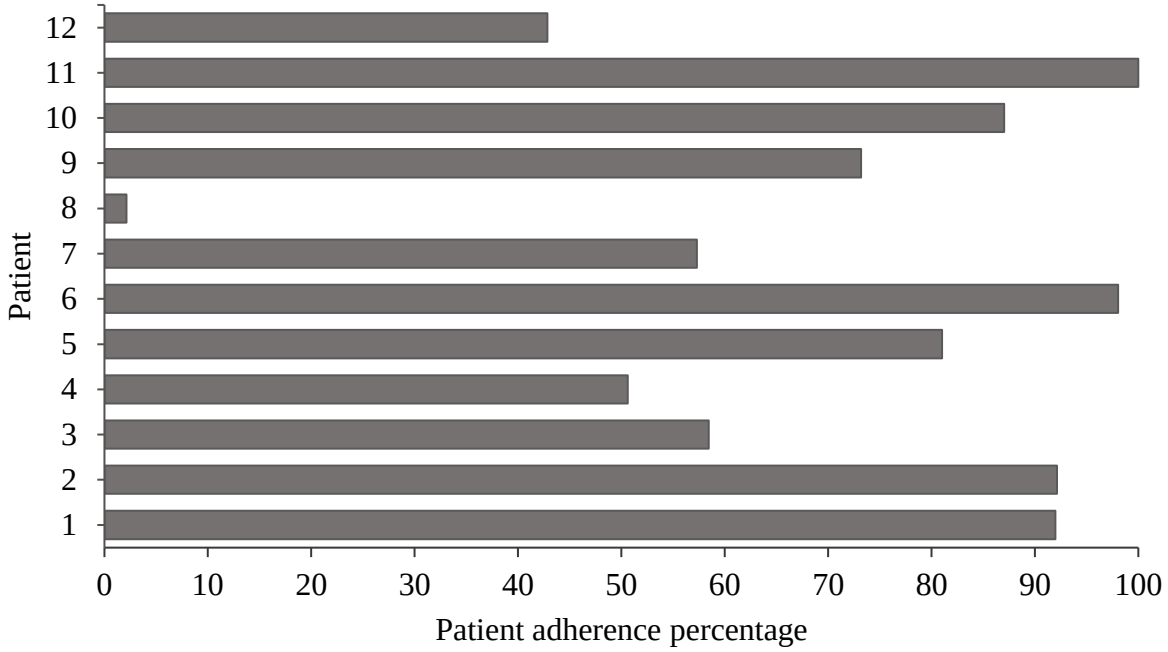

Figure 4: Patient adherence percentage to their nebulised medications.

Figure 4 shows that while 50% (n=6) of adolescent patients adhered at least 80% of the time to their I-nebulised medication prescriptions, 42% (n=5) adhered to them less than 60% of the time. Of particular note within this low adherence group is Participant 8, who adhered just 2.13% of the time. Although this value was not considered an outlier statistically, it varies greatly from the mean, and from the next-lowest adherence value of 42.86%.

Adherence by medication type

Average adherence percentages were also calculated separately by antibiotic (n=4) and mucolytic (n=13) medication categories. Findings showed that, on average, patients were more adherent to mucolytic (mean 71.05, median 81.01) than antibiotic medications (mean 66.26, median 65.55), but that adherence was more variable for mucolytic (S.D. 30.11, range 2.13 – 100), than for

antibiotic medications (S.D. 20.71, range 46.43 – 87.5). This difference was not however, found to be significant (*U*=21, *p*=.57).

Examination of the distribution of adherence behaviour between the medication categories showed a similar level of high adherence for both, with 53% of nebulised mucolytic medication prescriptions and 50% of antibiotic prescriptions adhered to at least 80% of the time by patients. However, a higher rate of low adherence was found for antibiotic than mucolytic medications; 50% of antibiotic prescriptions were adhered to less than 60% of the time, compared to 31% of mucolytic medication prescriptions.

Adherence by sociodemographic and clinical characteristics

Differences in adherence behaviour by patients' demographic and clinical characteristics can be seen in Table 15 below.

Table 15: *Examining differences in nebulised medication adherence by patients' demographic and clinical characteristics.*

Patient demographic and clinical factors		Adherence Mean and SD	p
Gender	Male (n=3)	92.40 (5.50)	.079
	Female (n=9)	61.94 (29.46)	
Age	<170 months (n=6)	85.43 (16.74)	.041
	>170 months (n=6)	53.68 (30.55)	
FEV1%	<75% (n=6)	57.15 (35.10)	.150
	>75% (n=6)	81.97 (14.74)	
Inpatient stays	Yes (n=8)	63.14 (32.34)	.308
	No (n=4)	82.40 (16.14)	
Pseudomonas growths	Yes (n=5)	79.00 (22.44)	.465
	No (n=7)	62.81 (32.44)	

Two-tailed significance test using Mann Whitney U.

Table 15 shows that although adherence to nebulised medications was higher for males (92.40) than for females (61.94), this difference only approached significance ($U = 4$, $p = .079$). A

significant difference was, however, found for age; patients aged under 170 months had significantly higher and less variable adherence (85.43, 16.74) than those aged over 170 months (53.68, 30.55) ($U = 5$, $p < 0.05$). For FEV1% ratings adherence behaviour was found to be lower (57.15 vs. 81.97) and more variable (35.10 vs. 14.74) for those with low (<75%) rather than high ratings (>75%), though this difference was not found to be significant. Finally, patients who had an inpatient stay within the last year had lower (63.14 vs. 82.40) and much more variable (32.34 vs. 16.14) adherence behaviour than individuals who had not had a hospital stay, and those who had experienced a pseudomonas growth in the last year had higher adherence rates than those who had not (79.00 vs. 62.81). These differences, too, were not found to be significant.

The relations between patients' age, FEV1% ratings, and adherence behaviour were also examined. A moderately strong negative relationship was found between patient age and adherence ($rs(12) = -.616$, $p = .032$) and a moderately strong positive relation between patients' FEV1% ratings and adherence ($rs(12) = .636$, $p = .026$), both of which were significant. A moderate negative relationship was found between inpatient stays and adherence ($rs(12) = -.502$, $p = .096$) and a weak positive relationship between pseudomonas growths and adherence ($rs(12) = .223$, $p = .486$), neither of which were significant.

The Belief about Medicines questionnaires

Necessity and concern beliefs for both categories of nebulised medications were elicited separately, using both the original BMQ-Specific and the CF-BMQ-Specific. Importantly, the CF-BMQ-S concern subscale had 7 items, causing the summed score to range from 7 to 35, while the necessity subscale for the CF-BMQ-S, and the necessity and concern subscales for the BMQ-S, all have 5 items, so range between 5 and 25. To allow comparisons between these measures in analysis and calculation of necessity-concern differentials, these summed scores were computed to means, by dividing each subscale by the number of items in that scale. This provided a range of 1 to 5 for the necessity and concern scales, and between -4 and +4 for the necessity-concern differential. When the BMQ-S was developed, the elicited necessity and concern belief scores were categorised into high- or low-strength categories to allow description, through the use of a midpoint (Horne, et al. 1999). The midpoint for this study was placed at 3, similarly to Horne et al., (2004) when they used this same scale. It is also important to note that the final item within the CF-BMQ-S necessity subscales 'I only need to take my nebulised medications when I am unwell' was reverse scored, as the nature of this item means that increased disagreement, rather than agreement, relates to adherence. Finally, although all 12 patients and 10 parents completed these questionnaires, one patient only completed one side of each, so the decision was made to remove their data from the analysis. No other missing data occurred in these questionnaires.

Examining reliability of the measures

In order to assess the internal reliability of the original and adapted measures, Cronbach alpha was calculated for necessity and concern belief subscales across all versions of the medication belief questionnaires. These calculations are presented in Table 16.

Table 16*: Cronbach alpha values for each subscale in each version of the medication belief questionnaires.*

		Patient		**Parent**	
		Antibiotic (N=3)	Mucolytic (N=11)	Antibiotic (N=4)	Mucolytic (N=10)
Measure					
Original BMQ-S	Necessity (5 items)	0.84	0.39	-0.40	0.87
	Concerns (5 items)	-5.30	0.77	0.73	0.37
CF-BMQ-S	Necessity (5 items)	0.73	0.74	0.73	0.91
	Concerns (7 items)	-2.50	0.69	-1.42	0.61

Debate exists within the literature regarding the alpha value needed to ensure the internal consistency of a measure, although accepted thresholds often range between 0.70 and 0.95 (e.g. Bland & Altman, 1997; Devellis, 2003; Polit & Beck, 2004). In this study, only half (8/16) of the subscales, across the original and revised BMQ-Specifics for patients and parents, exceeded this minimum value of 0.70. Also, half (4/8) of these values on the antibiotic questionnaire versions were found to be negative. Further data inspection showed that removal of just one item in 5/8 of these subthreshold subscales would have allowed the threshold to be met for all but the Parent BMQ-S mucolytic concern subscale, and both Patient and Parent CF-BMQ-S antibiotic concerns subscales. Low values generally suggest that multidimensionality is present within a subscale, with negative values also suggesting inverse relations. However, the low sample sizes, particularly for the antibiotic versions, may have underpinned these findings. Although the literature is not consistent on the sample size required to ensure the reliability of Cronbach alpha (e.g. Yurdugul, 2008; Samuels, 2015; Bonnett & Wright, 2015; Conroy, 2016) there is some consensus that reliability analysis should not be completed for samples of less than 30 (e.g. Yurdugul, 2008; Conroy, 2016). In view of this, this study's sample sizes are inadequate to reliably examine the internal consistency of the subscales. Therefore, great

caution was applied in considering these internal reliability findings, and the decision was made to retain all items and to complete further analysis on an exploratory basis.

Examination of medication beliefs

Descriptive statistics for the necessity and concern subscales for the BMQ-Specific and CF-BMQ-Specific are presented in Table 17 by medication category (i.e. antibiotic or mucolytic) and respondent (patient or parent).

Table 17*: Descriptive statistics for the necessity and concern subscales for the BMQ-Specific and CF-BMQ-Specific.*

		Mean and Std. Deviation			
		Patient		**Parent**	
Measure		Antibiotics (N=3)	Mucolytics (N=11)	Antibiotics (N=4)	Mucolytics (N=10)
BMQ-S	Necessity	3.73 (1.10)	3.62 (0.49)	4.55 (0.25)	3.80 (0.69)
	Concerns	1.93 (0.23)	2.00 (0.66)	2.65 (0.75)	2.04 (0.55)
CF-BMQ-S	Necessity	4.27(0.64)	4.54 (0.48)	4.65 (0.30)	4.34 (0.63)
	Concerns	2.19 (0.22)	2.00 (0.60)	2.75 (0.47)	2.34 (0.61)

Table 17 shows that mean necessity beliefs were high across all versions of the BMQ-S and CF-BMQ-S. Indeed, all exceeded a mean value of 3, and several exceeded a value of 4. Interestingly, mean necessity beliefs for the CF-BMQ-S measures exceeded 4 across medications and respondents, while for the BMQ-S measures, only the parent antibiotic version exceeded this value. Examination of these differences in mean necessity scores between the original and adapted measures showed that mean mucolytic necessity belief scores for patients (U = 14.5, p < .001) and parents (U = 22.5, p <. 05) were significantly higher on the CF-BMQ-S than the BMQ-S, but that those for antibiotic beliefs were not.

Concern belief mean scores were much lower than necessity belief scores across all versions of the questionnaires, all falling at or below a mean value of 2.75. All mean concern scores were higher for the CF-BMQ-S than BMQ-S, apart from the patient-mucolytic-concern ratings, which were

the same across both. None of these increases in mean concern scores from the BMQ-S to the equivalent CF-BMQ-S were, however, found to be significant.

Differences in mean belief scores will now be considered between medication categories and respondents for each measure separately. On the BMQ-S, patient necessity and concern beliefs' mean ratings were found to be very similar for antibiotic and mucolytic medications. Antibiotic medications gained a slightly higher necessity score (3.73 vs. 3.62), and slightly lower concern score (1.93 vs. 2.00). However, it is interesting to note that antibiotic necessity ratings were twice as variable as those for mucolytics. For parents, antibiotic necessity (4.55 vs. 3.80) and concern (2.65 vs. 2.04) mean belief scores were much higher than for mucolytic medications. This difference was found to be significant for necessity beliefs (U = 4, p <. 05) but not for concerns. Finally, although parents' mucolytic mean necessity and concern scores were similar to those of their children (3.80 vs. 3.62, 2.04 vs. 2.00), parents' antibiotic mean necessity and concern ratings were much higher than their children's (4.55 vs. 3.73, 2.65 vs 1.93). These differences in mean belief scores between patients and parents for antibiotic medications were non-significant for necessity and concern beliefs.

On the CF-BMQ-S, patients' necessity beliefs were lower for antibiotics than mucolytic medications (4.27 vs. 4.54), and concern beliefs higher for antibiotics than mucolytics (2.19 vs. 2.00). Neither of these differences were found to be significant. Parents' mean necessity and concern scores were found to be lower for mucolytics (4.34 vs. 2.34) than for antibiotics (4.65 vs. 2.75), but again neither of these differences were significant. Parents' belief ratings were found to differ from their children's for both mucolytics and antibiotics. For antibiotic medications, parents' necessity and concern mean scores were higher than those of their children (4.65 vs. 4.27, 2.75 vs. 2.19), while for mucolytic medications, parents' necessity scores were lower than their children's (4.34 vs. 4.54), and their concern beliefs higher (2.34 vs. 2.00). All of these differences in mean belief ratings between patients and parents were found to be non-significant; though the increase in mean antibiotic concerns score in parents from patients was found to approach significance (U = 1, p = .067).

Examining correlations between the original and adapted BMQ-S measures

Correlations were computed between necessity and concern subscale scores in the original and adapted BMQ-S measures, in order to assess whether equivalent belief subscales scores in the measures positively related. They were also computed between patient and parent necessity and concern scores, in order to examine whether patients' beliefs related to those of their parents in the equivalent measure. These correlations are first presented for antibiotics and then for mucolytics.

Table 18*: Correlations between the subscales of the BMQ-Specific and CF-BMQ-Specific across respondents for Antibiotic medications.*

Measure			BMQ-Antibiotic				CF-BMQ Antibiotic			
			Patient		Parent		Patient		Parent	
			Necessity	Concerns	Necessity	Concerns	Necessity	Concerns	Necessity	Concerns
BMQ-Antibiotic	Patient	Necessity	1	.000 .500	.866 .167	-.500 .333	1.0* .01	-.500 .333	.866 .167	-.500 .333
		Concerns		1	.500 .333	.866 .167	.000 .500	.886 .167	.500 .333	.866 .167
	Parent	Necessity			1	.316 .342	.866 .167	.000 .500	.000 .500	-.500 .250
		Concerns				1	-.500 .333	1.0* .01	.775 .113	632 .184
CF-BMQ Antibiotic	Patient	Necessity					1	-.500 .333	-.866 .167	-.500 .333
		Concerns						1	.866 .167	1.0* .01
	Parent	Necessity							1	.544 .228
		Concerns								1

Note: * = $p \leq 0.01$

Table 18 shows that patients' necessity and concern belief subscale scores in the BMQ-S positively related to the equivalent subscales in the CF-BMQ-S for antibiotic medications. However, for parents, only concern beliefs positively related across the measures, with necessity beliefs showing no correlation. All these positive correlations were at least moderate in strength, with the relation between patient antibiotic necessity beliefs between the original and revised measure, showing a significant and perfect correlation ($rs(3) = 1$, $p < 0.05$).

Relations between patient and parent necessity and concern subscale scores in both the BMQ-S and CF-BMQ-S can also be viewed in Table 18. For the BMQ-S these findings showed that relations between patient and parent necessity and concern beliefs were positive and strong. While for the CF-BMQ-S, although a significant and perfect correlation was found between patients' and parents' concern beliefs ($rs(3) = 1$, $p < 0.01$), the relation between patients' and parents' necessity beliefs was strongly negatively correlated.

Table 19*: Correlations between the subscales of the BMQ-Specific and CF-BMQ-Specific across respondents for Mucolytic medications.*

Measure			BMQ-Mucolytic				CF-BMQ Mucolytic			
			Patient		Parent		Patient		Parent	
			Necessity	Concerns	Necessity	Concerns	Necessity	Concerns	Necessity	Concerns
BMQ-Mucolytic	Patient	Necessity	1	-.213 .264	.326 .196	-0.82 .417	.428 .095	-.72 .417	.670* .024	.231 .275
		Concerns		1	.505 .083	.233 .273	-.452 .081	.860* .000	.376 .160	.103 .396
	Parent	Necessity			1	-.252 .241	.057 .442	.588* .048	.511 .065	-.300 .200
		Concerns				1	-.571 .054	.389 .150	-.494 .073	.663* .018
CF-BMQ Mucolytic	Patient	Necessity					1	-.379 .125	.331 .192	.017 .483
		Concerns						1	.165 .336	.392 .149
	Parent	Necessity							1	.165 .336
		Concerns								1

Table 19 shows that patient necessity and concern belief subscale scores in the BMQ-S positively related to the equivalent subscales in the CF-BMQ-S for mucolytic medications. Both of these relations were of a moderate strength, with the relation between patient mucolytic necessity beliefs between the original and adapted measures reaching significance ($rs(11) = .860$, $p < 0.05$). Similarly, for parents, both necessity and concern beliefs positively correlated across the measures, and both were of a moderate strength, with the relation between necessity beliefs between the measures approaching significance ($rs(9) = .511$, $p = 0.65$), and that for concerns reaching significance ($rs(9) = .663$, $p < 0.05$).

Relations between patient and parent necessity and concern subscale scores in both the BMQ-Specific and CF-BMQ-Specific can also be viewed in Table 19. Findings showed that, although the relations between patients' and parents' necessity and concern subscale belief scores were positive in both the BMQ-S and CF-BMQ-S, they were all weak in strength and none were significant.

Beliefs about medicines and their relationship to medication adherence

Table 20 shows that although all the correlations between beliefs and adherence behaviour were non-significant, the strength of these relations differed between medication categories, respondents, and belief measures, with the strongest relations occurring within antibiotic medications. These relationships will now be considered in detail. First, the relationships between patient mucolytic beliefs, as measured by the BMQ-S and CF-BMQ-S, and adherence behaviour will be examined and compared with those found for antibiotic medications. These same relations will then be examined and compared for parents, before they are considered between respondents.

Table 20*: Examining correlations between necessity and concern belief subscales, including the differential, as examined by the BMQ-Specific and CF-BMQ-Specific, to adherence behaviour for antibiotic and mucolytic medications.*

			Respondent			
Measure	Medication Category	Belief type	Patient		Parent	
			rs	p	rs	p
BMQ-S	Mucolytic	Necessity	-.253	.226	.409	.120
		Concern	.279	.203	.135	.355
		Differential	-.220	.258	.231	.260
	Antibiotic	Necessity	-.500	.333	-.316	.342
		Concern	-.866	.167	-.400	.300
		Differential	.500	.333	.200	.400
CF-BMQ-S	Mucolytic	Necessity	-.373	.129	.118	.372
		Concern	.191	.287	-.043	.453
		Differential	-.456	.080	.103	.388
	Antibiotic	Necessity	-.500	.333	.258	.371
		Concern	-.500	.333	-.316	.342
		Differential	.500	.333	.800	.100

Significance testing was one tailed.

Patient mucolytic necessity beliefs and the necessity-concerns differential were found to negatively correlate with adherence to mucolytic medications, while concern beliefs were found to positively correlate with adherence. This same pattern occurred in both the BMQ-S and CF-BMQ-S. These relations were all weak in the BMQ-S, while in the CF-BMQ-S, the necessity-concerns

differential was found to moderately relate to adherence behaviour, with the latter approaching significance ($rs(11) = -.456$, $p = 0.80$).

For antibiotics, patients' necessity and concern beliefs were both found to negatively relate to adherence behaviour, while the differential was found to positively relate with adherence. This same pattern was found in the BMQ-S and CF-BMQ-S, with all relations occurring at a moderate level, apart from the correlation between antibiotic concern beliefs in the BMQ-S which was strong.

For parents, different patterns were found between mucolytic beliefs assessed by the BMQ-S and CF-BMQ-S, and adherence behaviour. For the BMQ-S, parents' necessity and concern beliefs, and the necessity-concern differential, were all found to positively relate to their child's adherence behaviour. Although these relations were weak, apart from that between necessity beliefs and adherence, which was moderate. The CF-BMQ-S, like the BMQ-S, found positive relations between necessity beliefs and the differential, but these relations were weaker. However, unlike for the BMQ-S, the CF-BMQ-S concern scale negatively related to adherence. The patterns and strength of these relations in both measures did not closely resemble those of their children for either questionnaire. Most notably, for the BMQ-S, while patients' necessity beliefs and the necessity-concerns differential negatively correlated with adherence, those of parents positively correlated (e.g. -.253 and -220 vs. .409 and .231), with the same pattern found for the CF-BMQ-S (e.g. -.373 and -456 vs .118 and .103). Also, for the CF-BMQ-S, while patients' mucolytic concerns were found to positively relate to adherence, those of parents were found to negatively relate, although both relations were very weak.

Again, for parents, different patterns were found between antibiotic beliefs and adherence behaviour between the BMQ-S and CF-BMQ-S. Necessity and concern beliefs as measured by the BMQ-S were found to negatively relate to adherence, with this relationship reaching a moderate strength for concerns, while the differential had a weak but positive relationship to adherence. For the CF-BMQ-S, although concerns also showed a moderate (albeit slightly weaker) relation to adherence, necessity beliefs showed a weak positive, rather than moderate negative relationship, and the differential showed a much stronger relationship (.200 vs .800). The relational pattern between beliefs and adherence behaviour for the BMQ-S matched those shown by their children for the equivalent measure, although the relations were all weaker than for the parent measure. For the CF-BMQ-S, the pattern and strength of relations differed. Most notably, necessity beliefs were negatively related to adherence for children but positively related for parents (-.500 vs. .258), and while the relationship between concerns and adherence was weaker for parents than for their children (-.500 vs. -.316), the relationship between the differential was stronger for parents than for their children (.800 vs .500).

To further examine the relations between medication beliefs and adherence behaviour the data will now be presented in Tables 21 (for nebulised antibiotics) and Table 22 (for nebulised mucolytics) and inspected on an individual level.

Table 21: *Individual adherence and belief subscale scores for antibiotic medications, for both patients and parents, in the BMQ-Specific and CF-BMQ-Specific.*

No.	**Antibiotics adherence %**	**Patient belief score for antibiotics**						**Parent belief score for antibiotics**					
		BMQ Necessity	BMQ Concern	BMQ Differential	CF-BMQ Necessity	CF-BMQ Concern	CF-BMQ Differential	BMQ Necessity	BMQ Concern	BMQ Differential	CF-BMQ Necessity	CF-BMQ Concern	CF-BMQ Differential
1	87.50	3.00	1.80	1.20	3.80	2.14	1.66	4.20	2.40	1.80	4.80	2.71	2.09
2													
3	80.41							4.80	2.80	2.00	4.80	2.43	2.37
4													
5													
6													
7	50.70	5.00	1.80	3.20	5.00	2.00	3.00	4.60	1.80	2.80	4.20	2.43	1.77
8													
9	46.43	3.20	2.20	1.00	4.00	2.43	1.57	4.60	3.60	1.00	4.80	3.43	1.37
10													
11													
12													

Table 21 shows that all adolescent patients' and parents' mean necessity scores fell at or above the midpoint value of 3 across the original and revised measures, showing that all participants held strong beliefs about the necessity of their nebulised antibiotic medications. For concerns, all patients' mean scores, and all but one of parents' mean scores, fell below midpoint, in both the original and revised questionnaires, indicating that all patients and nearly all parents held weak concerns about adverse effects from these medications. All differential subscale scores were positive, which shows that, for both patients and parents, beliefs in the necessity of their nebulised antibiotic medications outweighed their concerns in both the BMQ-S and CF-BMQ-S.

Regarding individual belief scores and adherence rates for nebulised antibiotics, scores for patients 7 and 9 are particularly notable. Patient 7, despite reporting the highest possible level of necessity beliefs and low concern beliefs, and their parent showing a similar belief pattern, adhered to nebulised antibiotics just 50.07% of the time. Patient 9 and their parent reported the highest concern scores in both measures and had the lowest adherence rate of 46.43%.

Table 22: *Individual adherence and subscale scores for mucolytic medications, for both patients and parents, in the BMQ-Specific and CF-BMQ-Specific.*

No.	**Mucolytic(s) adherence %**	**Patient belief score for mucolytics**						**Parent belief score for mucolytics**					
		BMQ Necessity	BMQ Concern	BMQ Differential	CF-BMQ Necessity	CF-BMQ Concern	CF-BMQ Differential	BMQ Necessity	BMQ Concern	BMQ Differential	CF-BMQ Necessity	CF-BMQ Concern	CF-BMQ Differential
1	96.43	2.60	2.40	.20	3.60	2.00	1.60	4.00	2.20	1.80	4.00	2.00	2.00
2	92.13	4.00	1.60	2.40	5.00	1.43	3.57	4.00	1.20	2.80	5.00	1.14	3.86
3	36.49							3.80	1.80	2.00	4.60	2.14	2.46
4	50.62	4.00	1.00	3.00	4.80	1.00	3.80						
5	81.01	3.40	1.20	2.20	5.00	1.43	3.57	3.60	1.60	2.00	4.00	2.29	1.71
6	98.04	3.80	2.00	1.80	3.80	2.43	1.37	4.00	2.00	2.00	4.60	2.14	2.46
7	63.89	4.20	2.00	2.20	4.60	1.86	2.74	3.80	2.20	1.60	5.00	2.71	2.29
8	2.13	3.80	3.20	.60	4.60	2.86	1.74						
9	96.15	3.60	2.80	.80	4.80	2.71	2.09	5.00	1.60	3.40	5.00	2.29	2.71
10	87.04	4.00	1.80	2.20	4.60	2.57	2.03	4.00	3.20	.80	4.00	3.43	.57
11	100	3.40	2.40	1.00	4.00	2.14	1.86	3.60	2.40	1.20	4.20	3.00	1.20
12	42.86	3.00	1.60	1.40	4.20	1.57	2.63	2.20	2.20	.00	3.00	2.29	.71

Table 22 shows that, on the BMQ-S, nearly all of patients' (91%) and parents' (90%) mean necessity scores fell at or above the mid-point value of 3, while for the CF-BMQ-S, all patients mean scores fell at or above this midpoint for both patients and parents. For concerns, all but one patient (92%) and one parent (90%) held mean belief scores which fell below the midpoint in the BMQ-S, while on the CF-BMQ-S all fell below midpoint for patients, and two (20%) above midpoint for parents. Together, these findings suggest that almost all patients and parents held strong beliefs regarding the necessity of nebulised mucolytic medications, and weak beliefs regarding adverse effects from these medications. All differential scores were positive across the measures and respondents, apart from one parent score, which was neutral on the BMQ-S. This shows that all patients' and nearly all parents' beliefs in the necessity of nebulised mucolytic medications outweighed their concerns, across the original and revised measures.

Regarding individual belief scores and adherence rates for nebulised mucolytics, those for patient 8 are of most interest. Patient 8 reported the highest concern subscale scores in both measures and had the lowest adherence rate of just 2.17%.

Illness perceptions

Descriptive statistics for patient and parent illness perceptions and statistical testing of the difference in belief strength between them, are shown in Table 23.

Table 23*:* Descriptive statistics for the B-IPQ subscales for patient and parent.

	Mean and Std. Dev		Difference
Illness perceptions	Patient (N=11)	Parent (N=10)	p
Consequences	5.55 (2.16)	6.10 (3.35)	.500
Timeline	9.18 (1.66)	10.0 (0)	.083
Personal control	6.73 (1.85)	5.50 (2.37)	.128
Treatment control	8.27 (2.41)	9.30 (0.82)	.597
Identity	4.45 (1.64)	5.80 (2.15)	.154
Illness concern	5.36 (1.63)	8.50 (2.42)	.005*
Coherence	7.73 (1.60)	8.30 (1.89)	.367
Emotional representation	4.55 (3.73)	6.40 (2.91)	.189

Significance testing was two tailed.

Overall, Table 23 shows that all illness perceptions across respondents were either moderately (i.e. >3) or strongly held (i.e. >7), and that all mean illness perception scores were higher for parents than patients, except for personal control, which was higher for patients. Patients' strongly held illness perceptions were timeline, treatment control and coherence. This suggests that the majority of adolescent patients percieved their CF to be chronic, their treatments to be efficacious, and reported understanding their illness well. It is interesting, however, to note that larger variability was present in the mean scores for treatment control and emotional representation. Parents' strongly held illness perceptions also consisted of timeline, treatment control and coherence, but with the addition of illness concern. Interestingly, for parents, no variability occurred within timeline, and very little

within treatment control; while within consequences and emotional representations the largest variability was noted.

The largest mean subscale differences between childrens' and parents' illness perceptions were for illness concern, emotional representation, personal control and illness identity. Parents therefore reported higher levels of concern about the illness, increased heights of emotional distress, a lower sense of perceieved personal control and a higher experience of symptoms, than did their children. Although all subscale differences between patients and parents were examined statistically, only parents' illness concern beliefs were found to be significantly higher (8.50 vs. 5.36) than those of their children (U = 15.5, $p < 0.05$), although the difference between timeline (10.00 vs. 9.18) also approached significance (U = 40, p = .083).

Illness perceptions and medication adherence

Correlations were completed to examine whether illness representations reported by adolescent patients and their parents relate to adherence to nebulised mucolytic medications. These relations were only computed for mucolytic medications due to the extremely limited sample size for antibiotic medications.

Table 24*: Correlations between patient and parent B-IPQ subscales and adherence to nebulised mucolytic medications.*

Illness perception	Patient N=11		Parent N = 10	
	rs	p	rs	p
Consequences	.312	.350	.116	.750
Timeline	-.202	.551	.	.
Personal control	.077	.822	.414	.235
Treatment control	.077	.821	-.697*	.025
Identity	-.139	.683	-.447	.196
Illness concern	-.374	.257	-.266	.457
Coherence	.065	.848	.544	.104
Emotional representation	-.249	.461	.357	.311

Significance testing was two-tailed.

Table 24 shows that all relations between patients' illness perceptions and adherence to nebulised mucolytic medications were weak, and none were significant. While most of these relations were positive, those between timeline, identity, and illness concern were found to be negative. For

parents, a relationship could not be examined between timeline and adherence, as all parents' timeline responses were at the maximum rating for this item (i.e. all parents fully believed that their child's CF would continue forever). Of the remaining 7 illness perception items, over half (4/7) were found to moderately, rather than weakly, related to their child's adherence behaviour; these included personal control, treatment control, identity and coherence. Of these illness perceptions, identity and treatment control negatively related to adherence, with this latter relationship being significant ($rs(10) = .697$, $p < 0.05$). This significant relationship shows that, as parents' beliefs in the efficacy of their child's treatment increases, their child's adherence to their nebulised mucolytic medications significantly decreases.

Finally, patients were asked to complete a questionnaire assessing the accessibility and usability of the CF-BMQ-Specific questionnaire. They were asked to rate how well they understood the questionnaire items, and how well they liked them on a scale of 0-10, and to report any items that they did not understand, or notably disliked. Overall, 12 patients completed these questionnaires. The mean score for understanding the items was 7.75, with some variability (*SD* 1.76, range 5-9). However, when patients provided qualitative feedback on which items they did not understand, the majority of comments made (5/6) were related to items in the B-IPQ or original BMQ-S, with just one relating to the CF-BMQ-Specific, about the accessibility of the item '*I sometimes worry that taking my nebulised mucolytics now will mean that they won't work as well in future*'. Feedback regarding how much they liked the items was high, with a mean value of 9.58, and little variability (*SD* 0.90, range 7-10); only one comment criticised an item, again from the original BMQ-S. It appears that adolescents were confused about which questionnaire they were being asked to complete this document for, or thought it would be useful to comment on all. Either way, these limited findings do not give a clear view on the accessibility of the CF-BMQ-S.

Chapter 7: Study Two Discussion

Review of study two

The primary purpose of study two was to investigate the extent to which the Necessity-Concerns Framework can account for differences in adherence behaviour in adolescents with CF, to two categories of nebulised treatments. It also aimed to examine whether these relationships were best captured by the original BMQ-Specific or the revised CF-BMQ-Specific. Several secondary aims were also explored in this study. These included: i) exploration of adherence behaviour by medication type, demographic and health factors; ii) examination of medication beliefs between the medication categories and respondents; iii) assessment of illness perceptions of respondents, and their relation to nebulised medication adherence. However, assessment of these aims was limited by an inadequate sample which underpowered statistical analysis and led to the decision to examine study two as a pilot.

This section will first examine adherence behaviour, before considering medication beliefs descriptively, and their relation to adherence behaviour in nebulised medications, after which illness perceptions will be examined. For each aim, a summary of the main findings will be provided, and they will, where possible, be considered in relation to the literature and the literature relating to the Necessity-Concern framework. After this, the strengths and limitations of this study will be discussed in detail.

Adherence behaviour

Overall nebulised medication adherence in adolescents with CF

In this adolescent sample, mean adherence rates for nebulised medications were relatively high at 69.55% and somewhat variable, between participants. This pattern, and the adherence rates themselves, are comparable to previous studies which have recorded adherence to nebulised medications through I-nebulisers in this population (McNamara et al., 2009; Ball et al., 2013). This supports the generalisability of this research, corroborating existing evidence that paediatric adherence rates are higher and less variable than those recorded for adults in nebulised treatments (Latchford et al., 2009; Eakin et al., 2011; Daniels et al., 2011; Quittner et al, 2014). This is important, as it highlights the need for research to separately examine adherence behaviour between these groups. Importantly, these purely objective adherence rates are, on the whole, lower than those reported in studies which examined adherence through subjective and/or less reliable objective measures (e.g. pharmacy refill data) in this treatment and patient group (e.g. Suri, et al., 2002; Modi et

al, 2006; Zindani et al, 2006). This study therefore also highlights the need for future research to use such technology to avoid the measurement error that arises from other methods.

Nebulised medication adherence by medication category in adolescents with CF

Importantly, this study also examined adherence behaviour between nebulised medication categories. Adolescent patients' adherence to mucolytics was found to be higher, although more variable (mean 71.05, S.D. 30.11) than their adherence to antibiotics (66.26, S.D. 20.71). Although this difference was not found to be significant, the antibiotic group's small sample size, and the relatively large size discrepancy between the groups (N=12 vs. N=4), will have reduced the reliability of inferential analysis. Despite the small sample, this study's adherence rates for antibiotics were found to be very similar to a previous study by McNamara et al. (2009) which also used I-nebuliser technology to examine adherence to nebulised antibiotics in this population, supporting the generalisability of these findings. These adherence rates are much higher than equivalent research in the adult population, where reports range from 31% to 53% (Quinn, et al, 2004; Latchford et al., 2009), again supporting the need for research to separately examine adherence behaviour between these groups. Unfortunately, the adherence levels for mucolytics could not be compared to previous research, since studies using such electronic devices in the paediatric and adult CF populations have either examined adherence behaviour to nebulised antibiotics alone, or calculated adherence in a combined way across nebulised medication categories, a surprising oversight. Overall, these findings suggest that a difference in adherence behaviour may exist between these medication categories, and highlight the need for further research, especially in relation to mucolytic medications.

Nebulised medication adherence by demographic and health factors in adolescents with CF

Adherence in this sample of adolescents was found to significantly reduce with increasing age, supporting previous studies by McNamara et al. (2006) and Zindini et al. (2006) who also examined this relationship for nebulised medications in this population, but opposing the findings of Modi et al. (2008). Interestingly, mean adherence rates were also found to be higher for males than female adolescents in this sample. Importantly, no previous research exists which has explored this relationship in relation to nebulised medications specifically, but these findings highlight the potential importance of exploring this further.

Only FEV1% ratings were found to significantly relate to nebulised adherence behaviour in adolescents with CF in the current study, with patients with higher ratings found more likely to adhere than those with lower ratings. This supports previous research which has also examined this relationship in this population (Modi, et al., 2006). Although adherence-rate differences were also

found between the remaining health factors (i.e. inpatient stays, and number of pseudomonas growths), these inferential statistics did not reach significance. However, it is likely that the small sample size may have limited this analysis. Previous research did not exist to allow further comparison.

Nebulised medication beliefs

Medication beliefs by nebulised medication category and respondent

Overall, patient and parent necessity belief scores were high for nebulised antibiotic and mucolytic medications, while concern beliefs were low. This suggests that both patients and parents understood the importance of nebulised medications for maintaining health and did not hold strong concerns about their potential negative effects. This pattern of high necessity beliefs and low concerns has also been shown in previous research within this population, including within nebulised and oral antibiotic treatments, chest physiotherapy, and enzyme and vitamin treatments (Bucks et al., 2009; Goodfellow et al., 2015), and in inhaled corticosteroid treatment in asthma (Conn et al., 2007; Koster et al., 2015). The mean values and level of variability in patient belief scores for nebulised antibiotic and mucolytic medications cannot be directly compared to previous research, as none exists which has separately examined these medications. However, the variability scores found for nebulised mucolytics were generally comparable (if on the lower side) to those found in other treatments by Bucks et al. (2008), while those for antibiotics were more variable. Regarding the mean belief scores themselves, necessity scores as assessed through the BMQ-S were found to be similar to those previously reported in this population for chest physiotherapy, but lower than those reported for enzyme supplements or antibiotics. While concern beliefs were similar to those previously reported for enzyme supplements, but lower than those reported for chest physiotherapy and antibiotics. For the CF-BMQ-S all necessity scores were inflated, causing necessity beliefs to exceed any previously reported within CF, and concern beliefs for nebulised antibiotics to closely resemble those found for antibiotics.

Inspection of belief data on an individual level revealed that nearly all patients and parents held strong necessity beliefs, weak concern beliefs, and had necessity beliefs which outweighed their concerns, for both medications in both questionnaires. This data was not provided for the previous studies completed within CF, preventing comparison. However, in inhaled treatments in other chronic conditions within the paediatric population, greater variability in beliefs has on the whole been found. For instance, although Koster et al. (2015) also found a similar percentage of patients (10%) to have strong concern beliefs, over half (58.1%) were found to have weak necessity beliefs for inhaled corticosteroids, and, in parents, Conn et al. (2008) found approximately one third to have weak necessity beliefs and strong concern beliefs, with: 77% of parents' necessity scores outweighing

concern; 17% of parents' concerns outweighing necessity; 6% having equal scores. This suggests that the range of belief scores for nebulised treatments could be lower than for relatively similar treatments in other chronic conditions. One potential reason for this could be the difference in healthcare input between these populations. CF patients regularly attend clinic reviews at their CF centres, so have more exposure to their clinicians and, in turn, greater opportunity to be educated about the necessity of their treatments, and to have any concerns listened to and responded to. However, in asthma, due to less frequent contact, such information about treatments from patients' healthcare staff may be less readily available.

Interestingly, some variety was found in belief scores in this study between medication categories and respondents. Parents were found to hold stronger necessity and concern beliefs for nebulised antibiotic than mucolytic medications, while their children's beliefs were comparable across both. Parents' necessity and concern beliefs for antibiotic medications were also much higher than their children's, while their necessity and concern beliefs for mucolytics were comparable to those of their children. This suggests that parents perceive nebulised antibiotic and mucolytic medications differently in terms of their relative benefits and concerns, and hold stronger beliefs regarding antibiotic medications than their children do, supporting the importance of examining these beliefs separately between medication categories and respondents. Although such a difference in parents' beliefs between mucolytics and antibiotics is not surprising, since, as previously described, they have different properties, it is interesting that their adolescent children do not exhibit such differences. Reasons for this could be that adolescents struggle to differentiate between these medications, as both are delivered in the same manner, that they are less educated than their parents about these medications, and/or less aware of cultural narratives, especially in relation to antibiotics. Such narratives include the concept of antibiotic resistance and adverse effects of antibiotics on our immune system's ability to resist infection (Norris, Chamberlain, Dew, Gabe, Hodgetts & Madden, 2013). Previous research within this population has identified that parents often have stronger medication-related beliefs than their children across medications, supporting the difference found between parent and child antibiotic beliefs in this study. Goodfellow et al. (2015) found that parents had significantly higher necessity beliefs than their adolescent children for enzyme supplements and vitamins, and significantly higher necessity and concern beliefs for chest physiotherapy.

Within this study, correlations were also completed to assess the level of interdependence between children's and their parent's beliefs. Overall, these were positive for both antibiotic and mucolytic medications. However, although these relations were strong, and even significant, for antibiotic medications, the sample size is likely to have inflated these relations, and for mucolytic medications, they were found to be weak, which suggests that patient and parent beliefs are somewhat

independent. Although no previous research exists within CF which has examined medication beliefs for both patients and parents, previous research in asthma and preventer treatments has been conflicting. While Sonney et al. (2017) found treatment perceptions to be independent between parents and their children, Yilmaz et al. (2012) found significant correlations between parent and child BMQ-S necessity and concern beliefs.

Relations between medication beliefs and adherence behaviour

Patient and parent BMQ-Specific and CF-BMQ-Specific necessity and concern subscales, including the necessity-concerns differential, showed no significant relation to adherence behaviour for either nebulised mucolytics or antibiotic medications. This lies in contrast to the two previous studies completed in this population, which found that predictions based on the Necessity-Concerns Framework were significantly related to nebulised medication adherence behaviour (Bucks et al., 2008; Maclean et al., 2015). However, the inferential statistics used in the current study need to be considered with great caution, as the sample sizes within this study were very small. Eleven patients and ten parents completed the medication belief questionnaires for mucolytic medications, and only three patients and four parents completed the equivalent questionnaires for antibiotic medications. Therefore, to understand whether the findings support the Necessity-Concerns Framework and previous research, the direction and strength of relations found between the subscales in the different questionnaire versions and adherence behaviour will be considered.

Surprisingly, for mucolytic medications, the direction of relationships between patients' belief scores and their adherence behaviour, as assessed by both the BMQ-S and CF-BMQ-S, were in direct opposition to what the Necessity-Concern Framework would predict. In contrast, all relationships between parents' mucolytic-related beliefs and their children's adherence behaviour were supportive of the model, except the correlation between concern beliefs as measured by the original BMQ-S. Although most of these relationships were very weak, the correlation between parents' necessity beliefs and adherence behaviour, as assessed by the BMQ-S, was of a moderate strength. Overall, these findings suggest that the Necessity-Concerns Framework does not explain differences between adolescents' adherence behaviour for mucolytic medications when their own beliefs are examined, but that their parents' necessity beliefs may offer a potential means to understand this.

For nebulised antibiotic medications, however, unlike mucolytic medications, the direction of relationships between patients' concern beliefs and necessity-concern differential scores with adherence behaviour supported the predictions of the Necessity-Concerns Framework, in both the BMQ-S and CF-BMQ-S. Only the relationships between necessity beliefs and adherence did not support such predictions. Most of these relationships were of moderate strength, with a very strong relationship between concern beliefs, as assessed by the BMQ-S, and adherence. For parents, most

correlations between beliefs and adherence behaviour also supported the Necessity-Concern Framework's predictions, with only the relationship between necessity beliefs, as assessed by the BMQ-S, failing to do so. However, most of these relationships were weak - only the relationship between concern beliefs, as assessed by the BMQ-S, was of moderate strength, and only the necessity-concern differential, as examined by the CF-BMQ-S, was strongly related to adherence. Together, these findings suggest that patients' and parents' concern beliefs, and the necessity-concern differential, offer a potential means to understand adherence behaviour for nebulised antibiotics in this population, supporting the potential utility of the Necessity-Concerns Framework. Findings that the necessity-concerns differential relates to adherence support the cost-to-benefit weighting assumption of the Necessity-Concerns Framework, and calls from other researchers for future studies to consider this (e.g. Foot et al., 2016).

Together, these findings suggest that different aspects of the Necessity-Concerns Framework may mediate adherence behaviour between the two nebulised medication categories, that these relationships and/or their strength may change by respondent, and that the Necessity-Concerns Framework is potentially of stronger utility in understanding adherence to antibiotic than mucolytic medications. However, as before, the relationships between antibiotic medication beliefs and adherence behaviour need to be treated with great caution, as only three patients and four parents completed these questionnaires. While correlational analysis can theoretically be completed on samples of two and above, it is known that relationships can appear where none are present for samples below six (Aggarwal & Ranganathan, 2016). Therefore, it is not known whether this difference in strength, and indeed the relations themselves, are a true reflection or an artefact of a very small sample.

Previous research

It is difficult to directly compare these findings to the two previous studies completed in this area for nebulised medications, since they either examined antibiotics alone, or both categories in combination, did not consider the necessity/concerns differential, and either did not examine patients' and parents' beliefs, or collected either in isolation. Nonetheless, the next section will offer a comparison to this research within and outside of nebulised medications in the CF population.

Findings from this study that patients' necessity beliefs did not relate to their adherence to nebulised medications, are in opposition to those reported by Bucks et al. (2009), who found significant relationships between increased adolescent patient necessity beliefs and improved adherence behaviour to antibiotic medications. Although this difference may have arisen as Bucks et al. (2009) examined both orally delivered and nebulised antibiotics, and collected adherence data through self-report, it may equally reflect this study's limited sample size. Findings that concern

beliefs were related to antibiotic adherence behaviour support those by Maclean et al. (2015), who found that increased concern beliefs were significantly related to lower adherence to nebulised medications in a paediatric population, while findings from this study which show that patients' mucolytic-related concern beliefs did not relate to adherence, appear to oppose this study. However, Maclean et al. (2015) only examined relationships between medication beliefs and adherence to nebulised medications in a combined manner (i.e. antibiotic and mucolytic medications together), so it is unknown whether their findings applied to one medication category or both. Also, although Maclean et al. (2015) examined patients' and parents' beliefs, they combined them to create 'family beliefs', so it is not known if the relationship they found was present for patients, parents, or both, preventing comparison with the present study.

This study's findings of potential relationships between parents' medication beliefs and their adolescent children's nebulised adherence behaviour cannot be easily compared to previous studies, as none exist which have examined this. They will therefore be considered in relation to research outside of this treatment, and/or within inhaled treatments for other diseases, since arguably these medications most closely resemble nebulised medications in CF**.** The finding in this study that parents' necessity beliefs may predict their child's adherence behaviour, has previously been shown within the paediatric CF population, to both enzyme supplements and chest physiotherapy (Goodfellow et al., 2015), and to inhaled corticosteroid treatments in asthma (e.g. Klok et al., 2012). Similarly, this study's findings that parents' concern beliefs and the differential of their necessity and concern beliefs alone, may predict their child's adherence behaviour, has been previously found in asthma preventer medication (e.g. Conn et al., 2007; Sonney et al., 2017).

These findings have led such authors to highlight the importance of investigating parents' beliefs, to understand their possible influence on their child's adherence behaviour. This study therefore lends provisional support to such research, and the importance of parents' beliefs - indeed, relationships between beliefs and adherence for mucolytic medications were only present for parents' necessity beliefs. This finding potentially suggests that, for nebulised mucolytic medications, parents' necessity beliefs may be more important in ensuring their adolescent children's adherence behaviour than the child's own medication beliefs. This is a surprising finding when one considers that adolescents are considered to take a stronger role than their parents in their health management at this age (e.g. Modi et al., 2008), and suggests a stronger influence from parents supporting their child's adherence into adolescence than might be expected. However, further research is needed to understand whether such relations are replicable and capable of reaching significance in this population and treatment. As previously discussed, CF carries a burdensome treatment regime (e.g. Brennan et al., 2004), which parents are often involved in managing, so it is feasible that parents' beliefs may have a stronger and more prolonged impact on their children's adherence behaviour in CF compared to other conditions. In view of the influence of family and support systems beliefs on

adherence behaviour, some authors have raised the need for the self-regulation model to be placed more strongly within a social context, for such patient groups (Sonney et al., 2017; Kosse et al., 2019).

Inspecting belief data and its relationship to adherence on an individual level

Due to the limited sample, and the problem of data aggregation within adherence research, the data was also inspected on an individual level. Interestingly this revealed that the patient who reported the highest concern beliefs for nebulised antibiotics, and another who reported the highest concern score for mucolytics were both found to have the lowest levels of adherence to these medications. Importantly, this suggests that concerns may relate, but only when they reach a certain strength. As previously discussed, concern beliefs were on average low within this study, and little variability in classification strength was present. Indeed, within most of the concern subscales for the medication belief measures, only one patient and parent held strong concern beliefs, which will have therefore limited the ability of this study to detect such effects. For instance, the unpublished feasibility study by Maclean, et al. (2015) highlighted the following trend for nebulised medications in the paediatric population; participants with concern scores of $\geq$3 (i.e. strong concern scores) had adherence rates of <70%, while adherence rates of those with concerns score of <3 (i.e. weak concern scores) were >80%. This comparison was not examinable in this study.

Comparison of the BMQ-S and CF-BMQ-S

Correlations between the equivalent subscales between the measures were mainly positive, suggesting that the measures are related. Interestingly, findings also showed that all mean necessity subscales scores, and most mean concern subscale scores, for both medication types, were higher in the CF-BMQ-S than for the BMQ-S, for both patients and parents, and significantly so for necessity beliefs. This suggests that the revised measures are capturing beliefs more strongly than the original measure, and that the revised necessity and concern items were therefore of higher relevance to patients and parents. However, despite this apparent increase in relevance, overall, the subscales of the CF-BMQ-S were found to relate less strongly to adherence behaviour in the ways expected by the predictions of the Necessity-Concerns Framework than those of the original BMQ-S. For instance, for mucolytic medications, for parents, the relations between necessity beliefs and the differential were stronger on the BMQ-S than CF-BMQ-S, and for antibiotics, relationships found between concern beliefs and adherence behaviour were stronger when assessed through the BMQ-S than the CF-BMQ-S, for both patients and parents. The CF-BMQ-S was only superior to the BMQ-S in capturing the relationship between parents' necessity and necessity-concerns differential scores and adherence behaviour for antibiotic medications. Unexpectedly, this suggests that the BMQ-S is more effective

than the adapted CF-BMQ-S in capturing necessity and concern beliefs which relate to adherence behaviour. Possible reasons for this will be examined in the final discussion section, alongside consideration of wider literature which has also sought to develop established tools into more specific measures.

Illness perceptions

Illness perceptions by respondent

Overall, patients' and parents' illness perceptions were at least moderately strong for all illness perceptions assessed, and showed a relatively high level of variability. Patients' most strongly-held beliefs were for timeline, treatment control, illness coherence and personal control, suggesting that the majority of adolescents in this study perceived their CF to be chronic, their treatments to be efficacious, reported understanding their illness well, and felt that they had personal control over it. Parents also held strong illness perceptions for timeline, treatment control and illness coherence. Interestingly, parents' illness perceptions were stronger than those of their children for all illness perceptions, except personal control. The difference in strength of illness concerns was significant and that for timeline perceptions marginal. This suggests that parents hold more concerns about their child's CF than the child does, potentially since they are more aware of the trajectory of the disease and its potential impact on their child's future, so they, unlike their children, all understand that this disease will last forever.

These findings are similar to the only existing study to have previously assessed illness perceptions in adolescent patients with CF (aged 11-17 years). Bucks et al. (2009) found timeline perceptions to be the most strongly-held, followed by identity, treatment, and personal control. However, these findings differ from those found for adults in this population: Sawicki et al. (2011) found personal control, illness coherence and illness consequences to be most strongly held, followed by treatment control and illness timeline. Interestingly, this highlights how the relative strength of these perceptions may change between adolescents and adults with CF. Regarding parents' beliefs, these findings cannot be directly compared with previous research, since this is the first study to have examined parents' illness perceptions in CF. Previous research within other chronic conditions has, however, shown parents' illness perceptions to be stronger than those of their children in asthma (Sonney et al., 2017) and diabetes (Olsen et al., 2008; Gaston et al., 2011), supporting the differences found in this study. The novel evidence of differences between patients' and parents' illness perceptions in CF provided by this study highlights the importance of considering parents' beliefs about their child's illness in such populations.

Illness perceptions and adherence behaviour

For patients, no illness perceptions were found to significantly relate to adherence, and all were weak in nature, while for parents, several illness perceptions were found to moderately relate to adherence, significantly so for treatment control. This suggests that the Self-Regulatory Model only has predictive validity for parents in this group, however, as previously discussed, the inferential statistics used in the current study need to be considered with great caution due to the small sample sizes. Also, it is known from a meta-analysis of this research area that effect sizes between illness perceptions and adherence are on average very weak (Brandes & Mullan, 2014), which will have further reduced the power of statistical testing to detect effects. Therefore, to consider these findings in more detail, and their similarity to previous research, the direction and strength of the most promising relationships will now be considered in detail.

For patients, the strongest relationships between illness perceptions and adherence behaviour were found for illness consequences, illness concerns, and emotional representations, with inverse relations found for the latter two. These findings suggest that as adolescents perceive more consequences in their daily life from their CF, they are more likely to adhere. Conversely, when their concerns regarding their illness grow, or they experience more negative affect, they adhere less. Intuitively, the first finding makes sense; as individuals perceive the impact of their CF increasing on their daily life, this would increase adherence behaviour as a means to manage it. Similarly, increased concerns are likely to compound emotional wellbeing difficulties, which are considered to relate to more maladaptive coping mechanisms and thereby reduced adherence (Leventhal et al., 2001).

Interestingly, for parents, completely different perceptions related to adherence behaviour than in their children: treatment control, illness coherence, illness identity and personal control. The direction of these relations differed; treatment control and illness identity were inversely related to adherence, while illness coherence and personal control positively related. It makes sense that parents' increased understanding of CF would support their child's adherence, and that an increased sense of personal control over it for parents would likely relate to them being more in control of their child's treatments, which is also likely to improve adherence. However, the inverse relations suggest, rather counterintuitively, that as a parents' belief in the efficacy of their child's treatment increases, and they perceive their child as experiencing more symptoms of the illness, their child is *less* likely to adhere. One could speculate that parents who have stronger beliefs in the efficacy of treatments, and/or who notice more symptoms in their child, may engage in stronger 'controlling' behaviours to attempt to increase their child's adherence, to which the child might then rebel, effectively decreasing their adherence. This may be why, in this study, treatment control beliefs for patients showed the joint-weakest relation to adherence. Such findings potentially highlight the complex interplay between patients' and parents' illness perceptions and their influence on coping behaviours. Interestingly, these relations somewhat mirror those found above for nebulised mucolytic treatment beliefs, where

parents' necessity beliefs alone related moderately positively to their children's adherence, while their children's own beliefs related negatively; suggesting that a similar dynamic could offer an explanation for those findings.

It is difficult to compare the provisional relations found for patients' illness perceptions in this study to previous research, as, although Bucks et al. (2009) also examined illness perceptions in the adolescent population in relation to adherence, they only considered identity, timeline chronicity, treatment control, and emotional representations. Bucks et al., (2009) findings suggested that perceptions that CF is not amenable to treatment control, and that CF is not permanent, significantly related to poorer self-reported adherence to antibiotic treatments in adolescents with CF, and showed these effects to be moderately strong. In this study, relations between treatment control and adherence were very weak, and, for timeline chronicity, weak and inverse, suggesting the opposite relationship. In other words, in this study, adolescent patients who were more aware of the chronicity of their condition appeared less likely to adhere. However, Bucks et al. (2009) examined adherence behaviour in relation to a different treatment, and did so through self-report, which may underlie these differences, although equally they may be a reflection of this study's limited sample size. The findings from this study are also in direct opposition to broader previous research: Brandes and Mullan's (2014) meta-analysis identified personal control, treatment control and coherence to be the most significant predictors of adherence across conditions in both adolescents and adults, and Law et al.'s (2014) systematic review (N=15) highlighted the importance of treatment control to self-management, while, in this study, treatment control, personal control and coherence showed very weak - in fact, the weakest - relationships to adherence. Together, these findings suggest that illness perceptions which are typically found to be predictive of adherence behaviour across other treatments may be of less relevance to adherence behaviour in nebulised mucolytic medications. However, as previously discussed the sample size on which these findings are based is very low, so further research is needed to understand whether these findings are representative or generalisable.

As previously noted, this is the first study to have examined relationships between parents' illness perceptions and their adolescent children's adherence behaviour in CF. As such, again findings cannot be directly compared to previous research, but can be considered in relation to findings from other chronic conditions. The finding in this study that parents' treatment control beliefs can predict their child's adherence behaviour has been previously shown in other chronic conditions, including within inhaled corticosteroids in asthma (Klok et al., 2012; Sonney et al., 2017), insulin treatments in diabetes (Gaston et al., 2011; Prikken et al. 2019), and functional constipation (Koppen et al., 2018), although these relations were all positive in nature, unlike in this study. Regarding the relative strength of predictive relations for treatment control beliefs between patients and parents, similarly to this study, Gaston et al. (2011) also found that only parents' illness perceptions significantly predicted their child's adherence behaviour, while others have reported similar relations for both (Koppen et al.,

2018; Prikken et al., 2019). Interestingly, Prikken et al. (2019) noted a three-way interaction between patients' and parents' beliefs and adherence behaviour. Such findings have led these authors to advocate the importance of investigating the influence of parents' illness perceptions on their children's adherence behaviour, even within their adolescent years. This study therefore lends provisional support to such previous research and its conclusions.

Overall, though provisional, these findings suggest that different illness perceptions relate to adherence behaviour for nebulised mucolytic medications between patients and parents, and that parents' beliefs appear to relate to their child's adherence more strongly than their child's own beliefs. This surprisingly suggests that the Self-Regulatory Model could be of higher predictive validity for parents than patients in adolescent populations. However, further research is needed to determine the replicability and significance of such relationships.

Finally, it is interesting to compare the predictive relationship to adherence behaviour noted for illness perceptions (as considered by the Self-Regulatory Model), with those found for treatment beliefs (as assessed by the Necessity-Concerns Framework). As previously explained, it has been argued that necessity and concern beliefs are superior to illness perceptions in predicting adherence behaviour (Horne et al., 1999). However, although the results for this study are provisional and must be approached with caution, they do not appear to show an advantage for such treatment beliefs over illness perceptions in predicting adherence behaviour to nebulised mucolytics. Indeed, no necessity or concern treatment beliefs, for either patients or parents, were found to significantly relate to adherence behaviour, while parents' perceptions of treatment control were found to significantly relate to their child's adherence behaviour for nebulised mucolytic medications.

Study two strengths and limitations

Several strengths and limitations exist in study two, which will now be discussed in detail. The major strengths of this piece of research lie in its originality. It is the first known study to examine the utility of the Necessity-Concerns Framework, including the necessity-concerns differential, in accounting, separately, for adherence behaviour to the two categories of nebulised medications in CF, rather than examining these medications in a combined fashion. This allowed adherence rates and beliefs to be separately examined between these medications for the first time. This study recognised that the Necessity-Concerns framework is likely to extend beyond the individual in adolescent patients, and therefore assessed both patients' and their parents' beliefs, which have not previously been separately examined and compared, in nebulised medications. While several studies within the adherence-related literature have adapted the original BMQ-Specific to more accurately examine necessity and concern beliefs for the illness and treatment of interest, it is believed that this is the first study to compare the validity and reliability of the refined measure to the

original. This is also the first known study to have examined illness perceptions from the Self-Regulatory Framework, for both patients and parents, within this population, and to have examined the predictive validity of their beliefs to adherence behaviour in nebulised medications. Finally, in this study, adherence data was collected through a 'gold standard' objective measure, thereby overcoming the largest methodological barrier faced in adherence research and providing accurate data for this study.

The major limitation of this study is the low sample size. Within CF research, it is acknowledged that large participant numbers are often not feasible due to the relatively low prevalence of this condition, and reduced participation in studies due to the high level of burden individuals experience from the condition (Brennan, et al., 2004). This has led authors to report successful recruitment at sample sizes which would ordinarily be considered low, e.g. 38 participants (Bucks et al., 2008). Although, within this context, this study's sample size is more favourable, it is important to acknowledge why recruitment was so poor, especially since it was completed across the three sites. Several unforeseen difficulties arose during data collection; most notably, at the Leeds and Sheffield sites, I-nebulisers were suddenly and unexpectedly decommissioned, leading to their reduced use during the data collection period. Other difficulties included unexpected leave of physiotherapists involved in data collection at two of the sites, I-nebuliser malfunction, and families forgetting to bring their devices to clinic on several occasions.

Overall, despite the small sample size and poor recruitment rates, the sample appeared representative. Heterogeneity was apparent in patient and parent socio-demographics, and patients' health factors, and these factors were considered by the physiotherapists involved in the project to be representative of the target group. The only exception was gender, where females were overrepresented in both the patient and parent groups. The sample was recruited from three sites located in separate counties across England, which will have also increased the heterogeneity of the sample. Importantly, adherence behaviour was varied, with individuals with both low and high levels of adherence behaviour agreeing to participate, and the average adherence levels found in this study were found to be comparable to previous research in this area. However, it appears that the limited sample may have reduced the variability of treatment belief data available, and thereby reduced the ability of this study to detect effects.

It is important to acknowledge the significant impact that the limited sample size had on data analysis within this study. It both underpowered inferential statistics and prevented completion of several further analyses, which ultimately limited assessment of the reliability and validity of the original and revised medication belief questionnaires. For instance, although the internal reliability of each measure was computed for each subscale through Cronbach alpha, the reliability and usefulness of these computations were considered to be severely limited, so, despite potential problems in

internal consistency being revealed, no modifications were made. It also prevented assessment of construct validity through a confirmatory factor analysis. This analysis would be used to establish that items within the BMQ-S questionnaires are measuring one component i.e. necessity or concern beliefs. The correlational analyses between the belief questionnaire subscales and adherence behaviour are also questionable in their reliability, particularly for antibiotic medications, and all these relations were underpowered for statistical testing. The low sample size also prevented the use of regression statistics. This, in turn, prevented investigation of whether a regression model could be identified that would allow adherence behaviour to be predicted on the basis of an individuals' necessity and concern beliefs about their medications. It also limited the ability to examine the influence of age on medication beliefs and in turn adherence behaviour.

Although, as previously described, a key strength of this study lies in the use of I-nebuliser devices to collect adherence data objectively. It should also be noted that I-nebuliser recordings do not discriminate between different medications taken with the same device, preventing adherence behaviour from being objectively calculated for individual medications. To overcome this difficulty, where patients took more than one medication through the same I-nebuliser device, clinicians elicited patients' typical patterns of use for each medication, and used these to retrospectively identify which activations belonged to which medication. Although used routinely in clinical practice, and considered by the clinicians in this project to be robust, it is nonetheless open to error. Nonetheless, this project raises awareness of this method for future research to consider as a means to delineate adherence behaviour between these medications

Although this study was completed at two time points to allow a prospective design, and thereby prediction of adherence, it involved only a single assessment of patients' and parents' beliefs. Therefore, this study is not able to ascertain the direction of causality found between medication beliefs and adherence behaviour (i.e. if beliefs influence adherence, or vice versa) and is unable to examine a key time-based assumption of the Self-Regulatory Model: that coping behaviours (including adherence behaviour) are regularly evaluated over time following an individual's appraisal of their effectiveness in managing their illness. Longitudinal research designs are needed to address these shortcomings. Interestingly, a longitudinal design could also allow investigation of any possible transfer of beliefs from parents to children, or vice versa

Conclusion

Overall, this study provides an indication of possible relationships between the Necessity-Concerns framework and adherence behaviour in nebulised antibiotic and mucolytic medications. For nebulised mucolytics, parents' necessity beliefs most strongly related to adherence behaviour, while for nebulised antibiotics, both patients' and parents' concern beliefs, and parents' necessity-concern

differential scores did. This suggests that this model relates to adherence behaviour between the two nebulised medication categories and responders differently. Overall, these results highlight the importance of considering this model separately for the two categories of medication, the need to consider parents' beliefs, and the potential utility of examining the weighting of beliefs through the necessity-concerns differential.

This study also provides an indication of possible relations between patients' and parents' illness perceptions and adherence to nebulised medications, which has not previously been examined. As with the Necessity-Concerns Framework, parents' perceptions most strongly related to adherence behaviour for nebulised mucolytic medications, further highlighting the importance of considering parents' beliefs. However, once again, no firm conclusions can be drawn due to the small sample sizes, which unfortunately underpowered statistical testing, and may have also reduced the reliability of the analyses themselves. Nonetheless, this research adds to the literature in several ways, and provides several novel concepts and directions for future research. Interestingly, it appears that the original BMQ-Specific may be a more effective tool than the CF-BMQ-Specific at capturing the necessity and concern beliefs that influence adherence behaviour in this population, despite the latter being specifically and systematically refined for this purpose. This will be considered further in the final discussion section, as will suggestions for future research and implications for clinical practice.

Chapter 8: Overall Discussion

This final chapter will provide an overview of the main findings from the literature review, and the empirical results from the two studies completed in this thesis. Following this, the theoretical utility of the Necessity-Concerns Framework and Self-Regulatory Model for conceptualising adherence to nebulised treatments in adolescent patients with CF will be outlined, alongside the utility of adapting the BMQ-S specifically and systematically for this purpose, discussed within the wider literature. Novel contributions of these studies to the non-adherence literature will then be highlighted, and their strengths and weaknesses described. Finally, clinical implications and possible directions for future research to improve understanding and treatment of non-adherence will be presented.

Review of background and aims

This thesis assessed the ability of the Necessity-Concerns Framework to predict adherence behaviour to nebulised medications in adolescent patients with CF. Chapter 1 introduced the problem of sub-optimal adherence in CF, particularly in adolescents and within nebulised treatments. It explained how studies suggest that approximately 35% of such medication is not taken as directed in this patient group, and highlighted the potential consequences of this for individuals and society. These included reduced health outcomes, increased risk of morbidity and mortality, and increased use of health services, hospital admissions, and resource waste.

A critical review of the factors considered to underlie poor adherence was then presented, highlighting how identifying these factors and developing methods to address them is currently a priority for adherence research and practice. It was recognised how, although practical barriers such as time and forgetfulness are often reported by patients to explain poor adherence, and have been extensively studied, psychological barriers arising from illness and medication beliefs may be stronger underlying factors, and, indeed, driving factors, of practical barriers. The review introduced psychological models of health behaviour, which explain how such beliefs may influence behaviour, including treatment adherence, and the subsequent research examining their utility. From this, it was concluded that the exploratory power of psychological models, and in particular, the Necessity-Concerns Framework, appears to offer a promising means to understand how beliefs may influence adherence behaviour in chronic illnesses, in both adult and paediatric populations.

The Necessity-Concerns Framework provides a theoretical model for describing how beliefs may influence adherence behaviour. It is built upon findings which show that individuals make implicit common-sense appraisals regarding their illnesses and treatments to help them manage their health. For specific prescribed medications, these appraisals have been found to fall into two main

categories. The first category, necessity, refers to implicit judgements about personal need for medication (i.e. how much one feels they need the medication to maintain/improve current and future health), while the second, concerns, refers to implicit beliefs held about potential adverse side-effects of taking the medication as prescribed. This model predicts that these beliefs influence adherence behaviour differently; necessity beliefs are argued to promote adherence, while concern beliefs hinder it. Similarly, it predicts that their relative strength influences an individual's decision to adhere to treatment recommendations, with stronger necessity beliefs relative to concerns promoting adherence, and vice versa. It is argued that, while for some patients, non-adherence will represent an informed choice based on these evaluations, for others, non-adherence will arise when necessity and concern beliefs are based on misconceptions of their illness and treatment. Such misconceptions are theorised to be influenced by social, cultural and healthcare-system contexts, and the individual's personal experiences of their illnesses and treatments. For instance, the preventive nature of many treatments in CF means that direct symptom relief is not experienced, leading individuals to logically conclude that such medication is not effective, and therefore unnecessary. If found to have predictive validity to adherence, this framework would offer a convenient means for clinicians to elicit and address key beliefs underpinning patients' treatment decisions, in order to improve adherence.

The review highlighted how, in the past two decades, over a hundred studies have examined the explanatory value of the Necessity-Concerns Framework in predicting adherence behaviour across a wide variety of chronic conditions, healthcare settings, and cultures. In the adult population, two meta-analyses consolidated these findings, demonstrating the utility of this framework for such applications. Interestingly, the most recent study explicitly demonstrated that the strength of predicted relations varies across conditions: for instance, necessity beliefs were found to be of greater importance to asthma, while concerns were more salient for cardiovascular conditions. It was then considered how, in the paediatric population, multiple studies have also supported the predictions of this model across conditions, including two published studies in CF. However, there is less overall research, and less research by condition, in the paediatric population than in the adult population. Interestingly, across these studies, the pattern and strength of relations between belief subscales and adherence behaviour also seem to somewhat vary between treatments, even within the same condition. Ultimately, it was concluded that such findings highlight the need for more research in the paediatric population, and the need for the Necessity Concerns Framework to be examined by individual illnesses and treatments, in order to understand which treatments and conditions it best applies to, and in turn, to allow interventions to be developed which target the specific beliefs that influence patients' adherence.

The paediatric adherence literature also highlighted how parents often have a strong role in managing their children's health needs within chronic conditions, making it reasonable to assume that their own beliefs might, in turn, influence their children's adherence behaviour. This could occur through the active support they provide to their children, or through indirect transmission of beliefs, thereby sustaining their influence even as children may take increasing responsibility for their own health needs during adolescence. It was highlighted how several studies have shown that parents' treatment beliefs relate to their children's adherence behaviour, in a manner supported by the Necessity Concerns Framework, across various conditions, which suggests that examining beliefs of individuals alone may be missing a key component of this model in regards to paediatric populations.

This review then described how the Beliefs about Medicines Questionnaire Specific (BMQ-S) was developed as a means to assess the Necessity Concerns Framework. It is a generic measure which aims to assess necessity and concerns that are commonly shared across chronic health conditions, allowing it to be applied across treatments and illnesses. Due to its generic nature, the review highlighted how the wording and content of the questionnaire items have been modified in several studies to try to better capture beliefs influencing adherence behaviour to the specific condition and medication of interest. Within the review, it was highlighted that without such adaptation, certain items of the BMQ-S might be rendered irrelevant, or that beliefs relevant only to certain unusual characteristics of particular conditions and treatments might be missed entirely. Improved assessment of idiosyncratic beliefs is therefore considered to increase the psychometric properties of a measure, including predictive validity. In turn, this would increase the utility of this questionnaire as a screening measure, and provide a better picture of how to improve negative outcomes through the development of specific clinical interventions which account for these beliefs. For instance, CF and its medications have several unique characteristics, including the fact that patients can feel relatively healthy and asymptomatic, even when their organ functions are declining, and the fact that nebulised mucolytics provide no immediate symptom relief and work prophylactically. However, although the rationale for adapting the BMQ-S seems logical, it was recognised that the superiority of the questionnaire developed from such adaptations, compared to the original measure, has been assumed rather than assessed. This may be limiting assessment of the framework if these adapted questionnaires assess beliefs which are, in fact, less strongly related to adherence than those elicited in the original questionnaire. It was also highlighted how the process of adapting the BMQ-S to treatments of interest across health conditions is often not well described, or systematic, within existing adherence literature, with some studies seemingly relying on the research team's knowledge alone to complete this task, or simply describing the process of adaptation as a 'discussion'. It was suggested that such assumptions could present a major unexplored methodological issue in this research area.

The largest methodological barrier faced in adherence research: its commonplace reliance on subjective methods to record adherence behaviour, was then considered. Research has consistently shown that subjective report (e.g. self-report) is inaccurate, preventing robust assessment of adherence behaviour, and, in turn, accurate investigation of the factors that influence it, including beliefs. It was highlighted how nebulised treatments in CF offer a unique means to overcome this problem through 'gold standard' objective recording of adherence, provided by the I-nebuliser devices used to deliver nebulised medications. Therefore, examining the Necessity-Concerns Framework through adherence data collected by I-nebulisers offers a singular opportunity to test this model with robust data, something not currently afforded to other chronic illnesses and treatments. Despite this, the review showed that research using this measurement method is extremely sparse.

The surprising paucity of research considering the Necessity Concerns Framework in relation to nebulised medications was then highlighted, considering the unique opportunity to robustly test this model afforded by I-nebuliser devices, and the key role of nebulised treatments in preventing and treating lung infections - primary causes of morbidity and early mortality in CF. It was recognised that, although the two existing studies to have examined this framework within nebulised treatments showed promising results, only one measured adherence through an I-nebuliser device, and both used a refined BMQ-S which was found to have inadequate psychometric properties on the concerns scale, which limited analysis. It was also highlighted how one of these studies failed to apply this model separately to the two categories of nebulised medications, while the other did not examine both categories. The Necessity Concerns Framework is intended to be applied to individual treatments, not categories of treatment delivery - although two medications may both be delivered in a nebulised manner, they may share virtually no other relevant properties. The amalgamation of different nebulised medications together therefore represents a significant oversight when their different properties and purposes are considered. Taken alongside the research highlighted above, this suggests that the strength and manner in which this model relates to adherence is likely to differ between treatments. Also, the role of parents' beliefs, although previously considered in one of these studies, were combined with their children's beliefs rather than examined separately. It was considered that further research was warranted to overcome these shortcomings in adherence measurement and questionnaire development, and two studies were devised to address this in this thesis.

Study one, presented in chapter 2, aimed to develop and explicitly describe a process for adapting the BMQ-S to separately examine necessity and concern beliefs pertinent to nebulised antibiotic and mucolytic medications in CF, and to create a second version of each questionnaire for completion by patients' parents. Study two, presented in chapter 5, assessed whether the beliefs

elicited by the original and/or adapted measure could account for differences in adherence behaviour within either/both category of nebulised treatments, in accordance with the predictions of the Necessity-Concerns Framework, and assessed whether one was superior to the other. It also considered whether patients' or parents' beliefs captured these relations differently. Further, secondary aims included: i) exploration of adherence behaviour by medication type, sociodemographic and health factors; ii) examination of medication-related beliefs between the medication categories and respondents; iii) assessment of illness-related beliefs between respondents, and their relation to nebulised medication adherence.

Summary of findings

Study one: Developing the CF-BMQ-S

Study one used a modified two-round Delphi survey to systematically gain feedback from a panel of experts (individuals with clinical expertise in supporting adherence to nebulised medications in CF) on the content of items within two BMQ-S questionnaires that the research team had already partially adapted from the original. These questionnaires aimed to capture necessity and concern beliefs relevant to nebulised antibiotic and mucolytic medications that may influence adherence behaviour in adolescent CF patients. The first round aimed to assess consensus from the panel regarding the items' usefulness and clarity, while the second round aimed to increase this consensus with final revisions, driven by the first round's feedback. In each round, participants rated the usefulness and clarity of each item in both questionnaires, and were asked to comment on their ratings and/or provide suggestions for new items.

In round one, initial consensus was positive regarding the value of items in both questionnaires, but findings regarding clarity were more variable. Of the 21 items rated, just 4 items failed to achieve statistical consensus for value, while 10 failed to attain consensus for clarity, and seven suggestions were provided for new items. As a result, for the second round, three concern items (two from the CF-BMQ-A and one from the CF-BMQ-M) were removed, eight items (four necessity and four concern) were identically revised in each questionnaire, and one new necessity and two new concern items were created. In round two, only two items failed to reach statistical consensus for value (one on each questionnaire, including a newly-added concern item), all items attained consensus for clarity, and just one suggestion was made for a new item. As a result of this high level of consensus, no further alterations were made. It was considered by the supervisory team that any further alterations were equally likely to reduce consensus as improve it, and that there would be no further means to assess this, as the final round was already concluded. Importantly, the decision was also made by the supervisory team to make both questionnaires the same in content (differing only in

their reference to 'mucolytics' or 'antibiotics'), even though some items were considered of potentially less relevance to either medication treatment category, in order to support direct comparison between these questionnaires and their relation to adherence behaviour, in study two. The parent and patient versions of both questionnaires only differed in reference to 'my' or 'my child's' medication, for the same reason.

Study two: Evaluating the CF-BMQ-S

Study two explored the relationship between necessity and concern beliefs about medicines, as measured through the original BMQ-S and the adapted CF-BMQ-S, and adherence behaviour. Overall, findings showed no significant relationships between patients' or parents' necessity or concern beliefs, and adherence behaviour to either medication category, using either the BMQ-S or CF-BMQ-S. However, these correlational analyses were underpowered due to an inadequate sample size, leading the direction and strength of these relationships to be considered as an indicator of possible relations. For nebulised mucolytic medications, findings suggested that adolescents' own beliefs do not explain their adherence behaviour in accordance with the predictions of the Necessity-Concerns Framework, but that their parents' necessity beliefs may offer a potential means to understand this. For nebulised antibiotics, findings suggest that patients' and parents' concern beliefs, and the necessity-concern differential, offer a potential means to understand adherence behaviour in this population. These findings support the potential utility of the Necessity-Concerns Framework and highlight how this model may relate to adherence differently between medication categories and responders.

Findings also unexpectedly showed that these correlations between necessity and concern subscales and adherence behaviour were generally weaker for the CF-BMQ-S than for the unmodified BMQ-S, suggesting that the original measure is superior in assessing beliefs which relate to adherence behaviour in this population. Interestingly, this occurred despite mean necessity and concern belief scores being higher in the CF-BMQ-S than the BMQ-S across medication types and respondents, which suggested that these adapted items were indeed of increased relevance to patients and parents. These relations between treatment beliefs and adherence behaviour were also inspected on an individual level. Interestingly, this revealed that the patients who gained the highest concern scores for each medication type also had the lowest adherence rates to each. This potentially suggests that concern beliefs may only impact adherence once they achieve a certain strength - this will be considered further in the future research section.

Finally, relations between illness perceptions and adherence behaviour were considered. Overall, although this study's findings showed no significant relationships between patients' illness

representations and adherence behaviour, they did reveal a significant relation between parents' treatment control perceptions and their child's adherence behaviour to nebulised mucolytic medications. This finding counterintuitively suggests that, as parents' beliefs in the efficacy of the child's treatment increases, their child's adherence behaviour decreases. It was reasoned that this may occur as parents who strongly hold such beliefs may be more likely to engage in behaviours which they believe will support their child to adhere, but which inadvertently cause their child to 'rebel' and adhere less. Such findings further highlight the potential importance of parents' beliefs on adherence in this population. Perhaps most importantly, these findings suggest that treatment beliefs do not appear to be superior to illness perceptions in predicting adherence behaviour to nebulised medications. However, as discussed throughout, the provisional nature of these results prevents firm conclusions. The implications of these findings will not be discussed further here, as examining these relations was a secondary aim of this study. Reasons why the adapted measure could seemingly have more relevance, but more poorly relate to, the outcome of adherence, will be considered next and discussed within a wider empirical literature, where other studies have also adapted generic questionnaires in order to increase their clinical utility.

Adapting questionnaires measures within the context of psychological research

A convention exists within psychological research which assumes that measures become more meaningful as they are adapted to the specific topic of interest. As such, the BMQ-Specific has been adapted for certain conditions, in the belief that this will allow beliefs idiosyncratic to a particular illness and treatment to be measured more accurately, thereby increasing the psychometric properties of this measure. Several such adaptations of the BMQ-S have sought to improve the predictive validity of this measure for adherence. Across chronic conditions, such modifications have involved minor revisions to existing items, removals, and illness/treatment-specific additions targeting beliefs considered likely to influence adherence behaviour. Although the validity and reliability of these adapted measures has been examined, albeit to different levels, and has usually been found to be acceptable, no study was found during the review which compared the predictive validity of the original BMQ-S to an adapted version. Therefore, this is the first known study to directly compare the predictive validity of the original BMQ-S in adherence behaviour with that of an adapted measure.

Therefore, in order to support discussion of such findings, wider literature which has adapted the Illness Perception Questionnaire-Revised (IPQ-R; Moss-Morris et al., 2002) was considered, in order to examine if such comparisons have been made for this measure. The IPQ-R is the most highly researched illness perception measure. It was developed and structurally validated as a generic measure to provide quantitative assessment of illness perceptions across patient groups, as

conceptualised through the Self-Regulatory Model of adherence behaviour. Relationships have been shown, as predicted, between illness perceptions and a range of outcomes, including adherence, coping strategies and quality of life (e.g. Kosse et al., 2019; Knowles, Apputhrai; O'Brien, Ski, Thompson & Castle, 2020). As with the BMQ-S, researchers are encouraged to modify items in order to suit particular illnesses, cultural settings or populations (Moss-Morris et al., 2002). Modifications to increase specificity can range from the simple act of substituting the term 'illness' with the name of the specific condition being investigated, to removing, adding, or re-wording items, especially in the 'causes' and 'illness identity' subscales. These larger modifications are considered to allow in-depth insight into idiosyncratic beliefs held by specific patient groups, and thereby to improve the psychometric properties of the revised measure (French & Weinman, 2008).

Several studies have completed such modifications and validated them, for illnesses including fibromyalgia (van Wilgen, van Ittersum, Kaptein & van Wijhe, 2009), cancer (Moon, Moss-Morris, Hunter & Hughes, 2017), memory difficulties (Hurt, Brown & Barrowclough, 2010) and atrial fibrillation (Taylor, O'Neill, Hughes & Moss-Morris, 2018). Such validation has included assessment of test-retest reliability, internal consistency and construct validity. Again, the process of completing these modifications varies in its robustness; while some studies have relied on the clinical experience of the authors alone (e.g. van Wilgen et al., 2009), others have reported a clearer and more systematic process, including the use of qualitative interviews and think-aloud techniques (Moon, et al., 2017; Taylor et al., 2018). Indeed, within this research area, a mixed-method approach is advocated when modifying and validating the questionnaire (French & Weinman, 2008). Although, as described, these measures have been found to have adequate psychometric properties, no comparisons appear to have been made against the original measure within this validation process, or in subsequent studies.

The question of why the refined CF-BMQ-S may have related less strongly to adherence behaviour than the original questionnaire, despite it appearing of greater relevance to patients, will now be considered. One factor could be that the refinements made weakened the strength of item statements, causing the variability of participant 'agree/disagree' responses to decrease. For instance, adaptations included changes which employed more moderate language: '*Without my nebulised medication I would be very ill'* became '*Without my nebulised medications, my health would be much worse'*. However, average variability scores in the necessity and concern subscales were largely comparable between the original and refined BMQ-S, across medication types and responders. The only exceptions were in the patient necessity subscale for antibiotics, and in the parent concerns subscale for antibiotics, where average variability was higher in the BMQ-S than in the CF-BMQ-S. Therefore, although reduced variability in some of the overall CF-BMQ-S subscales may account for some of the weakened relations between these measures and outcome, it does not offer a full explanation.

Another reason could be that some items were made more specific in the refined measure. During refinement of the BMQ-S, it was recognised that certain items were vague and general in their wording, particularly in the concerns scale. It was considered that this could lead to individuals having difficulty in interpreting the items, and/or cause participants to interpret them in different ways. For instance, in the original item *"I sometimes worry about becoming too dependent on my medications"*, the word 'dependent' could be interpreted in terms of addiction, interference on daily life, or diminishing medication effects. This item was replaced with the most plausible interpretation of a dependence concern for this client group *"I sometimes worry that taking my nebulised medications now will mean that they won't work as well in future"*. Although this refinement sought to increase the item's clarity, it may have inadvertently reduced the ability of participants to interpret the question more broadly, and thereby reduced the ability of the measure to capture wider concerns that influence their adherence behaviour.

A further reason could simply be that the new items in the CF-BMQ-S genuinely related less strongly to adherence behaviour than the original items. In the development of the CF-BMQ-S, two fundamentally new items were added, extending the nature of 'necessity' and 'concern' within this questionnaire. These items were *"I only need to take my nebulised medications regularly if I feel unwell"* and "*Taking my nebulised medications is embarrassing*". The first was considered to broaden the definition of necessity, by considering not only if a medication is needed to maintain or improve current health, but also when, or how frequently, it needs to be taken. Although an interesting item, as it illustrates how symptom perceptions influence patients' perception of medication necessity, in retrospect it may be more of a surface belief; one could know logically that they need to take medication regardless of their current health, but could still believe that it does not work for them. The second refinement is considered to extend the definition of concern, by moving from concerns regarding health and the medication itself, to the medication delivery system, and related social aspects. Although it is interesting to consider the I-nebuliser as a delivery device alongside beliefs concerning the medications themselves, it is not known if such beliefs influence adherence.

Overall strengths and limitations

The individual strengths and limitations of both studies that comprise this thesis have been considered in their respective discussion sections, so this section will present them in an aggregate manner. Ultimately, the strengths of this project are its areas of originality, and how it was implemented through a two-part process, which uniquely allowed the CF-BMQ-S to be both developed and then evaluated for its utility. This is the first known study to have adapted the BMQ-S to nebulised medication categories in CF. It is also the only known study to have examined the

predictive validity of the Necessity-Concerns Framework to adherence behaviour separately for the two medication categories in nebulised treatment, and to have compared these relations between the original and revised measures, and between patients' and parents' beliefs. The findings which arose from these novel elements have extended the existing body of research and raised several clinical and research implications for current practice, which will be discussed in the following section.

The overall weakness shared by both studies within this thesis was their limited sample sizes, which, importantly, limited the psychometric assessment of the original and revised medication belief questionnaires in both studies. In study one, only clinicians evaluated the questionnaire items, and only the minimal number required took part. This small sample, alongside the homogeneity of respondents, is very likely to have reduced the variability of group judgements, and thereby the face validity and generalisability of the developed CF-BMQ-S. Research recommends that a heterogenous panel of experts by both profession and experience is needed to support the face validity of a measure (e.g. Hardy et al., 2004). Therefore, due to poor recruitment, the face validity of this measure was only partly ascertained; future input by patients and parents with lived experiences of these medications would be needed to fully assess the face validity of the CF-BMQ-S.

In study two, the sample size was so limited that the reliability of the analyses themselves were rendered unclear, the statistical tests that were completed were underpowered, and several analyses could not be undertaken at all. Most importantly, this limited the assessment of the predictive validity of the original and revised BMQ-S questionnaires, since the reliability and statistical significance of the correlations were unclear, particularly for antibiotic medications. Regression analysis could also not be computed, so this study was unable to examine how much of the variance within nebulised adherence behaviour could be accounted for by medication beliefs, nor determine the utility of a predictive model to allow adherence behaviour to be predicted on the basis of an individuals' necessity and concern beliefs about their medications. Ultimately, the assessment of predictive validity in this study was limited to providing an indication of potential relations between the belief subscales and adherence behaviour. The small sample also prevented assessment of the construct validity of the CF-BMQ-S through confirmatory factor analysis. As previously discussed, several revisions were made to items from the original BMQ-S when developing the revised questionnaires, and it is subsequently unknown whether these revised items would fit within the original two-factor structure of this questionnaire and model, and how strong the item loadings would be. Also, although the internal reliability of each measure was computed for each subscale through Cronbach alpha, the reliability and usefulness of these computations was highly questionable, so, despite potential problems in internal consistency being revealed, no actions could be taken. More broadly, this study was also unable to examine how certain variables, such as age, may have mediated relations between beliefs and adherence behaviour, or allow examination of data by belief strength;

for instance, adherence behaviour between respondents with strong and weak beliefs could not be compared, or separately related.

Clinical implications and future research

This study has several implications for clinical practice and future adherence research. In relation to adherence rates, the findings show that poorer adherence to nebulised medications is more likely in older adolescents, and suggest that adherence may be poorer for nebulised antibiotics than nebulised mucolytics. However, further research is needed with a larger sample to generalise this. Nonetheless, the finding that adherence rates may differ between these medication types highlights the need for future research to consider separate medications separately in order to properly understand adherence to them. More broadly, such insights raise the likelihood that different factors affect adherence to different medications, even within the same patient and treatment category. Importantly, this is the only study to have produced objective adherence data for mucolytic medications in this population, despite mucolytics' daily consumption by most CF patients, which strongly highlights the need for future research to focus on this treatment. For clinical practice, such findings suggest that health professionals may need to take a more active role in monitoring adherence for older than younger adolescents, and for nebulised antibiotics than nebulised mucolytics. Finally, the finding that reported adherence rates in this study were comparable to previous research using I-nebuliser devices, but lower than those generated from subjective and/or less reliable objective measures, further reinforces the need for future research to use such objective adherence measurement to avoid measurement error from subjective methods, as advocated by previous authors.

Regarding medication beliefs, findings suggested that parents hold weaker beliefs, both necessity and concerns, for nebulised mucolytics than nebulised antibiotics, and that both such beliefs about antibiotics were stronger than those of their children. This shows that nebulised medication beliefs may differ by respondent and medication category. Again, while the ability of this study to assess the significance of these differences was limited, such findings nonetheless highlight the need for future research to examine treatment beliefs separately by nebulised medication category and respondent, rather than aggregating this data, in order to understand the beliefs that different individuals hold towards these treatments, and how they relate to different outcomes. This research was unable to examine differences in medication-related beliefs between younger and older adolescents, due to the limited sample size. It would be interesting for future research to assess whether beliefs of older adolescents differ from those of younger adolescents for nebulised medications, and how both compare to those of their parents.

As previously discussed, this study is unable to provide firm conclusions on the ability of the Necessity-Concerns Framework to account for differences in adherence behaviour to nebulised

medications. Nonetheless, the results suggest that the belief subscales, including the necessity-concerns differential, may mediate adherence behaviour in separate ways for both medication categories. These findings highlight the need for future research to assess the replicability of these findings. As discussed in the introduction, if adherence to these medications can be accounted for by this framework, it would offer clinicians a means to quickly identify those at risk of non-adherence through the BMQ-S, or an adaptation of it, and subsequently apply a targeted intervention to modify unhelpful beliefs, thereby increasing adherence. Inspection of the individual data also suggested that concern beliefs may only affect adherence once they reach a certain strength. The limited sample, alongside the almost exclusively weak level of concern beliefs across this sample, prevented further analysis. To examine this question, future research could divide participants into two groups, in order to relate 'low' concerns and 'high' concerns to adherence. Such examination of attitudinal groups is common practice in several other studies in adult and paediatric populations (e.g. Clatworthy et al., 2009; Koster, et al., 2012; Goodfellow et al., 2015), since it is considered that beliefs may only relate to adherence when they are of a certain strength, or display a certain pattern.

Findings that parents' beliefs alone related to adherence for nebulised mucolytics, and that parents' beliefs related to adherence behaviour for nebulised antibiotic medications, raises the potential importance of considering parents' beliefs within this framework. If such findings can be replicated, they would highlight the potential need for the Self-Regulation Model to be placed more strongly within a social context, and for subsequent research to examine both patients' and parents' beliefs, and their separate and combined influence on adherence behaviour. These ideas support those of Sonney et al. (2017), who reformulated this model to create the Common Sense Model of Parent–Child Shared Regulation, which considers parent and child illness representations as separate constructs, but also places parent and child illness representations together to form a shared overall illness representation which reflects shared illness management. In practice, replications of such findings would suggest that clinicians should consider family beliefs, rather than patient beliefs alone, in order to identify individuals at higher risk of low adherence. It would also suggest that interventions could be more effective if targeted at a family rather than individual level, and that future research should in turn seek to examine the efficacy of individual vs. family-based interventions. It would also be interesting for future research to more closely examine these relations; for instance, whether the relative importance of patients' or parents'/family beliefs change as adolescents age - perhaps until a specific age - due to parents being less actively involved in their children's treatments as they get older. Such findings may show that aggregating data from older and younger adolescents, as in much previous research (e.g. Bucks et al., 2009; Goodfellow et al., 2015; Koster et al., 2015), and indeed this study itself, might be a methodological flaw.

Overall, study two requires replication with a larger sample, and, ideally, a longitudinal design. A larger sample would allow assessment of whether these findings can be replicated, and therefore, are generalisable. It would allow several further analyses to be completed, including regression analysis, and further assessment of the validity and reliability of both the adapted and original BMQ-S measures. The former analysis would reveal whether predictive models can be identified for these treatments, allowing adherence behaviour to be predicted based on treatment-related beliefs. The latter would allow assessment of the psychometric properties of the original BMQ-S and CF-BMQ-S as applied to this population and treatment, potentially leading to further refinement of the questionnaire content. A longitudinal design would help to clarify the direction of the relationship between medication beliefs and adherence behaviour, which would, in turn, help to determine causality. It would also allow assessment of the stability of such beliefs over time, and of adherence behaviour itself, in this group. This would then allow assessment of the time-based assumption of the Self-Regulatory Model, within which the Necessity-Concerns Framework sits, i.e. that adherence decisions are regularly reviewed over time, following an individual's appraisal of the effectiveness of their current behaviours in managing their illness. Such longitudinal studies have been completed in other medical conditions, including HIV, depression, Rheumatoid arthritis and diabetes (e.g., Aikens et al., 2005; Horne et al. 2007; de Thurah et al. 2010; Aikens & Klinkman, 2012), but not within CF.

The findings in this study highlighted how the targeted and systematically-adapted CF-BMQ-S appeared, surprisingly, inferior to the original BMQ-S in assessing how necessity and concern beliefs influence adherence to nebulised medications. This result has potentially important implications for research within this field, including questioning whether adaptation of the original BMQ-S is needed at all, and, if so, how best to undertake such a process. As previously discussed, current research within this field simply assumes that adapting the BMQ-S will increase its validity - however, the findings of this study highlight that this may be based on a false premise. This, in turn, highlights the need for future research to compare the psychometric properties of the original and adapted measures, in order to ensure that the utility of the Necessity-Concerns Framework is not being compromised by inadequate and/or inappropriate adaptations. The importance of future research having more systematic and explicit processes for such adaptation is also likely to be significant. This study presents the Delphi survey to support this process, however, other methods such as a think-aloud qualitative methodology could also be used to complement this approach, as has been used in adaptation of the IPQ-R (Moon et al., 2017; Taylor et al., 2018). This would allow additional understanding of how questionnaire items are interpreted, and how the questionnaires are completed by patients and parents. However, more broadly, further qualitative research is needed to explicitly explore necessity and concern beliefs for nebulised medications for adolescents and their parents. Although, as discussed in the introduction, some such research exists which has examined

this, these studies either considered several medications which limited detailed exploration (George et al., 2010), or were only conducted with adults (Hogan et al. 2015; Hoo et al. 2017).

This thesis also raised the subject of the medication delivery device, and its potential impact on beliefs regarding the medications, and thereby, adherence to them. Indeed, it is likely that many of individuals' beliefs about their medications will include the means by which they are taken; for instance, concerns regarding swallowing might affect appraisals of oral antibiotics, or the time burden of cleaning a nebuliser might affect appraisals of nebulised antibiotics, but neither represents a necessity or concern belief about the antibiotics themselves. It would therefore be interesting for future research to further consider the delivery mechanisms of treatments, and potentially complete a qualitative study with patients about this. In the first instance, such research could aim to identify whether medication-related beliefs do differ when the same medication is administered in different ways. It is likely that for devices such as a nebuliser, such beliefs may generalise across conditions such as asthma and COPD, which also use inhaler delivery devices.

It is important to recognise that the Necessity-Concerns Framework is just one means of examining the potential impact of beliefs on adherence behaviour, and that the application of one model alone, even to assess only beliefs as a factor, is very likely to be an over-simplification. Adherence behaviour is a complex and multifaceted subject which is likely to be impacted by a range of practical and psychological factors, differentially for each individual treatment, in each individual. As such, recent research in this field is increasingly examining how several models, applied together, may improve our understanding of the role of health beliefs in medication-taking behaviour, and how multivariate analysis is needed to detect such effects. For instance, Foot et al. (2019) examined interactions between the BMQ-S, B-IPQ (Brief Illness Perception Questionnaire), MHLCS (Multidimensional Health Locus of Control Scale; Wallston, Stein & Smith, 1994), and self-reported adherence to inhaled corticosteroids in adult asthma patients, and found interactions between these measures, suggesting that the manner in which beliefs relate to adherence behaviour changes depending on other beliefs individuals hold. Overall, they argue that failure to recognise these interactions risks diluting or obscuring the relations between beliefs and adherence behaviour, and thereby potential effect sizes. This could be a fruitful next step for future research, once the usefulness of the Necessity-Concerns Framework on adherence behaviour to nebulised medications has been adequately determined, and the BMQ-S itself appropriately adapted, if necessary.

Conclusion

This thesis, completed through two studies, describes the systematic adaptation and application of the BMQ-Specific questionnaire, to assess the extent to which the Necessity-Concerns Framework can explain objectively-validated adherence behaviour to nebulised antibiotic and

mucolytic medications in adolescents with CF. It represents the first known study to have explicitly and systematically adapted the BMQ-S to nebulised medications in CF, to have examined and compared the predictive validity of the Necessity-Concerns Framework through both an original and adapted measure, and to have assessed these relations separately for the two medication categories of nebulised treatment, and for both patients' and parents' beliefs. However, such examination by either the revised or the original BMQ-S, was limited due to inadequate sample size, which underpowered statistical testing, and may have also reduced the reliability of the analyses themselves, leading this study to be examined as a pilot.

Nonetheless, findings provided an indication of possible relationships between the Necessity-Concerns Framework and adherence behaviour to nebulised CF medications in adolescents. The results suggest that the model relates to adherence behaviour between the two nebulised medication categories and responders differently, and, crucially, that the original BMQ-Specific might be a more effective tool than the adapted measure in capturing the necessity and concern beliefs that influence adherence behaviour in this population. Importantly, the novelty of this study's design, even with only provisional results, provides several recommendations and directions for future research. These include: the importance of considering this model separately for multiple categories of medication, of considering the influence of parents' medication beliefs on their child's adherence behaviour, and, perhaps most crucially, the importance of critically comparing the adapted and original BMQ-S questionnaires, rather than simply assuming that refined or adapted versions will necessarily display increased psychometric properties.

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Appendices

Appendix A: study one invitation email to clinicians

Dear Clinician,

You are being invited to take part in an online survey which seeks to gain your views on two questionnaires that we have adapted from an existing measure called the Beliefs about Medicines Questionnaire-Specific. Our revised questionnaires aim to examine beliefs that adolescents with cystic fibrosis and their parents may hold towards nebulised mucolytic and antibiotic medications.

This survey will be completed in two rounds. In the first round, you will be asked to give your opinion on how valuable and clear you think the items are in the two questionnaires, and in the second round, you will be asked to reconsider your rating after also viewing the ratings and comments of other reviewers. On average, the first-round survey should take 15 minutes to complete, and the second, 20 minutes. Your responses will be anonymised and analysed as part of a Leeds Doctorate of Clinical Psychology thesis project, and are likely to be presented and published in a journal.

We are using this survey to gain feedback from patients, parents and professionals. We hope that this survey will allow us to develop a valid and reliable tool to examine beliefs in this population and therapy.

Please read the attached participant information sheet for more information and details regarding the study.

If you decide that you would like to take part, please complete the participant eligibility form and email this to Bronwyn Stirzaker at umbms@leeds.ac.uk. Your eligibility form will then be assessed, if it meets our criteria and recruitment is ongoing you will be emailed a link to our online survey.

Appendix B: study one information sheet for clinicians

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

INFORMATION SHEET FOR CLINICIANS
(Version 2: 24/11/18, IRAS: 249889)

Project title: Refining the Beliefs about Medicines Questionnaire-Specific to nebulised medication categories in Cystic Fibrosis

Introduction

You are being invited to take part in a two-part online Delphi survey which aims to gain feedback on two questionnaires that we have revised from an established measure. These questionnaires aim to examine specific treatment beliefs that adolescents (aged 12-17) with cystic fibrosis and their parents hold towards nebulised mucolytic and antibiotic medications.

These questionnaires have been developed from the Beliefs about Medicines Questionnaire-Specific (BMQ-Specific), a measure developed to access treatment beliefs across chronic conditions (Horne, Weinman & Hankins, 1999). This measure is commonly adapted to the condition and medication of interest (commonly asthma, diabetes) through the rewording, removal, and, where relevant, addition of items. However, it has rarely been examined with respect to cystic fibrosis and has never been specifically adapted to nebulised medications.

This questionnaire is based on the Necessity-Concerns Framework (Horne & Weinman, 1999), which suggests that primary common-sense evaluations that people make about treatment fall into two categories. The first category, necessity, refers to implicit judgements about personal need for medication (e.g. how much one feels they need this treatment to maintain and/or improve current and future health). The second, concerns, refers to implicit beliefs individuals hold about potential adverse reactions and consequences from using their prescribed medication. We have revised the questionnaire to incorporate necessity and concern beliefs that we feel are pertinent for nebulised mucolytic and antibiotic medications in this client group.

We hope to use this survey to gain feedback from patients, parents and professionals alike, on the value and acceptability of our adapted questionnaires. We hope to use these revised questionnaires to help us improve support for patients in completing their nebulised treatments.

What is a Delphi survey?

A Delphi survey is used to ask experts about a topic through a series of questionnaires with the aim of combining opinions and achieving agreement. The responses from each round of questionnaires are fed back to the experts through an updated questionnaire.

Who is organising the research?

This study is being completed by Bronwyn Stirzaker (Psychologist in Clinical Training) as part of her degree at the University of Leeds, alongside Dr. Gary Latchford and Dr. Alistair Duff, who are Clinical Psychologists in the Leeds CF unit. It is important that you read the information below before making your decision about whether you want to take part.

Why have we been invited to take part?

You have been chosen to take part because you are a healthcare professional who has worked within CF for at least a year, and as you have experience of discussing nebulised medications with your patients.

What will I need to do?

We will ask you to complete a series of two online surveys. In the first round you will be asked to read our two questionnaires (one for mucolytics and one for antibiotics) and to rate the value and clarity of each questionnaire item. A text box will also be made available so that you can write any comments that you may have. At the end of the survey, a text box will also be available to enable you to suggest new items. Within 14-30 days, the second-round survey will be sent. You will be asked to rate the same questionnaires, but this time, you will also see your answers from the first survey, the average score from all participants for each item, and some of their comments. This means that other participants may see your comments, but they will be anonymous. You will be asked to re-evaluate your ratings after considering the views of others. On average, it is expected that it will take you approximately 15 minutes to evaluate our questionnaires the first time, and 20 minutes the second time.

We will require you to complete the questionnaires within 14 days of receiving the links, though we would prefer for you to complete them as soon as you are able to, since we are only able to create and email out the second-round surveys once all the responses from the first round have been received. If you haven't completed it within 7 days, we will send you a reminder by email.

If you wish to take part, please complete the eligibility criteria document and email this to Bronwyn Stirzaker at umbms@leeds.ac.uk. Your eligibility form will then be assessed if we are still recruiting. We plan to recruit the first few clinicians who reply and who are eligible for the study. We will send an email to you to let you know whether you have or have not been selected. If you have been selected, we will email you with a link to access the first round of the online survey.

What are the possible advantages or disadvantages of taking part?

If you take part, we cannot promise that this study will have any direct benefit for your patients / practice, but it might help other CF centres or future treatment. We are looking at this to help CF centres understand the beliefs that young people and their parents hold towards their nebulised medication, so that they can improve the support they offer to help young people to take these medications.

Do I have to take part?

No, it is up to you whether you wish to take part and you may discontinue at any time. If you choose not to take part or discontinue, this will have no consequence and you will not be expected to give a reason. If you begin a survey but wish to withdraw before completing it, you can do so by exiting from the questionnaire screen. In this instance, your data will not have been stored, as you will have exited the survey prematurely. If you complete a survey but later wish to withdraw your data, you can do so up to 7 days after completing the survey by emailing the researcher: Bronwyn Stirzaker (umbms@leeds.ac.uk). After this time data analysis will have started, so you will be unable to withdraw your data.

What happens to the information and who will see it?

Your data will initially be stored on the secure Online Survey database. It will later be downloaded to a secure drive at the University of Leeds to allow data analysis to be completed. Your questionnaire responses will be stored under a participant number, will be kept in a password-protected file on a password-protected computer, and will only be accessible to members of the research team. Your identifiable information (i.e. your name and email address) will be stored and accessed in the same way but will be kept in a separate electronic file. Your survey responses will be deleted in 3 years' time, and your personal details will be deleted after the second survey has been completed, or when no further correspondence is required between yourself and the researcher.

This study will be written into a thesis document which will be made available online. We also hope to publish this study in online academic journals and to present the results to other

professionals; this will include your ratings and may include your comments, but you will not be identifiable. If you would like to receive a summary of the findings, please email Bronwyn Stirzaker on umbms@leeds.ac.uk.

Contacts for further information

If you could like any further information or would like to make a complaint, please contact: **Researcher**: Bronwyn Stirzaker, Psychologist in Clinical Training, or the **Project supervisors**: Dr Gary Latchford, Joint Programme Director, Clinical Psychology Training Programme, Leeds Institute of Health Sciences, g.latchford@leeds.ac.uk and Dr Alistair Duff, Clinical Psychologist, The Leeds Regional Cystic Fibrosis Centre, A.J.Duff@leeds.ac.uk. You can also contact Dr Alistair Duff or Dr Gary Latchford, through telephone through contacting the Leeds CF centre on **0113 3927125**. You will be asked to leave a name and a contact number so that they can return your call.

Who has reviewed the study?

This study was given ethical approval by the Research Ethics Committee (ref: 18/YH/0496).

Thank you for reading, please do email to ask any questions that you may have.

Appendix C: study one clinician eligibility form

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The Leeds Teaching Hospitals NHS
NHS Trust

ELIGIBILITY FORM FOR CLINICIANS
(Version 2: 24/11/18, IRAS: 249889)

Title: Refining the Beliefs about Medicines Questionnaire-Specific to nebulised medication categories in Cystic Fibrosis

Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Please read the following and confirm if the following statements are true by checking the box.

1. I have worked in CF services for at least one year as a clinician ☐
2. I am a qualified Physiotherapist ☐
3. I have experience of discussing nebulised medications with patients ☐

Appendix D: study one patient and parent information sheets

Appendix D.1: study one patient information sheet

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The Leeds Teaching Hospitals NHS
NHS Trust

INFORMATION SHEET
(Version 2: 24/11/18, IRAS: 249889)

Project title: Refining the Beliefs about Medicines Questionnaire-Specific to nebulised medication categories in Cystic Fibrosis

What is the study about?

You and your parent are being invited to take part in a in a two-part online Delphi survey, which aims to provide us with feedback on two questionnaires that we have developed. We want to use these questionnaires to measure thoughts that young people (aged 12-17) and their parents have, about nebulised mucolytic and antibiotic medications.

More specifically, we want to use these questionnaires to measure how necessary people think these nebulised medications are to control their/their child's symptoms and to keep them healthy, both now and in the future. We also want to know what they think the consequences of taking nebulised medications are, and how concerned they are about these. We hope to gain the opinions of patients, parents and professionals on our questionnaires, so that we can make sure that we are asking useful questions which are easy to understand.

What is a Delphi survey?

A Delphi survey is used to ask experts about a topic through a series of questionnaires with the aim of combining opinions and achieving agreement. The responses from each round of questionnaires are fed back to the experts through an updated questionnaire.

Who has made the study?

This study is being run by Bronwyn Stirzaker (Psychologist in Clinical Training) as part of her doctorate degree at the University of Leeds, alongside Dr. Gary Latchford and Dr. Alistair Duff, who are Clinical Psychologists in the Leeds CF unit. It is important that you read the information below before making your decision about whether you want to take part. You can talk to other people (e.g. friends, family, medical professionals) about it if you like.

Why have we been invited to take part?

You have been chosen to take part because you have CF, you have used nebulised antibiotics and mucolytics within the last 12 months for at least 2 months, and you are aged between 16 and 17 years.

What will I need to do?

We will ask you to complete a series of two online surveys. In the first round you will be asked to read our two questionnaires and let us know how useful and clearly-worded you think each question is. You will also be able to write comments about each question, and, at the end, you will also be able to suggest ideas that you may have for additional questions. When you complete the survey the second time, you will be able to see your answers from the first time, as well as the average score other people gave the questions, and some of their comments. This means that other participants may see your comments, but they will be anonymous. You will be asked to make your ratings again after looking at what other people thought.

It should take around 15 minutes for you to complete the questions the first time, and 20 minutes the second time. You would need to complete these this survey yourself without asking your parent for answers, but they can help you to understand other things if you are unsure. We will need you to complete the questionnaires within 14 days of receiving the links, and ideally as soon as you are able. We are unable to make and email out the second-round survey until everyone has completed the first round. If you haven't completed the first survey within 7 days, we will send you a reminder by email to help you remember.

If you, your parent or both of you decide that you would like to take part, then you will need to email the researcher (Bronwyn Stirzaker) directly on umbms@leeds.ac.uk. We will select the first patient and the first parent who email us to take part in the project. We will send an email to you know whether you have or have not been selected. If you have been selected, we will send an email to you with a link to our survey. You will be asked to complete our survey twice, approximately 14 to 30 days apart.

Do I have to take part?

No, it is up to you whether you wish to take part and you can take this information sheet away to think about it. If you choose not to take part, or leave the study early, this will not have any consequence or effect on your treatment. You do not need to give a reason if you do not want to complete the study or if you decide to leave the study early. If you begin a survey but wish to withdraw before completing it, you can do so by exiting from the questionnaire screen. In this instance, your data will not have been stored, as you will have exited the survey prematurely. If you complete a survey but later wish to withdraw your data, you can do so up to 7 days after completing the survey by emailing the researcher: Bronwyn Stirzaker (umbms@leeds.ac.uk). After this time data analysis will have started, so you will be unable to withdraw your data.

What are the possible advantages or disadvantages of taking part?

If you take part, we cannot promise that this study will have any direct benefit for you, but it might help your CF centre. We are looking at this to help CF centres understand the beliefs that young people and their parents hold about their nebulised medication, so that they can improve the support they offer to help young people to take these medications.

What happens to the information and who will see it?

Your data will initially be stored on the secure Online Survey database. It will later be downloaded to a secure drive at the University of Leeds to allow data analysis to be completed. Your questionnaire responses will be stored under a participant number, will be kept in a password-protected file on a password-protected computer, and will only be accessible to members of the research team. Your identifiable information (i.e. your name and email address) will be stored and accessed in the same way but will be kept in a separate electronic file. Your survey responses will be deleted in 3 years' time, and your personal details will be deleted after the second survey has been completed, or when no further correspondence is required between yourself and the researcher.

We hope to write about what we find, put these findings on research related websites and present them to other professionals. This may include your ratings and comments, but these will be presented anonymously. If you would like to receive a summary of the findings, please email Bronwyn Stirzaker on umbms@leeds.ac.uk.

Can I get further information?

If you would like any more information about the study before you and your parent make your decision, or would like to make a complaint please contact Bronwyn Stirzaker at umbms@leeds.ac.uk, or the projects supervisor's Dr Alistair Duff or Dr Gary Latchford who are based at the Leeds CF centre, and can be contacted on **0113 3927125**. You will be asked to leave a name and a contact number so that they can return your call.

Who has reviewed the study?

Before any research goes ahead, it must be checked by an independent group of people called the Research Ethics Committee (REC). They make sure the research is fair. They approved this study (ref: 18/YH/0496).

Thank you for reading this information! Please ask any questions that you have.

Appendix D.2: study one parent information sheet

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

INFORMATION SHEET
(Version 2: 24/11/18, IRAS: 249889)

Project title: Refining the Beliefs about Medicines Questionnaire-Specific to nebulised medication categories in Cystic Fibrosis

Introduction

You and your child are being invited to take part in a two-part online Delphi survey, which aims to provide us with feedback on two questionnaires that we have developed. We want to use these questionnaires to measure beliefs that young people (aged 12-17) and their parents have about nebulised mucolytic and antibiotic medications.

More specifically, we want to use these questionnaires to measure how necessary people think these nebulised medications are to control their/their child's symptoms and to keep them healthy, both now and in the future. We also want to know what they think the consequences of taking nebulised medications are, and how concerned they are about these. We hope to gain the opinions of patients, parents and other professionals on our questionnaires, to ensure that we are asking useful and relevant questions, which are clear to understand.

What is a Delphi survey?

A Delphi survey is used to ask experts about a topic through a series of questionnaires with the aim of combining opinions and achieving agreement. The responses from each round of questionnaires are fed back to the experts through an updated questionnaire.

Who is organising the research?

This study is being run by Bronwyn Stirzaker (Psychologist in Clinical Training) as part of her doctorate degree at the University of Leeds, alongside Dr. Gary Latchford and Dr. Alistair Duff, who are Clinical Psychologists in the Leeds CF unit. It is important that you read the information below before making your decision about whether you want to take part. You can talk to other people (e.g. friends, family, medical professionals) about it if you like.

Why have we been invited to take part?

You have been chosen to take part because your child is aged 16-17, has CF, and has within the last year used nebulised antibiotics and mucolytics for at least 2 months.

What will I need to do?

We will ask you to complete a series of two online surveys. In the first round you will be asked to read our two questionnaires. We will ask you how useful and clearly-worded you think each question is. You will also be able to write comments about this and will have the opportunity to suggest ideas you may have for additional questions at the end. When you complete the survey the second time, you will be able to see your answers from first time, the average score other people gave the questions, and some of their comments. This means that other participants may see your comments, but they will be anonymous. You will be asked to make your ratings again after considering the opinions of others alongside your own.

It should take you approximately 15 minutes to evaluate our questionnaires the first time, and

20 minutes the second time. We will need you to complete the questionnaires within 14 days of receiving the links, and ideally as soon as you are able. We are unable to make and email out the second-round survey until everyone has completed the first round. If you haven't completed the first survey within 7 days, we will send you a reminder by email to help you remember.

Should your child also be selected to participate, we asked that you evaluate our questionnaires individually and do not help each other choose answers, as we are interested in your and your child's separate opinions. You could, however, help your child to understand what they are doing if they are unsure.

If you, your child or both of you decide that you would like to take part, then you will need to email the researcher (Bronwyn Stirzaker) directly on umbms@leeds.ac.uk. We will select the first patient and parent who email us to take part in the project. We will send an email to let you know whether you have or have not been selected. If you have been selected, we will send an email to you with a link to our survey. You will be asked to complete our survey twice, approximately 14 to 30 days apart.

Do I have to take part?

No, it is up to you whether you wish to take part and you can take this information sheet away to think about it. If you choose not to take part, or leave the study early, this will not have any consequence or effect on your child's treatment. You do not need to give a reason if you do not want to complete the study or if you decide to leave the study early. If you begin a survey but wish to withdraw before completing it, you can do so by exiting from the questionnaire screen. In this instance, your data will not have been stored, as you will have exited the survey prematurely. If you complete a survey but later wish to withdraw your data, you can do so up to 7 days after completing the survey by emailing the researcher: Bronwyn Stirzaker (umbms@leeds.ac.uk). After this time data analysis will have started, so you will be unable to withdraw your data.

What are the possible advantages or disadvantages of taking part?

If you take part, we cannot promise that this study will have any direct benefit for you or your child, but it might help your CF centre. We are looking at this to help CF centres understand the beliefs that young people and their parents hold towards their nebulised medications, so that they can improve the support they offer to help young people to take these medications.

What happens to the information and who will see it?

Your data will initially be stored on the secure Online Survey database. It will later be downloaded to a secure drive at the University of Leeds to allow data analysis to be completed. Your questionnaire responses will be stored under a participant number, will be kept in a password-protected file on a password-protected computer, and will only be accessible to members of the research team. Your identifiable information (i.e. your name and email address) will be stored and accessed in the same way but will be kept in a separate electronic file. Your survey responses will be deleted in 3 years' time, and your personal details will be deleted after the second survey has been completed, or when no further correspondence is required between yourself and the researcher.

This study will be written into a thesis document which will be made available online. We also hope to publish this study in online academic journals and to present the results to other professionals; this will include your ratings and may include your comments, but you will not be identifiable. If you would like to receive a summary of the findings, please email Bronwyn Stirzaker on umbms@leeds.ac.uk.

Can I get further information?

If you would like any more information about the study or would like to make a complaint, please contact Bronwyn Stirzaker at umbms@leeds.ac.uk, or the projects supervisor's Dr Alistair Duff or Dr Gary Latchford, who are based at the Leeds CF centre, and can be contacted on **0113 3927125**. You will be asked to leave a name and a contact number so that they can return your call.

Who has reviewed the study?

Before any research goes ahead, it must be checked by an independent group of people called the Research Ethics Committee (REC) to ensure the research complies with the relevant ethical standards. They approved this study (ref: 18/YH/0496).

Thank you for taking the time to read this information. Please ask any questions that you may have.

Appendix E: study one ethics approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Bronwyn Stirzaker
The Leeds Teaching Hospitals NHS Trust
Leeds Institute of Health Sciences, University of Leeds
Level 10 Worsley Building, Clarendon Way
Leeds
LS2 9NL

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

21 December 2018

Dear Miss Stirzaker

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

Study title:	**The role of beliefs in predicting adherence to nebulised therapy in adolescents with cystic fibrosis.**
IRAS project ID:	**249889**
REC reference:	**18/YH/0496**
Sponsor:	**University of Leeds**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

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

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

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

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

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

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Miss Bronwyn Stirzaker
Tel: 0113 343 2732
Email: umbms@leeds.ac.uk

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

Your IRAS project ID is **249889**. Please quote this on all correspondence.

Yours sincerely

Michael Higgs
Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Gary Latchford, University of Leeds (Academic supervisor)*
R&D office, University of Leeds
R&D office, Leeds Teaching Hospitals NHS Trust

Appendix F: study one draft CF-BMQ-A and CF-BMQ-M

Appendix F.1: study one initial draft CF-BMQ-A

sn1	**My health at present depends on me taking my nebulised antibiotics**
sc1	**Having to take nebulised antibiotics worries me**
sc2	**I sometimes worry about long-term effects of taking my nebulised antibiotics**
Sn2	**Without my nebulised antibiotics I would be very ill**
sc3	**I don't understand why I need to take my nebulised antibiotics**
Sn3	**My health in the future will depend on my nebulised antibiotics**
sc4	**Taking my nebulised antibiotics disrupts my life**
sc5	**I sometimes worry about becoming too dependent on my nebulised antibiotics**
Sn4	**My nebulised antibiotics stop me from becoming worse**
Sc6	**Taking my nebulised antibiotics is unpleasant**
Sc7	**My nebulised antibiotics cause unpleasant short-term side-effects**

Appendix F.2: study one initial draft CF-BMQ-M

sn1	**My health at present depends on me taking my nebulised mucolytics**
sc1	**Having to take nebulised mucolytics worries me**
sc2	**I sometimes worry about long-term effects of taking my nebulised mucolytics**
Sn2	**Without my nebulised mucolytics I would be very ill**
sc3	**I don't understand why I need to take my nebulised mucolytics**
Sn3	**My health in the future will depend on my nebulised mucolytics**
sc4	**Taking my nebulised mucolytics disrupts my life**
sc5	**I sometimes worry about becoming too dependent on my nebulised mucolytics**
Sn4	**My nebulised mucolytics stop me from becoming worse**
Sc6	**My nebulised mucolytics cause unpleasant short-term side-effects**

Appendix G: study one CF-BMA-A and CF-BMQ-M following Delphi survey round one

Appendix G.1: study one CF-BMQ-A following Delphi survey round one

sn1	**To be healthy now, I need to take my nebulised antibiotics**
sc1	**Having to take my nebulised antibiotics worries me**
sc2	**I sometimes worry about the long-term effects of taking my nebulised antibiotics**
Sn2	**Without my nebulised antibiotics my health would be much worse**
sc3	**I don't understand why I need to take my nebulised antibiotics**
Sn3	**To be healthy in the future, I need to take my nebulised antibiotics now**
sc4	**Taking my nebulised antibiotics gets in the way of my life**
sc5	**I sometimes worry that taking my nebulised antibiotics now will mean that they won't work as well in future**
Sn4	**My nebulised antibiotics stop my health from becoming worse**
Sc6	**My nebulised antibiotics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick)**
Sc7	**Taking my nebulised antibiotics is embarrassing**
Sc8	**I only need to take my nebulised antibiotics when I feel unwell**

Appendix G.2: study one CF-BMQ-M following Delphi survey round one

sn1	**To be healthy now, I need to take my nebulised mucolytics**
sc1	**Having to take my nebulised mucolytics worries me**
sc2	**I sometimes worry about the long-term effects of taking my nebulised mucolytic**
Sn2	**Without my nebulised mucolytics my health would be much worse**
sc3	**I don't understand why I need to take my nebulised mucolytics**
Sn3	**To be healthy in future, I need to take my nebulised mucolytics now**
sc4	**Taking my nebulised mucolytics gets in the way of my life**
Sn4	**My nebulised mucolytics stop my health from becoming worse**
Sc6	**My nebulised mucolytics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick)**
Sc7	**Taking my nebulised mucolytics is embarrassing**
Sc8	**I only need to take my nebulised mucolytics when I feel unwell**

Appendix H: study one CF-BMA-A and CF-BMQ-M following Delphi survey round one

Appendix H.1: study one final CF-BMQ-A following Delphi survey round two

The CF Beliefs about Medicines Questionnaire Specific
ADOLESCENT ANTIBIOTICS
(Version 1: 14/04/19, IRAS: 249889)

Patient Identification Number: _____

YOUR VIEWS ON THE NEBULISED MEDICATION PRESRIBED FOR YOUR CYSTIC FIBROSIS						
We would like to ask you what you think about the nebulised medication prescribed for your CF. **These are statements that other people have made about their medications. Please show how much you agree or disagree with them by ticking the appropriate box.** **There are no right or wrong answers. We are just interested in what you think. Please complete this without asking your parent/guardian for the answers. Please only tick one box per question.**						
Please only consider ……. (nebulised <u>Antibiotic</u>) when you answer.						
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
1.	**To be healthy now, I need to take my nebulised Antibiotics**					
2.	**Having to take my nebulised Antibiotics worries me**					
3.	**I sometimes worry about the long-term effects of my nebulised Antibiotics**					
4.	**Without my nebulised Antibiotics my health would be much worse**					
5.	**I don't understand why I need to take my nebulised Antibiotics**					
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**

6.	**To be healthy in future, I need to take my nebulised Antibiotics now**					
7.	**Taking my nebulised Antibiotics gets in the way of my life**					
8.	**I sometimes worry that taking my nebulised Antibiotics now will mean that they won't work as well in future**					
9.	**My nebulised Antibiotics stop my health from becoming worse**					
10.	**My nebulised Antibiotics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick)**					
11.	**Taking my nebulised Antibiotics is embarrassing**					
12.	**I only need to take my nebulised Antibiotics when I feel unwell**					

Appendix H.2: study one final CF-BMQ-M following Delphi survey round two

The CF Beliefs about Medicines Questionnaire Specific
ADOLESCENT MUCOLYTICS
(Version 1: 14/04/19, IRAS: 249889)

Patient Identification Number: _____

YOUR VIEWS ON THE NEBULISED MEDICATION PRESRIBED FOR YOUR CYSTIC FIBROSIS
We would like to ask you what you think about the nebulised medication prescribed for your CF. **These are statements that other people have made about their medications. Please show how much you agree or disagree with them by ticking the appropriate box.** **There are no right or wrong answers. We are just interested in what you think. Please complete this without asking your parent/guardian for the answers. Please only tick one box per question.**
Please only consider ……. (nebulised <u>Mucolytic</u>) when you answer.

		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
1.	**To be healthy now, I need to take my nebulised Mucolytics**					
2.	**Having to take my nebulised Mucolytics worries me**					
3.	**I sometimes worry about the long-term effects of my nebulised Mucolytics**					
4.	**Without my nebulised Mucolytics my health would be much worse**					
5.	**I don't understand why I need to take my nebulised Mucolytics**					
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
6.	**To be healthy in future, I need to take my nebulised Mucolytics now**					

7.	**Taking my nebulised Mucolytics gets in the way of my life**					
8.	**I sometimes worry that taking my nebulised Mucolytics now will mean that they won't work as well in future**					
9.	**My nebulised Mucolytics stop my health from becoming worse**					
10.	**My nebulised Mucolytics can cause unpleasant side-effects (e.g. bad taste, coughing, feeling sick)**					
11.	**Taking my nebulised Mucolytics is embarrassing**					
12.	**I only need to take my nebulised Mucolytics when I feel unwell**					

Appendix I: study two information sheets for patients and parents

Appendix I.1: study two patient information sheet

Phase 2 Information sheet for adolescents

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

INFORMATION SHEET
(Version 3: 26/04/19, IRAS: 249889)

Project title: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

What is the study about?

You are being invited to take part in a study. The study is looking at how often young people take their nebulised CF medications, and whether this is affected by what they and/or their parents/guardian think about inhaled medication. The study is taking place at three CF centres in England: at Leeds, Liverpool and Sheffield.

Who has made the study?

This study is being run by Bronwyn Stirzaker (Psychologist in Clinical Training) as part of her degree at the University of Leeds, with Dr. Gary Latchford and Dr. Alistair Duff, who work in the Leeds CF centre as Clinical Psychologists. It is important that you read the information below before making your decision about whether you want to take part. Please also talk to other people (e.g. friends, family, medical professionals) about it if you like.

Why have I been asked to take part?

You have been chosen to take part as you are aged between 12-17 years, have CF, and use nebulised medications.

What will happen if I do the study?

If you agree to take part, we will ask you and your parent/guardian to complete some short questionnaires. If you take nebulised mucolytics only, we will ask you to complete 3 questionnaires (which should take about 15 minutes). If you take both nebulised mucolytic and antibiotic medications, we will ask you to complete 5 questionnaires (this takes about 25 minutes). All but one of the questionnaires will list a set of beliefs a person might have about taking their nebulised CF medication, and it will ask you to say how much you agree with them. These questionnaires will often ask the same or very similar questions, but it is important that you complete them as carefully as you can. One other questionnaire will list beliefs a person might have about CF, and will, again, ask you how much you agree with them.

It is important that you fill out the answers to your questionnaires yourself without asking your parent/guardian for their opinions, as we are interested in what you think. However, your parents and/or medical professionals can help you if you don't understand something.

We will also ask to have access to the information stored on your nebuliser that is routinely collected on your clinic visits. This will tell us how often you're taking your medication. We also want to gain some information about you and your family e.g. who lives at your home and where you live, we will ask your parent for this. We will also ask you if your clinician can give us some information from your medical file, as we want to know what medications you take and how healthy

you are.

What are the possible advantages or disadvantages of taking part?

If you take part, we can't promise that this study will have any direct benefit for you, but it might help your CF centre and future patients like you. We are doing this study to help CF centres understand how they can improve the support offered to help young people to take their medication.

Do I have to do it?

No. You choose. You can take this information sheet away and think about it, and you can ask other people (e.g. friends and family) what they think. If you decide to take part, you will be asked to sign an assent form (if you are less than 16 years old), or a consent form (if you are 16 years old or above), on your next visit. If you choose not to take part, this will not affect your treatment. You can also change your mind about doing the study at any time and you don't need to give a reason. If you take part, but later do not wish for us to use your data, you can contact us and let us know up to two weeks after completing the study.

What happens to the information and who will see it?

We will photocopy your consent/assent form and your parents', so that we have three copies. The first will go in your medical file, so anyone who sees this will know that you and your parent have agreed to take part in this study. The second is for you to keep, and the third will be put in a research file at your CF centre before being moved to the University of Leeds. It will be stored safely in a locked cabinet and only the research team will look at them. The questionnaires that you, your parent and Physiotherapist complete will be stored in the same way. Your individual questionnaire answers will not be shown to, or discussed with, any member of staff in your care. Your iNebuliser data will be stored on a secure network drive at your CF centre before being moved to a secure drive at the Leeds CF centre (if this is not your centre) and at the University of Leeds

Your and your parents' research data will be pseudo-anonymised. This means that none of your questionnaires or your I-nebuliser data will have your name on, instead it will have a research number. We will have a separate document that matches this number with your name. Again, this will be stored securely and will be password-protected. Your data will be moved to the University of Leeds by the researcher once you have finished the study. At this time your paper-based questionnaire answers and details will be transferred to a secure computer database to allow the researcher to analyse it. All of the data collected in the study will be deleted in 3 years' time.

What will you do with what you find?

We hope to write about what we find, put these findings on relevant research websites and present them to other professionals. If you would like to receive a summary of the findings, please let your physiotherapist know. They will be able to give you this in a future appointment once the study has been completed.

Can I get further information?

If you would like any more information about the study before making your decision or would like to make a complaint, please email Bronwyn Stirzaker on umbms@leeds.ac.uk. Or contact Dr Alistair Duff or Dr Gary Latchford, they work at the Leeds CF centre, and you or your parents can call them on **0113 3927125**. You will be asked to leave a name and a contact number so that they can return your call.

Who has reviewed the study?

Before any research goes ahead, it must be checked by an independent group of people called a Research Ethics Committee (REC). They make sure the research is fair. They approved this study (ref: 18/YH/0496).

Thank you for reading! Please ask any questions you have.

Appendix I.2: study two parent information sheet

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

INFORMATION SHEET
(Version 3: 26/04/19, IRAS: 249889)

Project title: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

Introduction

You and your child are being invited to take part in a study which looks at how often young people take their nebulised CF medications, and whether this is affected by what they and their parents/guardians think about such medication. The study is taking place at three CF centres in England: at Leeds, Liverpool and Sheffield.

Who is organising the research?

This study is being run by Bronwyn Stirzaker (Psychologist in Clinical Training) as part of her research degree at the university of Leeds, alongside Dr. Gary Latchford and Dr. Alistair Duff, who are Clinical Psychologists in the Leeds CF unit. It is important that you read the following information before making your decision. Please also discuss this with other individuals (e.g. friends, family, medical professionals) if you like.

Why have I been asked to take part?

You have been chosen to take part as your child is aged between 12-17 years, has CF, and uses nebulised medication.

What will happen if I decide to take part?

If you and your child decide to take part, we will ask you both to complete some short questionnaires. If your child takes nebulised mucolytics only, we will ask you to complete 3 questionnaires (which should take about 15 minutes), and if your child takes nebulised mucolytic and antibiotic medications we will ask you to complete 5 (about 25 minutes). All but one of your child's questionnaires contain a set of beliefs a person with CF might have about taking their medication. Your questionnaires are similar, listing the same beliefs but from a parent's perspective. The questionnaires you will be asked to complete will often ask the same or very similar questions, so it is important that you read them carefully. The other questionnaire will list a set of beliefs that a person, and their parent/guardian, may hold about their CF in general, and you are again asked to consider this from a parent's perspective.

You will need to fill out your questionnaire independently of your child, as we are interested in each of your and their views separately. For this reason, we ask that you avoid helping them to choose answers, but you can of course help them if they don't understand something. Please ask a member of staff if anything is unclear.

We will also ask to have access to the information that is stored on your child's nebuliser which is routinely collected on your outpatient visits to the clinic. This will tell us how often your child is taking their medication. Lastly, we will ask you to provide some social and demographic information, and we will ask to have access to information from your child's medical file i.e. their medication prescriptions and current health status. This will be given to us by a member of their clinical care team, we will not directly look at your child's records.

What are the possible advantages or disadvantages of taking part?

If you take part, we cannot promise that this study will have any direct benefit for you or your

child, but it might help the CF centre that your child attends. We are undertaking this study to help CF centres understand how they can improve the support offered to help young people to take their nebulised medication.

Do I have to take part?

No. It is your and your child's decision whether you take part in this study. You can both take your information sheets away and take time to think. If you do decide to take part, you will be asked to sign a consent form, and your child will be asked to sign an assent or consent form depending on their age. If your child is aged under 16 years, you will also be asked to sign a consent form to indicate their agreement.

If you choose not to take part, this will not have any effect on your child's future treatment at the Centre. You can change your mind about participating at any time, without needing to give a reason for wanting to leave the study, and this will not impact your child's treatment. If you take part, but later do not wish for us to use your data, you can contact us and let us know up to two weeks after completing the study.

Who will know about my taking part and what happens to the information?

Three copies of your and your child's consent forms will be made. The first, the original, will be kept in your child's medical file. This means that any professionals who usually have access to your child's medical file will know that you and your child have agreed to participate in this study. The second copy you will be able to take away for your reference. The third will be placed in a research file in the CF centre before being moved to the University of Leeds. It will be stored in locked cabinets in access-controlled rooms at both sides, to ensure the data remains secure and confidential. Your and your child's questionnaire responses, and other paper-based details (i.e. socio-demographic, prescription and health information) will be stored in the same manner, but in a separate cabinet to support anonymity. Your individual questionnaire responses will not be shown to, or discussed with, any member of staff involved in your child's care. Initially your child's iNebuliser information will be stored on a secure network drive at your CF centre, before being moved to a secure drive at the Leeds CF centre (if this is not your centre) and at the University of Leeds.

Your and your child's research data will be pseudo-anonymised. This means that none of your questionnaires or your I-nebuliser data will have your name on, instead it will have a research number. We will have a separate document that matches this number with your name. Again, this will be stored securely and will be password-protected. The research data will be moved to the University of Leeds by the researcher once you have finished the study. At this time your paper-based questionnaire responses and details will also be transferred to a secure computer database to allow data analysis. All of the data collected in the study will be deleted in 3 years' time.

What will happen to the results of the study?

We hope to publish this study in an academic journal which is made available on relevant research websites. We also hope to present the results to other professionals. If you would like to receive a summary of the findings please let the physiotherapist know. They will be able to give you this in a future appointment once the study has been completed.

Can I get further information?

If you would like more information about the study before making your decision or would like to make a complaint, please email Bronwyn Stirzaker on umbms@leeds.ac.uk. Or speak to Dr Alistair Duff or Dr Gary Latchford, they are based at the Leeds CF centre and can be contacted on **0113 3927125**. You will be asked to leave a name and a contact number so that they can return your call.

Who has reviewed the study?

Before any research goes ahead it must be checked by an independent group of individuals on a Research Ethics Committee (REC). They approved this study (ref: 18/YH/0496).

Thank you for taking the time to read this information. Please ask any questions you have

Appendix J: study two ethics approval

Amendment Categorisation and Implementation Information

Dear Miss Stirzaker,

IRAS Project ID:	249889
Short Study Title:	Role of beliefs in predicting adherence to nebulised therapy in CF
Date complete amendment submission received:	20th August 2019
Amendment No./ Sponsor Ref:	Non-Substantial Amendment 1
Amendment Date:	20 August 2019
Amendment Type:	Non-substantial
Outcome of HRA and HCRW Assessment	**This email also constitutes HRA and HCRW Approval for the amendment,** and you should not expect anything further.
Implementation date in NHS organisations in England and Wales	35 days from date amendment information together with this email, is supplied to participating organisations **(providing conditions are met)**
For NHS/HSC R&D Office information	
Amendment Category	**A**

Thank you for submitting an amendment to your project. We have now categorised your amendment and please find this, as well as other relevant information, in the table above.

What should I do next?

Please read the information in IRAS, which provides you with information on how and when you can implement your amendment at NHS/HSC sites in each nation, and what actions you should take now.

If you have participating NHS/HSC organisations in any other UK nations please note that **we will** forward the amendment submission to the relevant national coordinating function(s).

If not already provided, please email to us any regulatory approvals (where applicable) once available.

When can I implement this amendment?

You may implement this amendment in line with the information in IRAS. Please note that you may only implement changes described in the amendment notice.

Who should I contact if I have further questions about this amendment?

If you have any questions about this amendment please contact the relevant national coordinating centre for advice:

- England – hra.amendments@nhs.net
- Northern Ireland – research.gateway@hscni.net
- Scotland – nhsg.NRSPCC@nhs.net
- Wales – HCRW.amendments@wales.nhs.uk

Additional information on the management of amendments can be found in the IRAS guidance.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

Please do not hesitate to contact me if you require further information.

Kind regards

Miss Jane Harker

Approvals Administrator

Health Research Authority
Ground Floor | Skipton House | 80 London Road | London | SE1 6LH
E.hra.amendments@nhs.net
W. www.hra.nhs.uk

Appendix K: study two parent demographic form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Parent Identification Number: _____

DEMOGRAPHICS FORM FOR PARENT TO COMPLETE
(Version 3: 14/04/19, IRAS: 249889)

Title: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Please complete the following in relation to yourself, NOT your child.

Your gender:	**Your age:**
Your ethnicity:	**Your religion:**
Your job:	**Your education level:** (e.g. high school, college, university)
Your postcode:	

1. **What is your relationship to the patient?** ……
2. **Are you currently married?** ……
3. **How many adults live in your home?** ……
4. **How many children live in your home?** ……

Please complete the following in relation to your child:

Religion:	**Ethnicity:**

Appendix L: study two patient demographic and health status form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Identification Number: _____

DEMOGRAPHICS AND HEALTH STATUS FORM FOR CLINICIAN TO COMPLETE
(Version 1: 17/08/18, IRAS: 249889)

Title: role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Patients age:	**Gender:**
Current FEV rating:	**Inpatient stays in last year:**
Current prescribed nebulised medications, including dose (please list). Please indicate which are currently taken through an I-neb devise. **1.** **2.** **3.** **4.**	
Changes to prescribed nebulised medications within the data collection period? (includes types and dose). Please provide details and dates: **1.** **2.** **3.**	

Appendix M: study two patient BMQ-A and BMQ-M

Appendix M.1: study two patient BMQ-A

The Beliefs about Medicines Questionnaire Specific
ADOLESCENT ANTIBIOTICS
(Version 2: 14/04/19, IRAS: 249889)

Patient Identification Number: _____

YOUR VIEWS ON THE NEBULISED MEDICATION PRESRIBED FOR YOUR CYSTIC FIBROSIS						
We would like to ask you what you think about the nebulised medication prescribed for your CF. **These are statements that other people have made about their medications. Please show how much you agree or disagree with them by ticking the appropriate box.** **There are no right or wrong answers. We are just interested in what you think. Please complete this without asking your parent/guardian for the answers. Please only tick one box per question.**						
Please only consider ……. (nebulised <u>Antibiotic</u>) when you answer.						
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
1.	**My health, at present, depends on my nebulised Antibiotics**					
2.	**Having to take nebulised Antibiotics worries me**					
3.	**My life would be impossible without my nebulised Antibiotics**					
4.	**I sometimes worry about the long-term effects of my nebulised Antibiotics**					
5.	**Without my nebulised Antibiotics I would be very ill**					
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
6.	**My nebulised Antibiotics are a mystery to me**					

7.	**My health in the future will depend on my nebulised Antibiotics**					
8.	**My nebulised Antibiotics disrupt my life**					
9.	**I sometimes worry about becoming too dependent on my nebulised Antibiotics**					
10.	**My nebulised Antibiotics protect me from becoming worse**					

Appendix M.2: study two patient BMQ-M

The Beliefs about Medicines Questionnaire Specific
ADOLESCENT MUCOLYTICS
(Version 2: 14/04/19, IRAS: 249889)

Patient Identification Number: _____

YOUR VIEWS ON YOUR PRESRIBED NEBULISED MEDICATION FOR YOUR CYSTIC FIBROSIS
We would like to ask you what you think about the nebulised medication prescribed for your CF. **These are statements that other people have made about their medications. Please show how much you agree or disagree with them by ticking the appropriate box.** **There are no right or wrong answers. We are just interested in what you think. Please complete this without asking your parent/guardian for the answers. Please only tick one box per question.**
Please only consider ……. (nebulised <u>Mucolytic</u>) when you answer.

		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
1.	**My health, at present, depends on my nebulised Mucolytics**					
2.	**Having to take nebulised Mucolytics worries me**					
3.	**My life would be impossible without my nebulised Mucolytics**					
4.	**I sometimes worry about the long-term effects of my nebulised Mucolytics**					
5.	**Without my nebulised Mucolytics I would be very ill**					
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
6.	**My nebulised Mucolytics are a mystery to me**					

7.	**My health in the future will depend on my nebulised Mucolytics**					
8.	**My nebulised Mucolytics disrupt my life**					
9.	**I sometimes worry about becoming too dependent on my nebulised Mucolytics**					
10.	**My nebulised Mucolytics protect me from becoming worse**					

Appendix N: study two parent BMQ-A and BMQ-M

Appendix N.1: study two parent BMQ-A

The Beliefs about Medicines Questionnaire Specific
PARENT/GUARDIAN ANTIBIOTICS
(Version 2: 14/04/19, IRAS: 249889)

Parent Identification Number: _____

YOUR VIEWS ON THE NEBULISED MEDICATION PRESRIBED FOR YOUR CHILD'S CYSTIC FIBROSIS

We would like to ask you about your personal views of the nebulised medication prescribed for your child's CF.

These are statements that other people have made about their medications. Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right or wrong answers. We are just interested in what your personal views are. Please complete this without speaking to your child about your answers. Please only tick one box per question.

Please only consider ……. (nebulised <u>Antibiotic</u>) when you answer.

		Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
1.	**My child's health, at present, depends on their nebulised Antibiotics**					
2.	**My child having to take nebulised Antibiotics worries me**					
3.	**My child's life would be impossible without their nebulised Antibiotics**					
4.	**I sometimes worry about the long-term effects of my child's nebulised Antibiotics**					
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**

5.	**Without their nebulised Antibiotics my child would be very ill**					
6.	**My child's nebulised Antibiotics are a mystery to me**					
7.	**My child's health in the future will depend on their nebulised Antibiotics**					
8.	**My child's nebulised Antibiotics disrupt their life**					
9.	**I sometimes worry about my child becoming too dependent on their nebulised Antibiotics**					
10.	**Nebulised Antibiotics protect my child from becoming worse**					

Appendix N.2: study two parent BMQ-M

The Beliefs about Medicines Questionnaire Specific
PARENT/GUARDIAN MUCOLYTICS
(Version 2: 14/04/19, IRAS: 249889)

Parent Identification Number: _____

YOUR VIEWS ON THE NEBULISED MEDICATION PRESRIBED FOR YOUR CHILD'S CYSTIC FIBROSIS

We would like to ask you about your personal views of the nebulised medication prescribed for your child's CF.

These are statements that other people have made about their medications. Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right or wrong answers. We are just interested in what your personal views are. Please complete this without speaking to your child about your answers. Please only tick one box per question.

Please only consider ……. (nebulised <u>Mucolytic</u>) when you answer.

		Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
1.	**My child's health, at present, depends on their nebulised Mucolytics**					
2.	**My child having to take nebulised Mucolytics worries me**					
3.	**My child's life would be impossible without their nebulised Mucolytics**					
4.	**I sometimes worry about the long-term effects of my child's nebulised Mucolytics**					
		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**

5.	**Without their nebulised Mucolytics my child would be very ill**					
6.	**My child's nebulised Mucolytics are a mystery to me**					
7.	**My child's health in the future will depend on their nebulised Mucolytics**					
8.	**My child's nebulised Mucolytics disrupt their life**					
9.	**I sometimes worry about my child becoming too dependent on their nebulised Mucolytics**					
10.	**Nebulised Mucolytics protect my child from becoming worse**					

Appendix O: study two patient and parent B-IPQ

Appendix O.1: study two patient B-IPQ

The Brief Illness Perception Questionnaire

ADOLESCENT
(Version 2: 14/04/19, IRAS: 249889)

Patient Identification Number: _____

Please read the following statements and **circle the number** that best fits your views.

There are no right or wrong answers. I am just interested in what you think. Please complete this without asking your parent what they think.

1 How much does your CF affect your life?

0	1	2	3	4	5	6	7	8	9	10
no effect at all										severely affects my life

2 How long do you think your CF will continue?

0	1	2	3	4	5	6	7	8	9	10
a very short time										forever

3 How much control do you feel you have over your CF?

0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme amount of control

4 How much do you think your treatment can help your CF?

0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful

5 How much do you experience symptoms from your CF?

0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms

6 **How concerned are you about your CF?**

0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned

7 **How well do you feel you understand your CF?**

0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly

8 **How much does your CF affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?**

0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally

Appendix O.2: study two parent B-IPQ

The Brief Illness Perception Questionnaire

PARENT
(Version 2: 14/04/19, IRAS: 249889)

Parent Identification Number: _____

Please read the following statements and **circle the number** that best fits your views.

There are no right or wrong answers. I am just interested in what you think. Please complete this without asking your child what they think.

1 How much does your child's CF affect their life?

0	1	2	3	4	5	6	7	8	9	10
no effect at all										severely affects their life

2 How long do you think your child's CF will continue?

0	1	2	3	4	5	6	7	8	9	10
a very short time										forever

3 How much control do you feel your child has over their CF?

0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme amount of control

4 How much do you think your child's treatment can help their CF?

0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful

5 How much does your child experience symptoms from their CF?

0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms

6 **How concerned are you about your child's CF?**

0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned

7 **How well do you feel you understand your child's CF?**

0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly

8 **How much does your child's CF affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?**

0	1	2	3	4	5	6	7	8	9	10
not at all affected emotionally										extremely affected emotionally

Appendix P: study two patient and parent consent forms

Appendix P.1: study two patient consent form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Identification Number: _____

CONSENT FORM FOR PATIENTS AGED 16 YEARS OR ABOVE
(Version 2: 14/04/19, IRAS: 249889)

Title of Project: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Please initial all boxes if you wish to take part in the study

1. I confirm that I have read and understood the participant information sheet (Version 1 dated **17/08/18**) for the above study, and that I have received enough information to know what the project will entail. ☐

2. I confirm that I have had the opportunity to consider the information, ask questions, and that I have had these answered satisfactorily. ☐

3. I understand that my participation is voluntary and that I am free to withdraw from this study at any time without giving a reason, and without my medical care being affected. I understand that I can withdraw my data up to the point of analysis, which is two weeks after I complete the study. ☐

4. I understand that my medical notes and data collected during the study may be looked at by individuals at my CF centre, regulatory authorities, the sponsor or the NHS Trust, where this is relevant to my participation in the research. I give permission for these individuals to have access to my records. ☐

5. I agree that readings taken from my iNebuliser from the past 2 months and for the next 2 months can be collected for use in this study. ☐

6. I understand that all my data from the questionnaires and my I-nebuliser will be pseudo-anonymised, and I agree for my responses, to be used in: reports, presentations, web pages and potential publications. ☐

7. I understand that my data will be kept confidential and stored securely. ☐

8. I agree to take part in the above study. ☐

Name of patient	Date	Signature
Name of researcher	Date	Signature

Thank you very much

When completed: 1 for participant, 1 for researchers file, 1 (original) to be kept in medical notes

Appendix P.2: study two patient assent form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Identification Number: _____

ASSENT FORM (for patients less than 16 years old)
(Version 3: 14/04/19/, IRAS: 249889)

Title: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis
Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Please circle your answers to the following questions:

Has somebody else explained this study to you? Yes/No

Do you understand what this study is about? Yes/No

Have you asked all the questions you want to? Yes/No

Are you happy to take part? Yes/No

You and the person who explained this study to you need to fill in your name, today's date and sign below:

Your name:	Today's date:	Your signature:
---	---	---
Name of person taking assent:	Date:	Signature:
---	---	---

Thank you very much for your help!
When completed: 1 for participant, 1 for researchers file, 1 (original) to be kept in medical notes.

Appendix P.3: study two parent consent form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Parent Identification Number: _____

PARENTAL CONSENT FORM
(Version 1: 14/04/19, IRAS: 249889)

Title of Project: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Please mark all boxes if you wish to take part in the study

1. I confirm that I have read and understood the participant information sheet (Version 1 dated **17/08/18**) for the above study, and that I have received enough information to know what the project will entail. ☐
2. I confirm that I have had the opportunity to consider the information, ask questions, and that I have had these answered satisfactorily. ☐
3. I understand that our participation is voluntary and that I am free to withdraw myself and my child from this study at any time without giving a reason, and without my child's medical care being affected. I understand that our data can be withdrawn up to the point of analysis. ☐
4. I understand that sections of my child's medical notes and data collected during the study may be looked at by individuals at our CF centre, the sponsor, regulatory authorities or the NHS Trust, where this is relevant to my child's participation in the research. I give permission for these individuals to have access to my child's records. ☐
5. I agree that readings taken from my child's iNebuliser from the past 2 months and for the next 2 months can be collected for use in this study. ☐
6. I understand that all my and my child's data from the questionnaires and my child's I-nebuliser will be pseudo-anonymised, and I agree for our responses, to be used in: reports, presentations, web pages and potential publications. ☐
7. I understand that our data will be kept confidential and stored securely. ☐
8. I agree for myself and my child to take part in the above study. ☐

Name of parent/guardian	Date	Signature
---	---	---
Name of consent taker	Date	Signature
---	---	---

Thank you very much

When completed: 1 for participant, 1 for researchers file, 1 (original) to be kept in medical notes.

Appendix Q: study two accessibility and usability of questionnaires form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Identification Number: _____

EVALUATING THE CF-BMQ SPECIFIC

(Version 3: 14/04/19, IRAS: 249889)

Title: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis
Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

We want to know what you thought of our CF-BMQ Specific questionnaire(s). Please read the following questions and <u>circle the number</u> that best fits your views.

1. Did you understand the questions in our questionnaire(s)?

0 1 2 3 4 5 6 7 8 9 10

I did not understand any — I understood all of them

2. Please write any questions that you did not understand in this box.

3. Were there any questions that you didn't like in our questionnaire(s)?

0 1 2 3 4 5 6 7 8 9 10

I did not like any of the questions — I liked all the questions

4. Please write the questions that you did not like in this box.

Appendix R: study two health and demographics form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

Parent Identification Number: _____

DEMOGRAPHICS FORM FOR PARENT TO COMPLETE
(Version 3: 14/04/19, IRAS: 249889)

Title: The role of beliefs in predicting adherence to nebulised therapy in adolescents with Cystic Fibrosis

Lead researcher: Bronwyn Stirzaker
Supervisors: Dr Gary Latchford and Dr Alistair Duff

Please complete the following in relation to yourself, NOT your child.

Your gender:	**Your age:**
Your ethnicity:	**Your religion:**
Your job:	**Your education level:** (e.g. high school, college, university)
Your postcode:	

1. **What is your relationship to the patient?** ……
2. **Are you currently married?** ……
3. **How many adults live in your home?** ……
4. **How many children live in your home?** ……

Please complete the following in relation to your child:

Religion:	**Ethnicity:**