

# **The Problem of Adherence in Paediatric Asthma**

**Christina Joanne Cassidy Pearce**

A thesis submitted for the degree of Doctor of Philosophy

First Supervisor – Professor Robert Horne

Second Supervisor – Dr Louise Fleming

Third Supervisor- Professor Andrew Bush

Fourth Supervisor- Dr Amy Hai Yan Chan

2020

I, Christina Joanne Cassidy Pearce confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis



## **Acknowledgements**

Firstly, I would like to thank my supervisors Professor Rob Horne, Dr Louise Fleming, Professor Andy Bush and Dr Amy Chan for their time, patience, sharing their wealth of knowledge in pharmacy, health psychology, adherence research and respirology. To be able to learn from such eminent academics has been an honour. Secondly, I would also like to thank my funders AUKCAR giving me the opportunity to conduct work in this necessary area. AUKCAR also provided support through the provision of excellent supervisors; fantastic training; a collaborative and friendly group of fellow PhD students and academics and for hosting annual conferences where I could present my work and network with experts in the field. I would like to also thank the patients and their families for their contribution to my research through SPEAKAsthma the young persons' Patient and public involvement group and the participants who took part in my study. Without the patients and family collaboration this PhD would not have been possible.

Thirdly, I would like to thank the staff at both UCL and the Royal Brompton Hospital for their support in my academic development and my understanding of asthma and its treatments. In particular I would like to thank the excellent team of Specialist Respiratory Nurses; outpatients nurses and Irene the administrator for their support in navigating the outpatient clinics. The Specialist Respiratory Nurses were instrumental in the recruitment of patients and their families and for accessing patients Smartinhaler™ data. Special thanks go to Angela Jamalzadeh who had a special interest in adherence and expertise in Smartinhaler™ and who supported my recruitment and always took the time to help me with hospital systems.

I would also like to thank my family in particular my parents for the support they have given me throughout the PhD process and prior to this in gaining an education. My parents have been a source of comfort during the most difficult times of my PhD and I thank them helping me to stay positive. To all of my friends who have done the same throughout the years, many thanks. Special thanks to Louise Raw, Amy Green and my PhD rocks: Caroline Katzer; Marissa Mes and the students from Centre for Behavioural medicine and AUKCAR. Finally, I would like to thank my incredible husband, Rupert whose support for my career throughout our relationship has been amazing and unwavering. This could not have been made clearer by the last four years in which his support has been invaluable in getting me through each day and to the thesis writing finish line.

## **Abstract**

Non-adherence to inhaled corticosteroids (ICS) is a key barrier in asthma management. However, few studies have explored patterns of non-adherence and the reasons for variations in adherence in young people with problematic asthma.

The aim of this thesis is to explore the potentially modifiable determinants of non-adherence in young people with problematic severe asthma in a tertiary care setting. This PhD comprises a systematic review of interventions to improve adherence in children with asthma; an analysis of patterns of non-adherence; a qualitative study of patients with poor adherence; and an adaptation study of the Beliefs About Medicine Questionnaire (BMQ). Each of these informs identification of interventions to improve adherence.

The review found that current interventions have limited effectiveness, with only half of the included trials able to improve ICS adherence (9/18). More complex interventions, tailored to the patient, which addressed both perceptions and practical aspects of non-adherence were more likely to be effective. Secondary analysis of electronic adherence data from this population (n=93) identified adherence patterns which have implications for intervention development. The interview study (n=20) identified perceptual determinants (e.g. poor understanding of asthma and ICS) and practical determinants (e.g. no routine and forgetfulness) of non-adherence. These findings informed an adaptation of the BMQ to identify beliefs underlying treatment non-adherence in this population; initial piloting (n=30) revealed high overall internal reliability but further research is needed to validate the questionnaire.

This PhD highlights the need for a tailored intervention for non-adherent young people with problematic asthma which addresses perceptual and practical barriers to adherence. The PhD identified new barriers to adherence including key differences between adults and young children. A belief-based questionnaire could be used to identify modifiable beliefs for inclusion in a tailored intervention addressing both perceptual and practical barriers for adherence to ICS.

## **Impact Statement**

Despite effective treatments, children still die of asthma. Poor adherence to inhaled corticosteroids (ICS) contributes to bad asthma outcomes. Although interventions have addressed adherence in asthma, little is known about the determinants of non-adherence for children with problematic asthma, and how best to intervene. This thesis will explore this in children with asthma in a tertiary care setting using electronic monitoring devices (EMDs) as the basis for both qualitative and quantitative analyses.

## **Impact for Research**

Central to this PhD is measurement of adherence in asthma with appropriate, objective, innovative tools such as EMDs and an adapted beliefs about medicine questionnaire for young people with asthma (BMQ-YPWA). Adherence needs to be measured as stringently as possible. Diagnostic criteria for asthma should be considered in recruitment to research. The systematic review highlights the need for objective tools for both the measurement of adherence and the diagnosis of asthma.

Through this PhD the extended-Common Sense Model (e-CSM) has been shown as a valuable tool for the investigation of adherence to ICS and the Perceptions and Practicality Approach (PAPA) as a useful framework for intervention development in children with problematic asthma. Future research should lead to a tailored intervention for this specific population exploring the use of the identified behaviour change techniques (BCTs) in addressing both perceptual and practical barriers to adherence. Interventions should include parents and encourage their practical support for their children's medication management.

## **Implications for Practice**

This PhD supports the recent NHS long-term plan in use of objective EMDs for monitoring of adherence and for the exploration of patterns of non-adherence. Following this PhD research, specialist respiratory nurses at the Royal Brompton Hospital now calculate day of the week adherence and look for changes to adherence over the monitoring period and gaps in adherence.

Health professionals can use EMD data as the basis for their consultation to enhance their discussions with patients about non-adherence. This PhD highlighted patients reporting of forgetfulness was commonly due to their treatment representations such as low perceived need for ICS and over-reliance on reliever inhalers rather than unintentional forgetting. Health care professionals can use these findings to explore beyond “forgetting” as a reason for non-adherence with patients based on the themes from the qualitative study and the statements from the BMQ-YPWA. This finding highlights that targeting forgetfulness with practical solutions will not work if the reasons behind forgetfulness are perceptual.

Patients’ illness representations should also be discussed as this PhD found patients to focus on the cause of their asthma attacks and symptoms rather than the long-term condition, and to treat their condition episodically based on their symptoms. The qualitative work in this PhD emphasised a lack of coherence between patients experience of asthma (episodic) and their prescribed ICS treatment (prescribed for daily use). This finding should form the basis of a consultation to increase the coherence of patients’ common-sense model of illness and treatment potentially leading to increased adherence.

## Dissemination of the PhD

### Chapter 2

**Pearce, C.J.** and Fleming L (2018) Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. *Expert Review of Clinical Immunology*, 14(12), 1055-1063.

### Chapter 4

**Pearce C.J.**, Jackson T, Bush A., Fleming L and Horne, R (2016). What are the Most Effective Aspects of Interventions for Adherence to Preventative Medication in Children with Asthma? - A Systematic Review (2016). Poster presented at the Asthma UK Centre for Applied Research – Annual Scientific Meeting.

**Pearce C.J.**, Chan A, Jackson T, Bush A., Fleming L and Horne, R. (2018) What are the effective aspects of adherence interventions for inhaled corticosteroids in children with asthma? A systematic review. Presented at the International Congress of Behavioural Medicine.

**Pearce C.J.**, Chan A, Jackson T, Bush A., Fleming L and Horne, R. (2018) What are the effective aspects of adherence interventions for inhaled corticosteroids in children with asthma? Presented at The European Health Psychology Society conference.

### Chapter 5

**Pearce C.J.**, Fleming L, Newby C., Bush A., and Horne, R (2017) Patterns of nonadherence in children with severe asthma. Poster presented at the European Society for Patient Adherence, Compliance and Persistence Conference.

**Pearce C.J.**, Jochmann A, Fleming L, Bush A., and Horne, R. (2016) Patterns of nonadherence in children with severe asthma (2016). Presented at the Asthma UK Centre for Applied Research – Annual Scientific Meeting.

**Pearce C.J.**, Jochmann A., Bush A., Horne, R., and Fleming L. Patterns of nonadherence in children with severe asthma (2016). Poster presented at European Respiratory Society: PA3349

## Chapter 6

**Pearce C.J.**, Fleming L, Chan, A, Jamalzadeh A., Bush A., and Horne, R. (2018). What's a preventer and why do I need it anyway?" A qualitative study in young people with asthma using Smartinhaler™. Presented at a symposium entitled Interventions to support optimal medical adherence at the 4<sup>th</sup> CBC Conference: Behaviour Change for Health: Digital and Beyond.

**Pearce C.J.**, Fleming L, Chan A, Jamalzadeh A, Bush A., and Horne, R (2017) "What's a preventer and why do I need it anyway?": A qualitative study in young people with asthma using Smartinhaler™. Poster presented at the European Society for Patient Adherence, Compliance and Persistence.

**Pearce C.J.**, Fleming L, Chan, A, Jamalzadeh A., Bush A., and Horne, R. (2018) "It's like trying to fit a piece into an already not working puzzle". Nonadherence in Inhaled Corticosteroids in young people with problematic severe asthma: A qualitative study. Presented at the International Congress of Behavioural Medicine.

## Chapter 7

**Pearce C.J.**, Chan, A, Fleming L, Bush A., and Horne, R. (2018) Adapting the Beliefs about Medicine Questionnaire for Young People With Asthma (BMQ-YPWA). Poster presented at The European Health Psychology Society conference.

**Pearce C.J.**, Chan, A, Fleming L, Bush A., and Horne, R. (2019) Adapting the Beliefs about Medicine Questionnaire for Young People With Asthma (BMQ-YPWA). Poster presented at the European Society for Patient Adherence, Compliance and Persistence.



## Table of Contents

Acknowledgements.....	3
Abstract.....	4
Impact Statement .....	5
Dissemination of the PhD .....	7
<b>Chapter 1: Asthma Aetiology, Diagnosis and Management.....</b>	<b>16</b>
1.1 An introduction to paediatric asthma.....	16
1.2 Aetiology and triggers.....	17
1.3 Diagnosis.....	18
1.4 Asthma: a heterogeneous disease.....	19
1.5 Subtypes in Severe Asthma.....	20
1.6 Pharmacological Treatment for Asthma.....	21
<b>Chapter 2: Measuring Medication Adherence in Asthma .....</b>	<b>25</b>
2.1 Definitions of Adherence .....	25
2.2 The problem of Adherence in Paediatric Asthma.....	26
<b>Chapter 3: Medication Adherence and Psychological Theoretical Frameworks .....</b>	<b>49</b>
3.1 Psychological Theory in Adherence Research.....	49
3.2 Theoretical Frameworks Commonly Applied in Medicines Adherence Research	50
3.3 Frameworks Underpinning Behaviour to Inform Interventions: A Summary of	
Research to Date .....	67
<b>Chapter 4: Systematic Review: What are the Most Effective Aspects of Interventions</b>	
<b>for Adherence to Preventative Medication in Children with Asthma? .....</b>	<b>79</b>
4.1 Introduction .....	79
4.2 Methods.....	80
4.3 Results.....	103
4.4 Discussion.....	121
<b>Chapter 5: Patterns of Adherence a Secondary Analysis of Smartinhaler™ Data ..</b>	<b>126</b>

5.1	Introduction .....	126
5.2	Methods.....	127
5.3	Results.....	131
5.4	Discussion.....	139
<b>Chapter 6:</b>	<b>The Patients' perspective of non-adherence .....</b>	<b>145</b>
6.1	Introduction .....	145
6.2	Methods.....	147
6.3	Results.....	156
6.4	Discussion.....	187
6.5	Conclusions .....	195
<b>Chapter 7:</b>	<b>Adapting the Beliefs about Medicine Questionnaire for Young People With Asthma (BMQ-YPWA) to Identify Determinants of Adherence .....</b>	<b>196</b>
7.1	Introduction .....	196
7.2	Methods.....	197
7.3	Results.....	203
7.4	Discussion.....	213
<b>Chapter 8:</b>	<b>General Discussion .....</b>	<b>222</b>
8.1	Summary of the Principle Research Findings.....	222
8.2	Strengths of the research and contribution to the literature.....	223
8.3	Limitations of the research .....	232
8.4	Implication for Research and Practice; and Future Research Questions.....	233
8.5	Conclusions .....	242
	References .....	281

## Appendices

Appendix 1: BCT Taxonomy (v1) .....	243
Appendix 2: Parental information sheet for the qualitative study.....	244
Appendix 3: Young Person information sheet for the qualitative study .....	248
Appendix 4: NHS ethical approval for the qualitative study.....	251
Appendix 5: HRA approval letter for the qualitative study .....	256
Appendix 6: Research and Development approval.....	257
Appendix 7: Qualitative study interview topic guide.....	259
Appendix 8: SPEAK Asthma Feedback .....	263
Appendix 9: Beliefs about Medicines Questionnaire.....	265
Appendix 10: Questionnaire pack including the BMQ-YPWA.....	269
Appendix 11: Ethical approval for the BMQ-YPWA study .....	273
Appendix 12: Ethical Approval for an extension for the BMQ-YPWA study.....	275
Appendix 13: BMQ-YPWA internal validity item deletion data .....	278

## List of Figures

Figure 1: The "Umbrella term of Asthma": source: Wenzel (2012) .....	19
Figure 2: British Thoracic Society/ Scottish Intercollegiate Guidelines Network Guideline on the management of asthma in children .....	24
Figure 3: Patterns of Adherence from Jochmann et al. (2017) .....	35
Figure 4: The Health Belief Model adapted from Ogden (2012).....	51
Figure 5: The Theory of Planned Behaviour adapted from Ajzen, (1988).....	55
Figure 6: The Transactional Model of Stress and Coping adapted from Hamilton-West (2011) and Ogden (2012).....	56
Figure 7: Social Support Theory adapted from Simoni (2002) .....	57
Figure 8: Self-Determination Theory.....	58
Figure 9: Simplified Common-Sense Model of Illness Representations adapted from Ogden (2012) .....	60
Figure 10: The extended-Common Sense/Self-Regulatory Model including the NCF (adapted from Horne (2003).....	64
Figure 11: The Perceptions and Practicalities Approach adapted from Horne (2001) .....	68
Figure 12: PAPA Including Prompts and Opportunity adapted from (Horne, 2001; Horne et al., 2019).....	69
Figure 13: The Behaviour Change Wheel from Michie et al. 2011 .....	74
Figure 14: The COM-B model: a framework for understanding behaviour (Adapted from Michie et al. (2011) .....	75
Figure 15: PRISMA flow diagram showing the second systematic search .....	105
Figure 16: PRISMA flow diagram showing the first systematic search .....	105
Figure 17: Risk of bias.....	114
Figure 18: Cluster analysis all data .....	129
Figure 19: A box and whiskers plot of monthly adherence over the monitoring period showing median, IQR and outliers (outliers as ) .....	132
Figure 20: Adherence clusters based on daily mean adherence .....	134
Figure 21: Box and whisker plot showing the percentage adherence for weeknights versus non-school nights .....	135
Figure 22: Box and whisker plot showing the percentage adherence for each day of the week .....	135
Figure 23: Boxplot of percentage adherence for each season.....	138

Figure 24: Seasonal effects on adherence with separate severity groups .....	139
Figure 25: e-CSM Results of the Framework Analysis: Diagram adapted from (Horne, 2003) .....	158
Figure 26: Patient 1's drawing of asthma with mucus in the airways .....	172
Figure 27: Patient 5's drawing of the airways before and after ICS (Seretide/ “the purple pump”) .....	176
Figure 28: Percentage of patients who responded (uncertain/ agree/ strongly agree) to each of the BMQ core necessity items.....	204
Figure 29: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the BMQ additional necessity items .....	205
Figure 30: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the BMQ core concern item.....	206
Figure 31: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the BMQ additional concern item.....	206
Figure 32: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the practicality items.....	207
Figure 33: Proportion of the sample allocated to each attitudinal group defined by beliefs about ICS adapted from Chater et al. (2014).....	207
Figure 34: Correlation between scores from the BMQ-YPWA domain and the B-IPQ timeline domain .....	212
Figure 35: .....	212

## List of Tables

Table 1: Pros and Cons of the most common adherence monitoring tools in children with asthma.....	41
Table 2: Database Search Terms and Dates .....	81
Table 3: Data Extraction Table .....	83
Table 4: Hierarchy of Asthma Diagnosis and Adherence Measurement Outcome .....	102
Table 5: Results for the adherence outcome .....	107
Table 6: Study reliability .....	112
Table 7: PAPA Categorisation and Reliability .....	116
Table 8: Examples of the Coded Behaviour Change Techniques .....	120
Table 9: Median and Interquartile Range for each day of the week .....	134
Table 10: Percentage adherence to ICS as prescribed compared to percentage of at least once a day use of ICS.....	136
Table 11: Monthly percentage adherence compared with a Kruskal-wallis test.....	137
Table 12: Seasonal percentage adherence compared with a Kruskal-wallis test .....	137
Table 13: An illustrative excerpt of Smartinhaler™ data output used for the AMI interview .....	149
Table 14: Results of the purposive sampling.....	156
Table 15: Framework, Themes, subthemes and exemplar quotes .....	159
Table 16: Internal reliability: items deleted .....	209
Table 17: Discriminant validity of the BMQ-YPWA domains based on dichotomised Smartinhaler™ percentage adherence.....	211
Table 18: Summary of content for future intervention development .....	236

## Abbreviations

ICS	Inhaled corticosteroids
PSA	Problematic Severe Asthma
DA	Difficult Asthma
STRA	Severe Therapy Resistant Asthma
SABA	Short Acting Beta Agonists
EMDs	Electronic Monitoring Devices
PAPA	Perceptions and Practicalities Approach
BCT	Behaviour Change Technique
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO	Population, Intervention, Comparison, Outcome
MARS-A	Medication Adherence Report Scale- Asthma
N	Number of participants
REC	Research Ethics Committee
ANOVA	Analysis of Variance
PRR	Prescription refill rate
e-CSM	extended- Common-Sense Model

## Chapter 1: Asthma Aetiology, Diagnosis and Management

### 1.1 An introduction to paediatric asthma

Although there is much debate around the exact definition of asthma it is considered to be an umbrella term for a clinical respiratory syndrome which includes wheeze, chest tightness and breathlessness with or without cough (Pavord et al., 2018). As the disease is heterogeneous the diagnosis should include exploration of which type of asthma the patient has (Holgate, 2008; Pavord et al., 2018). The condition is also characterised by periods of worsening airflow obstruction that increase shortness of breath, leading to loss of baseline control and asthma attacks. Due to the severity and life-threatening nature of these acute episodes this thesis will use the term attacks rather than exacerbations (Bush & Pavord, 2011; FitzGerald, 2011).

Globally, asthma affects up to 300 million people (GINA, 2019) and has been classified as the 16<sup>th</sup> most important worldwide disease in terms of both the physical disability of patients and number of years lived with the condition (The Global Asthma Network, 2018). Morbidity and mortality rates vary across the world with UK patient mortality amongst highest in Europe; particularly among children and young people (Shah, Hagell, & Cheung, 2019; Wolfe et al., 2013).

In the UK it is estimated that 5.4 million people are affected by asthma (Asthma UK, 2019). However, reporting of asthma prevalence differs depending on the criteria used; for example, in the UK population self-reported doctor diagnosed-asthma is 15.6% (9.8 million people), those that report being treated for asthma 9.6 % (6.0 million people), and clinician-reported, diagnosed-and-treated asthma 5.7 % ( 3.6 million people) (Mukherjee et al., 2016).

Although the prevalence is less clear in children, a recent Asthma UK survey has estimated 1 in 11 children have asthma, which equates to 1.1 million children in the UK (2010). Around one fifth of children “grow out” of asthma (Andersson et al., 2013). However, for those experiencing asthma in childhood and for those that do not “grow out of asthma” the disease can have a significant impact including a poorer quality of life (Luskin et al., 2014); frequent school absences (Harris et al., 2017) and insomnia and disturbed sleep (Luyster et al., 2016). In addition to affecting patient and parental quality of life, frequent hospital visits, general practice appointments and emergency care attendances are associated with high cost to the



NHS (Fleming et al., 2019; Gupta, Sheikh, Strachan, & Anderson, 2004; Mukherjee et al., 2016).

Despite effective asthma treatments being readily available, there are 1,200 deaths a year attributed to asthma in the UK (3 deaths per day)(British Lung Foundation, 2019). Data available for analysis on 195 UK asthma deaths ("National Review of Asthma Deaths (NRAD)," 2014) revealed that 12 percent of deaths were in children and young people (CYP) under the age of 20 years. Of the 28 deaths in CYP and 16 (57%) were in patients who had been receiving specialist secondary care. The NRAD report concluded that 67 percent of asthma deaths were avoidable; the most important modifiable factor being patients not taking their prescribed preventer asthma medication in the month and/or year before their death (Royal College of Physicians, 2014).

Adherence to asthma medication in adolescent children can be a particular challenge as the child becomes more independent from their parents, forming their own opinions and beliefs about asthma and their medication (Kaplan & Price, 2020). In adolescence children begin to take more responsibility over the management of their treatment and often reject parental support which can lead to conflict and reduced adherence as responsibility is transferred from parent to child. This is also the time where patients make a transition from paediatric to adult care which can be challenging especially for children who were diagnosed early and have a long-standing relationship with a healthcare team.

## **1.2 Aetiology and triggers**

Although extensive research has been conducted investigating the aetiology of asthma no one definitive cause has been found (Lemanske & Busse, 2006). In school age children and adults, the main underlying driver is Type 2 airway inflammation, characterised by airway eosinophilia driven by the classical Type 2 cytokines interleukin (IL)-4, -5, and 13 (Pavord et al., 2018). It is important to realise that an asymptomatic patient still requires inhaled corticosteroids (ICS) to suppress airway inflammation and reduce the risk of asthma attacks. There are also multiple triggers for asthma symptoms and asthma attacks. These include (Puranik, Forno, Bush, & Celedon, 2017): allergens e.g. animals (Lombardi, Savi, Ridolo, Passalacqua, & Canonica, 2017) , dust mites (Sporik, Chapman, & Platts-mills, 1992); environmental triggers e.g. passive smoking, aerosols, indoor and outdoor pollution (Gautier & Charpin, 2017), food (Caffarelli, Garrubba, Greco, Mastroilli, & Dascola, 2016); change in the weather (Hyrkas-Palmu et al., 2018); exercise (Del Giacco, Firinu, Bjermer, & Carlsen,

2015); viral infections (Papadopoulos et al., 2011); and emotional stress e.g. anxiety (Sandberg et al., 2000). Patients should be taught how to reduce their exposure to triggers where possible, as well as when and how to take medication (de Groot, Kreggemeijer, & Brand, 2015).

### **1.3 Diagnosis**

Diagnosing asthma is not simple as there is no one definitive test (NICE, 2017a). Additionally, many respiratory diseases have similar presentations. For these reasons diagnosis of asthma is complex and requires the exclusion of differential diagnoses such as preschool wheeze and cystic fibrosis (Ullmann et al., 2018) by careful history and examination and (preferably) demonstration of variable airflow obstruction and (non-invasively) Type 2 inflammation (GINA, 2019). Spirometry measures forced expiratory volume in 1 second (FEV<sub>1</sub>) and, in the presence of airflow obstruction, improvement after administration of a short acting  $\beta$ -2 agonist (SABA, reversibility) (see medications in asthma below). Other tests which can be used to help diagnose asthma include Fractional Exhaled Nitric Oxide (FeNO) (an indirect measure of Type 2 airway inflammation); induced sputum with measurement of cell count (not available in primary care); peripheral blood eosinophil count (another marker of airway Type 2 inflammation) and total and specific Immunoglobulin E (IgE) and skin prick testing (to define whether the child is atopic) (BTS/SIGN, 2016). . These diagnostic tests are difficult in children under the age of five particularly assessing FENO as the technique can be difficult for children to master. It is therefore challenging to diagnose a child under the age of five with asthma rather than cough or wheeze alone which may subside later in childhood left untreated (Bush, Grigg, & Saglani, 2014; Bush & Saglani, 2020). Rarely, bronchoscopy (a procedure to look inside the large airways) may be part of the diagnostic process, most usually to exclude a non-asthma diagnosis, and in severe disease to characterise the type of asthma.

Many of the tests for a more thorough diagnosis of asthma, including tests of airway hyper-responsiveness, are only available in secondary and tertiary care and this is one reason why patients with asthma are often over diagnosed (Bush & Fleming, 2016). However, the lack of access to objective tests can also result in a delay in the diagnosis of asthma which can be a challenging time for the whole family. Clinicians, particularly GPs, can be reluctant to apply an early diagnosis in the absence of definitive tests in contrast to those experiencing the disease who are seeking for their symptoms to be taken seriously. This conflict can cause frustration in the patients and their families and difficulties in the patient/ health care

professional relationships. The feelings of frustration can be heightened by the fact that patients are often prescribed asthma medication without a formal diagnosis (Lakhanpaul et al., 2014).

### 1.4 Asthma: a heterogeneous disease

Asthma is now considered to be a heterogeneous disease (Holgate, 2008; Wenzel, 2006, 2012) with different presentations in different patient groups. Groups of linked characteristics, also named phenotypes, have been defined and include biological, demographic and symptomatic factors. Four phenotypes have been found within adult asthma named (Figure 1): eosinophilic; neutrophilic; mixed inflammatory; paucigranulocytic asthma (Wenzel, 2006).

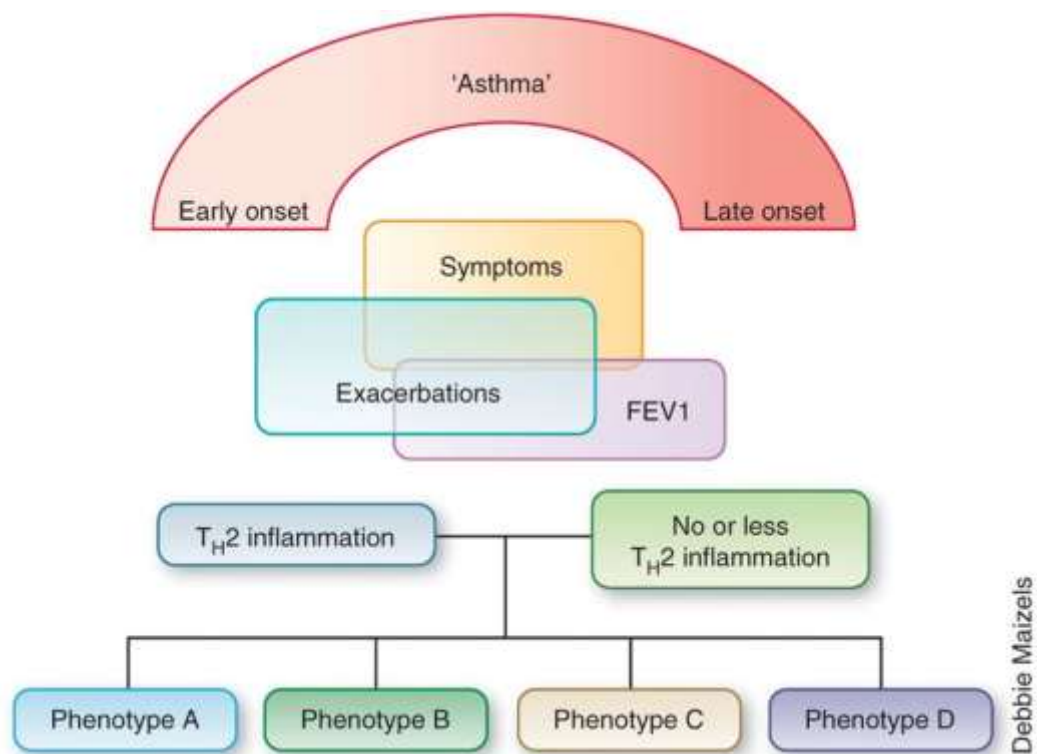


Figure 1: The "Umbrella term of Asthma": source: Wenzel (2012)

Eosinophilic asthma (or "allergic" asthma): Is the most common type of asthma which is characterised by an eosinophilic inflammatory response to a specific allergen ( $T_H2$  inflammation). This type of asthma is more often early onset. Those with eosinophilic asthma are more likely to have comorbid atopic diseases such as eczema, food allergy and allergic rhinitis.

Neutrophilic asthma: Is more likely in adult onset asthma and may be linked to airway infection.

Mixed inflammatory asthma: is defined as both neutrophilic and eosinophilic inflammation being present.

Paucigranulocytic asthma: shows normal levels of eosinophil and neutrophil cells and therefore no inflammation (or controlled inflammation due to steroids) and is less well understood.

However more recent investigations in children have shown that these phenotypes are not necessarily stable over time, with children's asthma being categorised as eosinophilic on one occasion and non-eosinophilic subsequently (Fleming, Tsartsali, Wilson, Regamey, & Bush, 2012). Within a paediatric STRA group asthma has been found to be characterised by eosinophilic and not neutrophilic airway inflammation with little evidence of Th2 inflammation (Bossley et al., 2012).

### **1.5 Subtypes in Severe Asthma**

Problematic severe asthma (PSA) is defined as asthma which is poorly controlled despite high levels of prescribed medications (Bush et al., 2008). It is estimated that around 5-10% of asthmatic children are diagnosed with PSA and that this type of asthma consumes a disproportionate amount of health care resources (Chung et al., 2014). PSA has been further sub-categorised into Severe Therapy Resistant Asthma (STRA) and Difficult Asthma (DA) (Bousquet et al., 2010; Bush et al., 2008; Hedlin et al., 2010). STRA is diagnosed in children whose asthma is poorly controlled on high dose ICS plus add-on therapies, despite potentially modifiable factors being addressed and alternative diagnosis being excluded. DA is diagnosed in children who present with poor asthma control despite similarly high levels of treatment but who are found to have modifiable factors which have not yet been addressed such as poor medication adherence, poor inhaler technique, allergen and other exposures, and important psycho-social factors. In addition to allergies many patients with asthma also have significant co-morbidities such as obesity and allergic rhinitis, these patients can be called 'asthma plus'. The majority of children presenting to tertiary care have been found to have DA as opposed to STRA although there is often overlap between the groups (Bush, 2019). As patients' asthma control worsens the likelihood of asthma attacks increase which may cause impaired lung growth or reduced lung function (Bush & Zar, 2011). Poor asthma control in

DA patients is particularly likely if a patient does not take treatment. As ICS are the primary treatment for all school age patients with asthma, it is important that adherence to these medications is confirmed before escalating treatment (Bush, 2018). Therefore, studying and accurately measuring adherence to ICS is of paramount importance. This is considered in more detail in the next chapter (Chapter 2:).

## **1.6 Pharmacological Treatment for Asthma**

The most commonly prescribed medications for patients who are diagnosed with asthma are ICS and SABA. ICS act over the long-term when taken regularly to reduce allergic inflammation in the airways and thus reduce asthma symptoms and severity, and the burden of attacks. Conventionally, ICS are prescribed regularly, usually twice a day (every 12 hours), to control asthma; however, the patient does not experience acute benefit from taking the treatment. SABA however, are prescribed for relieving asthma symptoms as needed and provide quick relief to the patient by bronchodilation. SABA is frequently over-relied upon and ICS are frequently used sub-optimally by patients (Byrne, Jenkins, & Bateman, 2017). Indeed, the Global Initiative for Asthma (GINA, 2019) has recently proposed that SABA alone should no longer be used in asthma, and instead should be replaced by a combined fast acting bronchodilator (which includes formoterol a long acting beta agonist (LABA) and ICS. This has been tested recently in a double-blind, placebo-controlled trial in adolescents with mild asthma which showed that this approach was superior to as needed SABA with or without low-dose ICS (O'Byrne et al., 2019). Patients have been categorised as having poor asthma control and being at risk of an asthma attack when using more than one 200-dose canister of SABA per month (GINA, 2019). Suboptimal use (poor adherence) of ICS is not specified in the GINA report (2019) however, usage less than 80% has been identified as increasing risk of death in patients with asthma (Suissa, Ernst, Benayoun, Baltzan, & Cai, 2000; Suissa et al., 1994) (see Chapter 2: for further details).

### **1.6.1 Add on medications**

Add on medications are often prescribed when a patient's asthma is not considered to be well controlled despite increases in ICS dosage. These include: leukotriene receptor antagonists (LTRA), long-acting beta-agonists (LABA), combined medications, which contain a LABA and an ICS, theophylline, prednisolone and in severe asthma anti-IgE or anti-interleukin-5 (IL5) therapy (biologics). Each of these are described briefly below and recommended management steps are outlined (Figure 2; (BTS/SIGN, 2016).

#### *1.6.1.1 Leukotriene receptor antagonists (LTRAs)*

LTRAs block the synthesis of cysteinyl leukotrienes, which stimulate mucus production, increase inflammation and cause constriction of airway smooth muscle. This oral medication is recommended in conjunction with ICS therapy as an additional medication as a first-line treatment by the NICE guidelines. The most frequently prescribed LTRA in paediatric asthma is montelukast.

#### *1.6.1.2 Inhaled long-acting beta agonists (LABAs)*

LABAs can be used as an add-on therapy to ICS as combination therapy (ICS/LABA inhalers) and are recommended as a first-line treatment by the BTS-SIGN guidelines. LABAs relax the smooth muscle of the airways for a longer time than SABA (typically 12 vs. 4 hours) but as with SABA they do not treat the underlying inflammatory process (Johnson, 1995). As they relieve symptoms but do not influence the underlying mechanism of asthma they can mask the symptoms of worsening asthma. LABA usage has been linked to severe asthma attacks and even death when administered without the use of ICS and therefore are not recommended as a stand-alone treatment (Anagnostou, Harrison, Iles, & Nasser, 2012; Beasley, Perrin, Weatherall, & Wijesinghe, 2010). Common LABA/ICS combination inhalers include Seretide™ (fluticasone and the partial  $\beta_2$ -agonist salmeterol) and Symbicort™ (budesonide and the full  $\beta_2$ -agonist formoterol).

#### *1.6.1.3 Maintenance and Reliever Therapy (MART)*

A new regimen has been introduced called MART whereby a patient uses their ICS/LABA (Symbicort™ because formoterol has a faster onset of action than salmeterol) as both their preventer and reliever medication (Bisgaard et al., 2006; Jorup, Lythgoe, & Bisgaard, 2018). They are asked to use the ICS/LABA when they feel symptomatic in addition to daily regular doses up to a specified dosage limit prescribed their doctor. Patients are still prescribed a SABA for more severe symptoms and in case of emergency.

#### *1.6.1.4 Long-acting muscarinic antagonist (LAMA)*

LAMA reduce the hyper-responsiveness of airway smooth muscle but is a non-steroidal and not an anti-inflammatory medication. Evidence suggests it is useful medication when combined with an ICS/LABA at reducing asthma attacks, increasing asthma control and improving lung function in adults (Kew & Dahri, 2016). The most commonly prescribed LAMA is tiotropium bromide which has been tested for use in children aged  $\geq 6$  years old (GINA, 2019; Hamelmann, 2018; Raissy & Kelly, 2017). However, its use is not currently widespread.

#### *1.6.1.5 Theophylline*

Theophylline is an oral medication with multiple effects including being anti-inflammatory in low doses, a weak bronchodilator and possibly enhancing respiratory muscle pump function (Weinberger & Hendeles, 1996). Theophylline is not commonly used in the UK as it requires frequent monitoring via blood tests, interacts with other commonly used medications, e.g. erythromycin, and has an unpleasant side-effect profile.

#### *1.6.1.6 Maintenance Prednisolone*

Prednisolone is a steroid tablet usually prescribed to reduce inflammation during an acute asthma attack. However, prednisolone can also be prescribed as a maintenance therapy when asthma cannot be controlled via inhaled corticosteroids or other add on-therapies with a lesser side-effect profile (BTS/SIGN, 2019). With the arrival of biologicals (below) regular oral steroids are used much less frequently.

#### *1.6.1.7 Anti-IgE and Anti-interleukin-5 therapy (Biologics)*

When asthma in children age six years and over remains uncontrolled despite high dose ICS and add on therapies, monoclonal antibodies (targeted biological medicines) may be considered. Where a patient has poor control and known allergies to aeroallergens they may be prescribed anti-IgE therapy. Anti-IgE therapy is a monoclonal antibody injectable treatment which is prescribed to patients to reduce asthma attacks. Mepolizumab has been developed to block the effects of the Type 2 cytokine IL5, reducing eosinophil recruitment to the airways. It has an especially beneficial effect in reducing the frequency of asthma attacks in patients with a raised peripheral blood eosinophil count (Gupta et al., 2018). There are other biologicals in the pipeline, mainly but not exclusively targeting Type 2 inflammation, but these are not yet licensed in children.

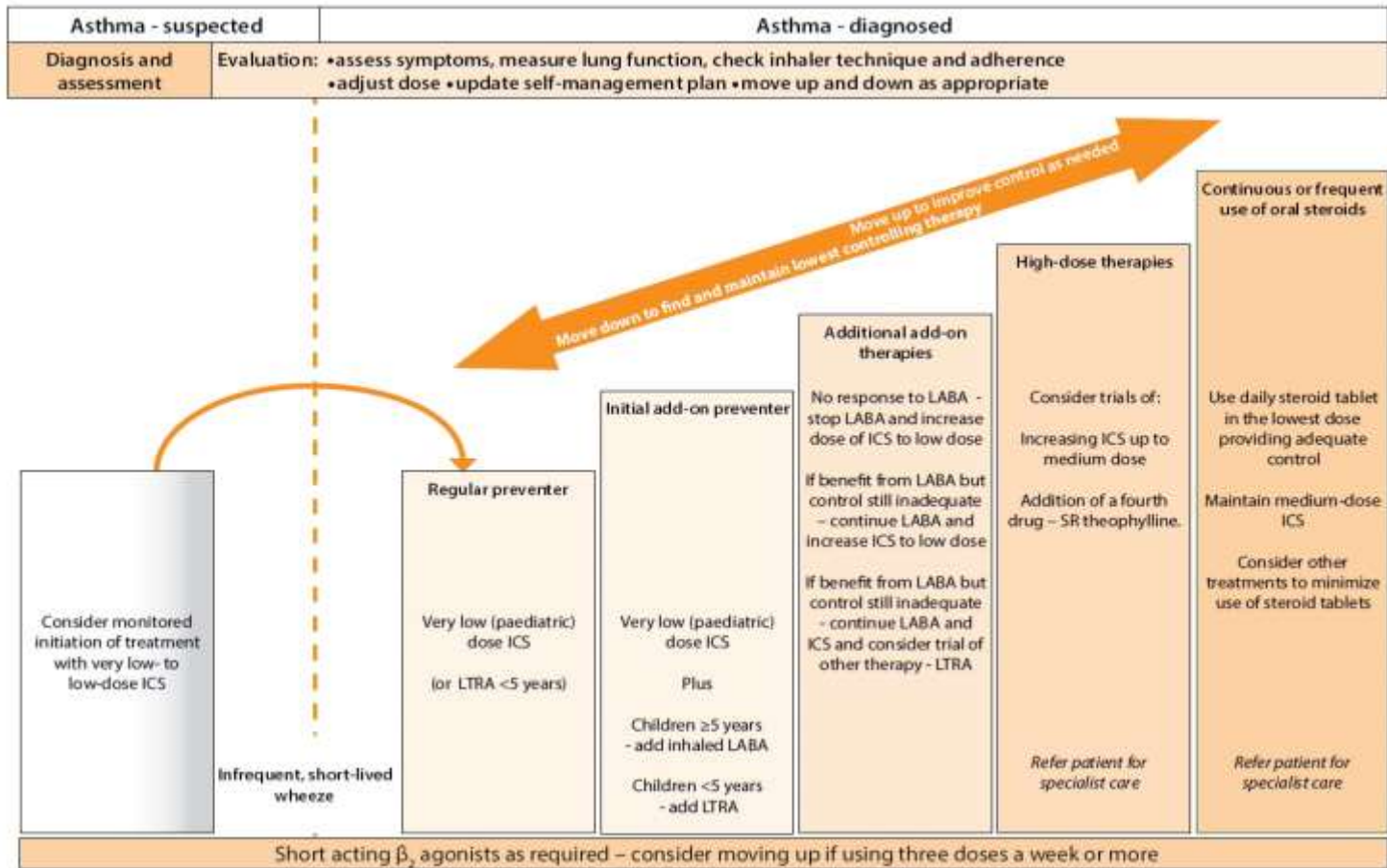


Figure 2: British Thoracic Society/ Scottish Intercollegiate Guidelines Network Guideline on the management of asthma in children



## Chapter 2: **Measuring Medication Adherence in Asthma**

### **2.1 Definitions of Adherence**

Adherence has been defined in several different ways over time although three key terms have been used in the literature: compliance, concordance and adherence (Horne, 2001). Compliance has been defined as the correlation between a patients' medication taking behaviour and the recommendations the prescriber has given. Within recent literature this definition is rarely used as it does not incorporate the patient having an active role in their decision regarding their medication, rather than passively obeying the prescriber (or not). Concordance is a term that defines the process of both the initial prescribing but also further support around medication use. Adherence shares similarities with the definition for compliance, however, the patient is not regarded as passively accepting the doctors' prescription. Rather, the prescription is agreed between the patient and the prescriber. This definition of adherence highlights that the patient has free will and opinions regarding their medication prescriptions (Horne, 2001). The term adherence emphasises the therapeutic partnership between patient and prescriber and therefore will be used within this PhD.

#### **2.1.1 Adherence: Initiation, Implementation and Discontinuation**

More recently adherence has been categorised by Vrijins et al (2012) into three phases:

1. Initiation
2. Implementation
3. Discontinuation

Initiation is defined as the behavioural decisions that are made when initially deciding whether to take a medication. This include the process of taking the prescription from the prescriber, collecting the medication from the Pharmacy and finally initiating taking the treatment. A patient can be non-adherent by not accepting the treatment, by not collecting the treatment, by not initiating the treatment or by starting the treatment at a later date than advised.

Implementation is defined as the extent to which the patient is taking the dose as prescribed once initiated i.e. the dose (number of puffs per day), the frequency (number of times a day)

and intervals between doses (12hrs or more). This is closest to the more traditional understanding of adherence i.e. is the patient taking the doses as prescribed?

Finally, discontinuation is the point at which the last dose is taken and no future doses are planned to be taken. Discontinuation can occur in response to the physician's instructions because the disease has gone into remission, due to side-effects or due to other patient factors, however this definition refers to patient discontinuation without discussion with the prescriber.

This PhD will primarily explore implementation of medication in patients who have begun taking their medications and who have not discontinued the medication completely. This area of adherence is the most applicable in paediatric tertiary care. In this setting, if parents unilaterally completely discontinue medication without medical consultation, this has legal ramifications of child safeguarding.

## **2.2 The problem of Adherence in Paediatric Asthma**

Non-adherence in paediatric asthma is a significant issue with reported adherence rates as low as 50% in children (Morton, Everard, & Elphick, 2014). Suboptimal adherence to ICS leads to poor asthma control, severe attacks of wheeze and hospitalisations in children with asthma (Williams et al., 2011). Good adherence in asthma is most commonly defined as taking at least 70-80% of the prescribed medication (Jochmann et al., 2017; Santos Pde et al., 2008). Lower cut off points (<60% adherence) are associated with significantly higher levels of healthcare utilisation (McNally et al., 2009). Although any cut off point for adherence is somewhat arbitrary, there is some evidence of clinical effect when adherence falls below certain thresholds. Risk of asthma death has been shown to increase with reduced ICS canister collection, including large increases in risk when ICS canister collection is less than nine per year (approximately 70-80% adherence) in a population-based cohort study (Suissa et al., 2000). In an observational study, improvements across a range of asthma control measures during a period of electronic monitoring were seen in children with  $\geq 80\%$  adherence, but no improvements were seen in those whose monitored adherence was <60% (Jochmann et al., 2017). Therefore, this PhD will consider less than using less than 80% of a patients' prescribed dose as sub-optimal.

There has been a call for change by several key asthma experts. The 2018 Lancet commission recommended that we "develop tests capable of identifying poor adherence and treatment

approaches capable of improving adherence” (Pavord et al., 2018). The United Kingdom national charity for asthma, Asthma UK, also highlighted the problem of non-adherence in their 2018 research priorities (<https://www.asthma.org.uk/research/strategy/research-priorities/>): “Regardless of how effective asthma treatments are, they will only work if people understand and appreciate their benefits and take them as prescribed... we know that a number of complex barriers exist which unnecessarily limit the level of control most people have over their asthma...”

The first European Respiratory Society/American Thoracic Society Task (ERS/ATS) Force on severe asthma recommend that non-adherence to treatment should be considered in all difficult to control patients before a label of “severe asthma” can be applied. However, the authors acknowledge that detecting poor adherence can be challenging (Chung et al., 2014). Similarly, NRAD (Royal College of Physicians, 2014) called for continual monitoring of adherence to ICS.

To achieve this goal, we need reliable and affordable ways for healthcare services to assess adherence in children with asthma. There are a number of methods for monitoring adherence which will be reviewed within this chapter. Some are subjective, while others utilise more objective measures. It is important that the correct tool is used to measure adherence in children with asthma so that adherence is measured accurately and therefore that the data produced are meaningful in addressing asthma mortality and morbidity. Each of the commonly used measurement tools have strengths and limitations which are summarised in this chapter alongside research which has used the tools either as an outcome measure or as part of an intervention.

### **2.2.1 Subjective Monitoring Tools**

#### *2.2.1.1 Practitioner Assessment of Adherence*

Practitioners have consistently been shown to be unable to accurately identify which of their patients are not adhering to their asthma treatment. A recent study found that health care practitioners were extremely poor at detecting non-adherence to ICS in their patients when assessing eligibility for increased treatment (Lee et al., 2018). Both specialist nurses and physicians were able to identify non-adherence in less than half of their patients when compared to EMD (Smartinhaler™ objective data). Adherence was significantly overestimated by nurses in 72% of cases and doctors in 85% of cases (Lee et al., 2018).

### *2.2.1.2 Parental and Child Self-Report of Adherence*

Self and parental assessment is often used as a measure of adherence in research studies and in clinical practise as validated assessment tools are generally quick for patients to complete and are viewed as cost effective. However, self and parental reported adherence are often measured using non-validated tools (Mosnaim et al., 2013; Stergachis, Gardner, Anderson, & Sullivan, 2002; Teach, Crain, Quint, Hylan, & Joseph, 2006; van Es, Nagelkerke, Colland, Scholten, & Bouter, 2001) . Whether or not a validated tool is used, adherence to ICS is frequently overestimated compared to objective measures (Bender, Wamboldt, O' Connor, et al., 2000). There can be a number of reasons for this including: wanting to demonstrate behaviour (adherence) that is desired by the medical team (social-desirability bias) and misremembering their level of adherence due to the time elapsed between the behaviour and the appointment (recall bias). This issue can in some way be addressed by creating a non-judgemental environment and asking empathic questions that acknowledge the likelihood of poor adherence (E.D. Bateman et al., 2018).

### *2.2.1.3 Self-Report Questionnaires*

Self-report questionnaires can be filled in by the parent or the child themselves depending on their development and validation. The most frequently used questionnaires to measure adherence in asthma are the Morisky Scale (Morisky, Green, & Levine, 1986) and the Medication Adherence Report Scale - Asthma (MARS-A (Cohen et al., 2009; Horne & Weinman, 1999).

#### *2.2.1.3.1 The Morisky Scale*

The Morisky scale was originally developed as a 4-item questionnaire for hypertension medication adherence with dichotomous yes/ no responses. The scale was found to have good concurrent and predictive validity for objective blood pressure readings at 2 and 5 years. More recently the scale was developed into a more predictive 8-item questionnaire with dichotomous answers, other than the final answer which is a five-point Likert scale (Morisky, Ang, Krousel-Wood, & Ward, 2008). The Morisky scale has been used in a variety of health conditions but has not frequently been used to measure adherence in children with asthma. The studies that have used the Morisky Scale were conducted in mixed populations which included both children and adults (Davis, Trudo. F, Siddall. J, & Small. M, 2018; Giraud & Allaert, 2009; Guenette et al., 2015; Ivanova et al., 2008; Morisky, Kominski, Afifi, & Kotlerman, 2009; Ngahane et al., 2016). In 2017 the Morisky scale was developed and validated for use in asthma as an 8 item questionnaire (Morisky Medication Adherence Scale,

MMAS-8) (Janezic, Locatelli, & Kos, 2017) in patients over 12 years old, but not for young children. The questionnaire was tested in a Slovenian population and correlated well with asthma control and quality of life. However, it has not been validated using objective measures of adherence or in other geographical populations.

#### 2.2.1.3.2 The Medication Adherence Report Scale (MARS)

The Medication Adherence Report Scale (MARS) was originally developed and validated in multiple disease populations including asthma (Horne & Weinman, 1999). The MARS consists of 9 items which are all scored on a 5-point Likert scale and it has been adapted for the asthmatic population specifically to address adherence to ICS. The MARS-A, a 10-item scale was validated in adult patients with asthma and has been found, in research studies, to be only moderately correlated with electronic monitoring data ( $r = 0.42$ ,  $P = 0.001$ ) (Cohen et al., 2009). However, in children it is often the parents who complete the questionnaire on behalf of the child (Klok, Kaptein, Duiverman, & Brand, 2012; Menard, Jbilou, & Lauzier, 2018) and both the MARS-A and MARS-5, a shortened version, have been found to be inaccurate in children when administered in clinical practice and compared to electronic monitoring device (EMD) data (Garcia-Marcos, Brand, Kaptein, & Klok, 2016; Jochmann et al., 2017).

Garcia et al. (2016) found MARS-5 (completed by parents) to be significantly correlated ( $r_s = 0.47$ ;  $p < 0.0001$ ) with electronic monitoring data (3 months of monitoring) in 13-year-old patients with persistent asthma. However, there was a considerable variation of electronically assessed adherence rates at every MARS-5 score and the MARS-5 performed poorly in predicting electronically assessed adherence using receiver operating characteristic curve analysis (Garcia-Marcos et al., 2016). Jochmann et al. (2017) found that there was no significant difference in MARS-5 scores (completed by the patients and their family) and EMD adherence groups ( $\geq 80\%$ , 60–79% or  $< 60\%$ ; 24 versus 23 versus 23 respectively). The MARS-5 and prescription uptake data could not distinguish between non-adherent and adherent patients (Jochmann et al., 2017). This could be due to the care team administering the questionnaire rather than a research team. Patients may be more inclined to respond in a socially desirable way when answering an adherence questionnaire for their doctor or nurse compared to an independent researcher.

#### 2.2.1.4 Objective Monitoring tools

##### 2.2.1.4.1 Prescription Data

Prescription data are an objective measure which are often used as a proxy for adherence (Garrett et al., 1994; Horspool et al., 2013). The data describe how often the patient (or parent of a patient) collects a prescription, usually for ICS or other maintenance therapy, and presented as a percentage of the expected number of prescriptions over a given time period (usually one year). Although objective, prescription data only give an indication of complete non-adherence rather than patterns of adherence. If no prescriptions are collected, then no medication can be taken but collecting a prescription script is not the same as collecting the medication from the pharmacy or inhaling it correctly. Although far from ideal, prescription data are relatively easy to obtain, particularly by the primary care physician and highlights at least some non-adherent patients.

Prescription refill rate (PRR) describes the amount of medication actually collected from a pharmacy. Although this gives a little more information than simple prescription data it also does not allow for the unknown factor of whether patients actually take the medication at all, whether someone else has taken the medication, if the patient has taken it correctly, or whether medications are just stored until they go out of date (Hazell & Robson, 2015). Despite the limitations of PRR can provide useful insights into medication use, such complete non-adherence and is a popular outcome for research studies targeting adherence and has been used in many intervention studies in children with asthma (Garrett et al., 1994; Gustafson, M, et al., 2012; Julious, M, et al., 2016). PRR can also provide useful information on salbutamol use and highlight overuse relevant to poor asthma outcomes (GINA, 2019).

##### 2.2.1.4.2 Weighing Inhaler Canisters

Inhaler canisters returned to the clinician/researcher can be weighed using a digital scale to calculate the number of doses used (or strictly, the number of times the inhaler has been at least activated). This method is costly and time-consuming, and it requires a digital scale to be accessible and for patients to remember to bring in their inhalers. Again assuming adherence from inhaler canister weight may be misleading as the patient may have engaged in dose dumping, where a patient actuates the inhaler multiple times in an attempt to appear adherent, just before bringing the inhalers back, or the inhaler could have been used by someone else (Rand & Wise, 1994). Canister weight is used more frequently in trials than in a clinical setting. Wiecha et al. (2015) used canister weight in comparison to self-report adherence from both children with asthma and their parents. Subjective assessment grossly

over-estimated even this crude estimate of adherence (canister weight), which itself is likely to over-estimate true adherence. This objective measurement allows researchers and clinicians to calculate how much of the medication was actuated (but not inhaled) but it does not have a mechanism to adjust for dose dumping.

#### 2.2.1.4.3 Dose Counters

Dose counters indicate to the patient how many doses remain in their inhaler. The counter decreases as doses are taken or the inhaler is actuated and is embedded in the inhaler device. Clinicians or researchers may use this as an indication of adherence as dose counters are included in some commercially available inhalers. However, as with weighing inhaler canisters, the dose counter can be manipulated by dose dumping as the investigator has no indication of when the doses were taken or even if they were inhaled. The dose counters also give no indication of patients' adherence behaviour for example the dose counter may show 50% adherence which could be the patients taking half doses daily or skipping every other day, very different patterns of inhaler use, which would not be captured by the dose counter. This is a limitation of many of the methods of measuring inhaler use.

#### 2.2.1.4.4 Directly Observed Therapy

Directly observed therapy (DOT) has a long history of use in diseases such as tuberculosis to ensure adherence with a prolonged treatment course. It can also be utilised in asthma to ensure a child takes inhalers regularly, usually observed by a member of school staff, local pharmacy or nursing team. A recent pilot study has utilised a mobile device platform for remote direct observation of inhaler use and technique (Shields, F, Rivey, & McElroy, 2018). Children are filmed using their device and then the video is uploaded via an App and reviewed by a specialist asthma nurse to assess inhaler technique. Mobile directly observed therapy (MDOT) is more flexible and convenient for children and their families than standard DOT and also, unlike many other measures of adherence, has the advantage that inhaler technique is observed by someone with appropriate expertise. However, MDOT is time intensive for clinical staff and therefore expensive. Importantly, the Shields et al. (Shields et al., 2018) study showed it took 5 weeks of MDOT for inhaler technique to be correct across a small group of participants (n=18), despite multiple previous teaching sessions at the hospital. Another issue with MDOT for measuring adherence is that failure to upload a video does not mean failure to take the inhaler as MDOT requires a two-step process, firstly to remember to take the inhaler and second to film and send the video to the nurses. It is therefore not a completely satisfactory measurement of adherence. Furthermore, it is also

time intensive for families and it creates additional issues around data security and confidentiality by introducing the internet and possible websites/software in comparison to usual care.

#### 2.2.1.4.5 Nurse Home Visits

Nurse led home visits can provide useful insights into adherence and provide information to complement self-report and prescription data. At the time of a home visit the location of all prescribed medications can be checked including whether medications are present, whether they are within their use by date and whether they are easily accessible. Stockpiling of medications demonstrates that although inhalers are collected, they are not being administered (Bracken et al., 2009).

#### 2.2.1.4.6 Electronic Monitoring Devices (EMDs)

EMDs for asthma inhalers have been the focus of adherence research over the last 15 years. With progressive advance in technology several types of devices have been developed, all with differing capabilities and prices. These EMDs are the current gold standard for measurement of adherence (Vrijens et al., 2016) as they measure when and how often patients activate their inhaler. However, devices are not currently clinically available that also measure correct inhalation of the medication. EMDs also do not provide information on why patients are non-adherent and they are currently not affordable for all clinical care settings. This section will discuss common electronic devices used in research to monitor adherence in children with asthma.

Although EMDs can be a useful tool for measuring adherence they raise a number of issues: the time and resources needed for clinical staff to regularly monitor adherence and contact families; establishing who is responsible for ensuring a child's adherence; and maintaining engagement and trust with the family rather than featuring in their lives as a "Big Brother" presence (Howard, Lang, Sharples, & Shaw, 2017; Stewart, Gannon, Beresford, & Fleming, 2018). These issues are currently ongoing and therefore likely to hinder the potential use of EMDs clinically. Further research and development of these tools is needed in order to facilitate integration into routine clinical practice.

##### 2.2.1.4.6.1 DOSER CT™

One of the first electronic monitoring devices for metered dose inhalers was the DOSER CT™ (Simmons et al., 1997) . The DOSER CT™ can be used with pMDIs to count the number of



daily doses used taken for up to 30 days (limited by battery life). The DOSER CT™ uses a microchip and displays the number of doses taken on the screen, although this is a simple sum of the doses taken as opposed to the time and date of each dose. Although this is a simple dose counter it does feedback to the patient that they have taken their inhaler and therefore gives some level of feedback to the patient which may change their behaviour. The DOSER CT™ is the cheapest EMD for ICS as it uses older technology than some of the newer EMDs, but the major disadvantage of this technology is its inability to detect dose dumping. The DOSER CT™ has been used in a recent randomised control trial (RCT) intervention based in America in children with asthma (Wiecha et al., 2015). The trial assessed changes in adherence between patients in the control group compared to those in the intervention group (a web-based self-management tool named Boston Breathes). The study was underpowered and did not find a significant difference in the DOSER CT™ adherence scores between groups however, a post hoc analysis looking at those with low baseline adherence did show a significant improvement in those randomised to the intervention group (Bender, Wamboldt, O' Connor, et al., 2000). As this was an early adherence electronic monitoring it only includes a simple digital dose counter.

#### 2.2.1.4.6.2 Smartinhaler™

Smartinhalers™ (Adherium, New Zealand) objectively and accurately records actuation adherence data in asthmatic patients (Burgess, Wilson, Cooper, Sly, & Devadason, 2006). The device is fitted to the child's usual inhaler; it contains a microchip which collects data on when and how often an inhaler is actuated. The calculation of adherence from this device is not affected by dose dumping as it records the exact time, day and number of doses actuated so that the clinician/researcher can see if dose dumping has occurred and disregard the over-use of medication (if it is not relevant to their research). The device can be fitted to many different types of inhalers and is easy for patients to transfer the device to a new inhaler when a prescription is renewed. Newer versions of the Smartinhaler™ are Bluetooth enabled and rechargeable. Children or their parents can download an App enabling them to monitor their own adherence, or health professionals can utilise this functionality to remotely monitor adherence and intervene rather than waiting for the device to be returned to clinic.

##### 2.2.1.4.6.2.1 Interventions using Smartinhalers™

As well as using Smartinhaler™ to monitor adherence, a number of studies have investigated the utility of these devices as an adherence intervention (Chan, Harrison, Black, Mitchell, & Foster, 2015; Morton et al., 2017). This is certainly plausible: one would expect that children

would be more likely to take their inhalers if they know they are being monitored and the reminder function on the Smartinhaler™ may help those whose poor adherence is due to forgetfulness and poor routine. Three paediatric randomised controlled trials of EMDs demonstrated significant differences in monitored adherence between the control and intervention arms (57.9% versus 79%, 30% versus 85% and 49% versus 70% respectively) (Burgess, Sly, & Devadason, 2010; Chan, Harrison, et al., 2015; Morton et al., 2017). Chan et al. (2015) utilised the reminder function of the Smartinhaler™, but the intervention did not include clinician feedback to patients on their adherence, noted significant improvement in a secondary outcome, asthma control scores, in the intervention group during the six month monitoring period. Morton et al. (2017) who used both the reminder function and clinician feedback around adherence, noted a significant reduction in asthma attacks over a 12-month period. Burgess et al. (2010) used Smartinhaler™ to monitor adherence with clinician feedback given but no reminders and did not find significant differences in the study's only clinical outcome FEV<sub>1</sub> % predicted. Similarly, significant difference in FEV<sub>1</sub> % predicted were not found between groups in the Chan et al. (2015) or Morton et al. (2017) studies. FEV<sub>1</sub> % predicted is a poor clinical outcome in children in comparison to adults as many children have normal spirometry despite severe asthma (Bacharier et al., 2004; Bush & Saglani, 2010; National Asthma & Prevention, 2007; van Dalen et al., 2008) and therefore may explain the lack of reported effect. The effectiveness of these studies may also have been reduced by the Smartinhaler™ measuring actuation and not inhalation. It is possible that those with apparently good adherence were using their devices incorrectly or deliberately manipulating them. A recent study demonstrated that real adherence is far less than actuations counted (Sulaiman, Seheult, et al., 2016). Furthermore, adherence remained suboptimal (<80%) in a significant proportion of those being monitored, suggesting that monitoring alone is insufficient as a sustained beneficial intervention or patients' medications were not effective and therefore, they were using them sub-optimally or not at all. None-the-less, important insights can be gained from the use of these devices. One study demonstrated that a period of monitoring is very helpful in determining management in those with problematic severe asthma (poor control despite prescription of high dose asthma treatment).

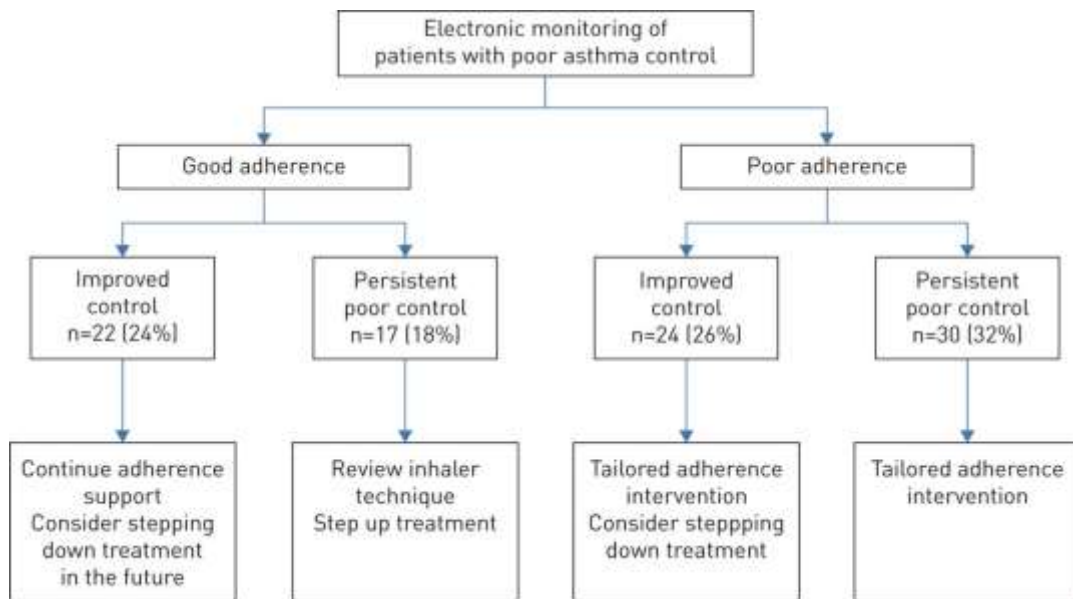


Figure 3: Patterns of Adherence from Jochmann et al. (2017)

Jochmann et al. (2017) identified four groups (Figure 3): those with genuine severe asthma i.e. persistent poor control despite monitored good adherence, such children are candidates for a step up in treatment including addition of expensive biologics; those with good adherence whose asthma control and FEV<sub>1</sub> improved, and FeNO normalised, during the monitoring period (likely as a result of improved adherence), they require support to maintain adherence; those with poor adherence but improved control who require a step-down in treatment as they are likely over treated; and those with poor adherence and poor control. In this group, the next step is to see what happens when the medication is properly used, by means of some form of directly observed therapy. Some will remain poorly controlled; these are patients with STRA who are non-adherent because they (correctly) perceive the medications are not working. The second group, who respond to directly observed therapy, are those for whom an adherence intervention is needed. Analysis of the adherence patterns can also be used as the basis for an honest and open discussion between patient and clinician about adherence and as the basis for planning an appropriate adherence intervention (Pearce et al., 2018; Pearce, Jochmann, Bush, Horne, & Fleming, 2016).

#### 2.2.1.4.6.3 Propeller Health (previously named Asthmapolis Device)

The Propeller Health electronic monitoring device attaches to the top of a pMDI inhaler canister or on the side of a DPI Diskus™ (Accuhaler) and measures the time and date of each inhaler actuation but not the inhaler technique and provides GPS location information. GPS information may be useful when discussing adherence with patients in terms of their routine

and for tracking patients' use of SABA in relation to known triggers e.g. pollen count and pollution. The adherence data from the device can be downloaded using a USB cable or Bluetooth to a specifically designed smartphone application. The device therefore could act as an intervention to change the patient's adherence with no input from a health care professional but only if they had access to the smartphone app. Without the app the device is only an adherence measurement tool. The battery is rechargeable and the patient can fit the device onto any repeat prescription of the same inhaler. Propeller Health, which is FDA approved, has been used to measure use of both SABA (Barrett et al., 2017) and ICS (Adams, Leach, Feudtner, Miller, & Kenyon, 2017; Hoch, Kempe, Brinton, & Szeffler, 2018). Propeller Health has recently been used to measure SABA use in a large RCT (Merchant et al., 2016) however, to date no RCT has been conducted on ICS use. SABA use is likely to be investigated more frequently in the future as an indirect surrogate of ICS use, as high SABA use often correlates with poor adherence to ICS, and is a marker of future risk (Buelo et al., 2018; Royal College of Physicians, 2014; Suissa et al., 1994). Propeller health devices are currently expensive, currently costing approximately \$300 US dollars per device.

#### 2.2.1.4.6.4 Inhaler Compliance Assessment (INCA) device

The Inhaler Compliance Assessment (INCA) device measures adherence by recording the time and date of the actuation but importantly also contains acoustic sensors which can detect inhalation (Holmes, D'Arcy, Costello, & Reilly, 2014; Sulaiman et al., 2018). This has clear advantages over the currently commercially available Smartinhaler™; however, it is only clinically available for the Diskus™ (Accuhaler) inhaler, a dry powder inhaler which is not suitable for younger children. The INCA device has only been evaluated in adults (Heaney et al., 2018). Current work is ongoing to make this technology adaptable to pMDIs for use in COPD and asthma within a clinical setting (Taylor et al., 2018).

Sulaiman et al. (2016) have used the INCA to develop an algorithm to measure adherence over time (an area under the curve (AUC) measure), which considers the time between doses as well as the inhaler technique, using acoustic sensors. Measuring actuation alone via a dose counter significantly overestimated adherence compared to the INCA AUC measurement (84.4% vs 61.8%,  $p < 0.01$ ). Furthermore, only improvement in the AUC method was significantly associated with positive changes in asthma quality of life, reliever use, and peak expiratory flow recordings over 3 months.

The device has recently been tested in a randomised controlled trial in adults with severe uncontrolled asthma (Sulaiman et al., 2018). Participants were randomised to an intensive education programme including inhaler technique or biofeedback based on data from the INCA device over a three-month period. Those in the biofeedback group had significantly higher actual adherence (both actuation and correct technique) in the third month of the intervention than the intensive education group (73% versus 63%; 95% CI 2.8%-17.6%;  $p=0.02$ ). Furthermore, the device enabled the identification of clinically meaningful groups, including those who remained “difficult to manage” (uncontrolled with poor adherence despite monitoring). Similar groups were described previously in the Jochmann study (2017); however, in that study the authors were unable to determine if those participants with poor control (despite documented good adherence) had poor inhaler technique, or were refractory to treatment. This device certainly shows promise. Adapting this technology for other inhaler devices would enable testing in a greater range of patient groups, including children. Further work is needed to see if a period of monitoring with biofeedback can lead to sustained improvements in inhaler technique. Additionally, this device currently only measures adherence as it does not provide any feedback to the patients regarding their medication taking either audibly or visually on the device.

#### 2.2.1.4.6.5 PUFFclicker and Activ8rlives Asthma+Me App

Another recently developed, commercially available and promising adherence tracker is the PUFFclicker by Activ8rlives (<https://www.activ8rlives.com/products/puffclicker/>). Much like other electronic monitors the PUFFclicker is a wraparound device for pMDI inhalers that records inhaler actuation. The device not only monitors adherence it can also act as an intervention to help patients improve their adherence. The PUFFclicker records whether or not the device has been shaken prior to use to improve inhaler technique and includes an accelerometer to measure step count, activity time and distance. Once shaken appropriately to disperse the medication the device screen shows a tick to feedback to the patients that the medication is ready to be inhaled. The device also contains a timer with visual feedback to the user for when the device is ready to be shaken and used again. The device can be accompanied by a subscription app which has a personalisable reminder function as well as a prescription refill reminder. The PUFFclicker was developed for children aged 5-18 with difficult or severe asthma in collaboration with an NHS paediatric respiratory consultant. The device is more affordable than other EMDs at £74.99 each however, subscription fees apply to access certain accompanying app functionality, the PUFFclicker does not record inhalation and this device has not been tested within published literature.

#### 2.2.1.4.6.6 Rafi-Tone

Rafi-Tone (Clin-E-Cal, UK) is a newly developed interactive game to encourage spacer use and medication adherence in a fun way for younger children (Clin-e-cal, 2018). The spacer is fitted with the Flo-tone device (Clement Clarke International, Harlow, UK) which is designed to improve inhalation technique using a whistle. The whistle activates the game App to incentivise inhaler use as well as recording the time and date of activation onto the inhaler tracker. Rafi-tine therefore not only monitors adherence but can act as an intervention to change behaviour particularly through the whistle and diary. The inhaler tracker can be used with or without the game to record medication use for self-management of asthma. The inhaler tracker is a calendar where medication doses can be systematically recorded by the parents of the child with asthma. Rafi-Tone was developed for use with pMDI inhalers and spacers.

#### 2.2.1.4.7 Integrating digital technologies

The increasing use of technology to monitor adherence affords the opportunity to integrate monitoring with digital adherence interventions. As discussed above a number of EMD devices have utilised reminder functions built into the device (Chan, Harrison, et al., 2015; Morton et al., 2017). However, an alarm will only be effective if it is in close proximity to its user. A number of studies have looked at other ways of providing prompts. The almost ubiquitous presence of a personal Smartphone suggests they would be a much more effective conduit for delivery of reminders. Short messaging service (SMS) / text or phone messages have been shown to have a positive impact on adherence (Tran, Coffman, Sumino, & Cabana, 2014). Propeller health devices have also been used in conjunction with text message reminders with children with asthma. This pilot study is registered on clinicaltrials.org but has yet to publish results (ref: [NCT02615743](#), (Adams et al., 2017). Within the current literature objective measures of adherence are generally lacking in text message studies and there has been little impact demonstrated on clinical control. In one study in adolescents only 37% of participants offered SMS medication reminders successfully adopted this feature (Johnson et al., 2016). However, such interventions need to be tailored to the target population. One such study used tailored text messages to deliver an intervention to patients with asthma aged over 16 years old. Petrie et al. (2012) were able to increase adherence to preventer inhalers by 10% compared to a control group by addressing illness and medication beliefs via text messages. However, text messages and telephone calls are not the standard means of communication for most young people who are now more likely to engage with smart phone applications (apps) and communicate

through WhatsApp and Snapchat. Newer versions of EMDs have an associated App enabling the reminder to be delivered via a mobile device. Such Apps also afford the user the opportunity to monitor their own adherence, providing support for directed self-management. Whether evidence of benefit can be demonstrated before technology has again moved on remains to be seen.

#### 2.2.1.4.8 Biomarkers of adherence

##### 2.2.1.4.8.1 Drug levels

Serum drug levels can be measured to assess adherence however in asthma this is limited to theophylline and oral steroids for which clinical assays are available. Measurement of theophylline levels (when this medication is prescribed) is usually undertaken to ensure the dose is in the therapeutic range; however very low or undetectable levels measured in either serum or saliva indicate poor compliance (Eney R.D & E.O, 1976). Interpretation of these levels depends on knowing when the drug was reported or scheduled to have been taken and are unreliable if taken more than 12 hours after administration of a slow release tablet or 2 hours after immediate release preparations. For those on maintenance oral steroids serum prednisolone levels can be measured (Robinson et al., 2003). This assay is only valid if measured within 6 hours of the dose. A suppressed random cortisol level would also be expected if prednisolone has been taken regularly; although levels fluctuate greatly over time, a high cortisol suggests the adrenals have not been suppressed because medication was not taken. However, a low level may be due to adrenal suppression by steroids, or simply the normal Circadian rhythm in a patient not using the prescribed steroids. Timing of prednisolone assays can be difficult particularly for children prescribed alternate day prednisolone, who always seem to attend clinic on the day they are not scheduled to take the dose! Whilst drug levels can be useful, only a very small number of children are prescribed theophylline or maintenance prednisolone. It is possible to measure inhaled steroid metabolites in blood and urine (George K.E, Ryan D.M, Keevil B, Niven R, & SJ., 2017), however at present these assays are generally only available in research settings or doping laboratories. Measuring adherence in this way is also invasive and may not be acceptable to parents and their children, particularly young children, and may not be practical for families or for clinicians for regular adherence monitoring.

##### 2.2.1.4.8.2 Exhaled nitric oxide

Fraction of exhaled nitric oxide (FeNO) is an indirect measure of eosinophilic airway inflammation and usually, but not inevitably, falls in response to ICS. FeNO at the end of a


period of monitoring with an EMD was found to have the best correlation with adherence and a significant fall in FeNO was observed in those with good ( $\geq 80\%$ ) and moderate (60-79%) adherence over the monitoring period (Jochmann et al., 2017). FeNO suppression has been shown to be useful in identifying non-adherence in children with asthma both in the context of research and clinically. Koster et al. (2011) explored this in patients with FeNO of ( $>25$  ppb) between those with good adherence (measured by a MARS score  $\geq 21$ ) and patients with poor adherence (measured by a MARS score  $<21$ ) in relation to their adherence to ICS. They found FeNO suppression to be a useful objective measure to detect poor adherence in a large sample of children aged 4-12 years old. FeNO is increasingly available in clinical care and could be combined with objective measures of adherence such as DOT or EMD monitoring to identify those with previous poor adherence as has been explored in adult asthma (Heaney et al., 2018). However, within a paediatric problematic asthma group 35% of the cohort had FeNO levels of  $<25$ ppb at enrolment and therefore FeNO suppression may be a less useful tool in this group (Jochmann et al., 2017). Furthermore, FeNO alone did not distinguish those with poor control and poor adherence and those with poor control and good adherence (Jochmann et al., 2017).



The key features of the different monitoring tools are summarised in Table 1.



Table 1: Pros and Cons of the most common adherence monitoring tools in children with asthma



Adherence Monitoring Tool	Development Year	Pros	Cons	Measurement tool or Intervention	Published data showing device reliability
2.1 Subjective					
2.1.2.1.2 Morisky Scale	MMAS- 1986 MMAS-8-2017	Short and easy to administer Inexpensive	Originally developed in hypertension Not used frequently in paediatric asthma research	Measurement tool	Yes (Morisky et al., 2008; Morisky et al., 1986)
2.1.2.1.3 Medicines Adherence Report Scale (MARS – A and MARS-5)	MARS MARS-5-2002 MARS-A-2009	Short and easy to administer Inexpensive Correlates to electronic monitor data in the adult validation study	Self-report generally over-estimates adherence in children in clinical settings	Measurement tool	Yes (Cohen et al., 2009)

2.2 Objective					
2.2.4 Mobile Directly Observed Therapy	2018	Inhaler technique can be checked in addition to adherence  MDOT reduces the travel burden for traditional DOT at the hospital or a community location	Patients may take their inhaler without uploading a video  Reviewing videos is time consuming for the clinicians (expensive)  Uploading the video relies on an internet connection	Measurement tool	Yes (Shields et al., 2018)
2.3 Electronic Monitoring Devices					
2.3.1 Doser CT™ 	1998	Most inexpensive of the electronic devices  Records the number of actuations	Does not record the time and date of each actuation- open to dose dumping  Memory is only 30 days long	Measurement tool and simple intervention	Yes (Simmons et al., 1997)

<p>2.3.2</p> <p>Smartinhaler™</p> 	2006	<p>Measures when and how often ICS is taken- avoids dose dumping</p> <p>Can be put onto different types on inhalers by the patient/parent</p> <p>It is commercially available</p> <p>Can have a reminder alarm enabled</p> <p>Rechargeable</p> <p>Bluetooth enabled link to a mobile app</p>	<p>Expensive</p> <p>Can be manipulated as actuation not inhalation measured</p> <p>It does not measure inhalation</p> <p>Bluetooth enabled</p>	Measurement tool and intervention	Yes (Burgess et al., 2006)
<p>2.3.3</p> <p>Propeller Health</p> 	2018	<p>GPS enabled</p> <p>Measures when and how often ICS is taken- avoids dose dumping</p> <p>It has a light which tells the user when in needs charging, when a</p>	<p>The most expensive device</p> <p>It is not currently available for routine clinical use</p>	Measurement tool (can be used as an intervention if in conjunction with the app)	Yes (Adams et al., 2017; Barrett et al., 2017)

		dose is taken and when it is plugged into the USB cable  It is Bluetooth enabled and has its own app	It does not measure inhalation		
2.3.4 Inhaler Compliance Assessment (INCA)	2013	Measures how, when and how often a dose is taken- avoids dose dumping  Measures inhalation technique	Not commercially available for clinical use  Only available for DPIs (pMDI in development)  It is not Bluetooth enabled and does not have an accompanying app  Only validated in adults with an effect over a three-month period	Measurement tool	Yes (Holmes, D'Arcy, et al., 2014; Sulaiman et al., 2018)



<p>2.2.1.4.6.5</p> <p>PUFFclicker and Activ8rlives Asthma+Me App</p> 	2018	<p>Measures when and how often ICS is taken- avoids dose dumping</p> <p>Measures inhaler technique (when the canister is shaken)</p> <p>It is Bluetooth enabled and has its own app</p> <p>Is rechargeable and has a battery life of between</p> <p>Developed for a paediatric difficult/severe asthma population</p> <p>Commercially available</p>	Not validated in any published literature	Measurement tool and intervention	No
<p>2.3.5</p> <p>Rafi-Tone</p> 	2017	Measures inhaler technique and use	<p>Only available for young children</p> <p>Does not measure inhaler use directly</p>	Measurement tool and intervention	No

### 2.2.2 Discussion

Over the past 15 years the development, and increasing use, of electronic monitoring devices has enabled a more accurate assessment of adherence – an essential starting point in identifying patterns of medication use, and consequently reasons for poor adherence and poor treatment response. However, these devices are not a panacea. They do not capture the patient’s “usual” adherence as the process of monitoring leads to improved adherence in many (Adair, 1984). If adherence monitoring is stopped the behaviour may revert back to the pre-intervention behaviour. Consequently, electronic adherence monitors do not appear to be a sufficient intervention in themselves to lead to sustained improvements in asthma control: adherence decreases the longer the monitoring period goes on (Bender & Zhang, 2008; Konstantinou, 2012), and crucially, in all but the INCA device, the devices monitor actuation and not inhalation. None-the-less they can provide valuable data both for the patient and the healthcare provider. Firstly, asthma control can be interpreted in the context of more objectively determined adherence likely to prevent doctors from unnecessarily escalating treatment in patients where adherence to their current treatment is a problem. Secondly the combination of adherence data and changes in asthma control during a period of monitoring can be used as the basis of a concordance interview and to identify and design with the patient an appropriate adherence intervention; and finally, the reminder functionalities and potential for connectivity with an App which records usage may be helpful for some patients as a tool to improve adherence.

The current costs and availability of EMDs limits their use and they are not part of mainstream care in most clinical settings. The NHS NICE guidance for Smartinhaler™ has stated that *“The **resource impact** would be greater than standard care, because of the cost of the device and software access, unless reductions in GP and hospital visits were realised” (NICE, 2017b)*. Given the huge costs of asthma management it is possible that the use of these devices could lead to financial savings (including reducing medication costs including medication wastage and escalation to unnecessary expensive treatments) making them attractive to providers/ payers, and therefore a health economic analysis of their use is needed. Furthermore, they may prevent asthma deaths by identifying those at risk due to low ICS usage. Given the extremely high UK asthma death outcomes in comparison to the rest of Europe (Wolfe et al., 2013), all possibly beneficial new approaches need to be considered. The recent NHS long term plan (Alderwick & Dixon, 2019) has in fact announced the piloting of Smartinhaler™ within respiratory medicine within the next 10 years. In the

meantime, other forms of adherence monitoring such as prescription refill rate and empathetic questioning have their role, provided the limitations, as discussed in this chapter, are recognised.

The further development of novel technology in health care is a fast-moving field. EMDs which include a measure of inhalation (either utilising acoustic or flow sensors or video capture) offer greater potential to improve asthma control by addressing practical barriers (i.e. inhaler technique). Further studies are needed to assess whether they do offer benefit over currently available devices. There is a risk that the greater the functionality, the greater the cost and likelihood of device failure. Improving reliability and driving down costs of current devices may yield greater benefit on a population level whereas more sophisticated devices may have greater utility for the individual. The differential pace of technology development compared to clinical trials is a challenge for those working in this area and a balance must be struck between the excitement of innovation and evidence of benefit.

Recognising poor adherence is an important step in asthma management; however, to optimise medication use requires meaningful engagement with the patient. Merely knowing whether a patient is adherent or not does not uncover the myriad reasons for poor adherence nor does it automatically lead to improved adherence. Non-judgemental patient doctor communication based on objective adherence data is vital to target adherence behaviour more effectively. Combining EMDs with a simple questionnaire tool to profile an individual's adherence beliefs and practical barriers to adherence could help to identify key areas for discussion between patients and healthcare providers and to personalise adherence interventions.

The importance of adherence in asthma care is well established. Decreasing costs and improved usability of EMDs offers the prospect of adherence monitoring becoming part of mainstream care. It is possible that in the near future all inhalers could contain some sort of in-built monitoring device. The technological challenges are relatively easy to address; implementing behaviour change on the part of the patient and the healthcare provider and acceptance of adherence technology (Stewart et al., 2018) is a mountain yet to be climbed.

#### *2.2.2.1 Conclusion*

Adherence measurement is a key part of asthma management, and there currently exists many potential methods of assessing adherence, each with differing pros and cons. Self-

report is the most convenient, cost-effective way to measure adherence but no single self-report questionnaire to measure adherence or adherence related beliefs has been developed and validated in children with asthma. Although other clinical tools such as prescription data can be a useful and low-cost way to assess what treatment is actually being administered, similarly to subjective measurements, they are likely to overestimate adherence. EMDs are currently seen as the gold standard for measurement of adherence in asthma. However, current EMDs have key limitations including the lack of measurement of inhalation and the high cost. The development of the next generation of EMDs which can assess inhalation and inhaler technique have the potential to revolutionise adherence measurement in asthma.

Although accurate measurement of adherence is important very few studies have used these measurement tools to explore the underlying reasons for low adherence. To enable an intervention to increase adherence it is paramount to understand the reasons for nonadherence for each individual and to tailor the intervention to these reasons. Limited research has been conducted in paediatric problematic asthma to understand the reasons for poor adherence and to explore differences in the ways in which patients are non-adherent (their patterns of adherence). Psychological frameworks can help researchers to explore adherence and the reasons behind non-adherence behaviour. The following chapter will outline where psychological theories have been utilised in adherence to asthma medication, mainly in adults, to inform the selection of a psychological framework which the remaining chapters research studies will be based on.



### **3.1 Psychological Theory in Adherence Research**

Psychological theoretical frameworks in health describe the process by which psychological and behavioural processes, (e.g. thoughts, feelings and behaviours) affect our health. Baum and Posluszny (1999) describe the recognition of the importance of these factors, and their influence on health, as representative of the shift in the understanding of the mind and body in modern conceptualisations of medicine. Psychological theoretical frameworks have been applied to intervention development, an approach which is recommended by the UK Medical Research Council in the development of all complex health interventions (Craig et al., 2013). Many health behaviours have been explored using psychological theory including eating behaviours; smoking; alcohol consumption; screening attendance; exercise and adherence to treatments (both pharmacological and behavioural e.g. physiotherapy). This thesis will focus specifically on theoretical frameworks that have been applied to medication adherence.

In a recent systematic review investigating adherence interventions over the previous twenty years (Holmes, Hughes, & Morrison, 2014), the most common theoretical models used were: The Health Belief Model (HBM)(Becker, 1974); The Transactional Model of Stress and Coping (Folkman, 1984); The Theory of Planned Behaviour (TPB) (Ajzen, 1988); Social Support Theory (Simoni, Frick, Lockhart, & Liebovitz, 2002), Self-Determination Theory (SDT)(Deci & Ryan, 1985) and The Common Sense Model (CSM; also known as the self-regulation theory including the extended CSM incorporating a framework of treatment representations (Horne & Weinman, 2002; Leventhal, Diefenbach, & Leventhal, 1992) . The review (Holmes, Hughes, et al., 2014) concluded that the most common domains across the theoretical frameworks used in psychologically based adherence research were treatment necessity and concern beliefs (Necessity and Concerns Framework (Horne & Weinman, 1999) (see 3.2.6) and self-efficacy (Bandura, 1977) (see 3.2.13.2.1).

Chapter 3: will briefly outline the most common theoretical models that have been applied to medicines adherence, as identified by the Holmes et al. (2014) review including, where possible, examples of their use in adherence research in asthma. Although an update of the systematic review is warranted, this is outside the scope of this PhD, therefore this chapter will discuss an update of the Holmes et al. (2014) review using a scoping literature review for

recent adherence studies in asthma and those that include children. This chapter will also justify the choice of theoretical model for the basis of this PhD.

## **3.2 Theoretical Frameworks Commonly Applied in Medicines Adherence Research**

### **3.2.1 Social Cognitive Models**

Social Cognitive Models stem from Social Learning Theory (Bandura, 1977)- highlighting that both the individual and the external social world influence learning and human behaviour- and refers to models and theoretical frameworks that include cognitive as well as social determinants of behaviour (French, 2010). Self-efficacy is a concept introduced by Bandura (1977) which originates from Social Learning Theory (see 3.2.1); it is defined as the individual's belief in their capability to perform a given behaviour. If an individual has high self-efficacy (believes they can perform the behaviour) they are thought to be more likely to perform a given behaviour compared to those who have low self-efficacy (believe they cannot perform the behaviour) (Bandura, 1977). Social Cognitive Models have been used in health psychology to explain a number of health behaviours and have more recently been used as a basis for intervention development. The following theoretical frameworks are social cognitive models: Social Cognitive Theory; The Health Belief Model; Theory of Planned Behaviour.

#### *3.2.1.1 The Health Belief Model (HBM)*

The Health Belief Model (HBM) (Becker, 1974) was originally developed by a group of public health service researchers to describe the cognitive processes which predict preventative health behaviours such as screening for diseases (Rosenstock, 1974). However, it was later put forward as a model to contrast with the traditional medical model of health in relation to illness behaviours. The HBM contrasts with the medical model which focuses on patient demographics (e.g. age and gender); the illness (e.g. severity, duration) and the medication regimen (e.g. complexity, discomfort of taking the treatment) as determining patient illness related behaviour (Becker, 1974). The HBM was developed to describe the elements related to a patient's health-related actions taking account of patients' beliefs. The HBM comprises six factors which are involved in a patients' perceptions of health behaviours/illness as a threat and influence the action which they take to mitigate said threat: a patient's perceived susceptibility to the health threat; the perceived severity of the health threat; perceived benefit and cost of carrying out the desired health behaviour; cues to action, and modifying

factors such as demographics. At a later date due to criticism of the original HBM, motivation to conduct the health behaviour was added to these six factors. The model was further developed by Becker and Rosenstock (1987) who suggested that perceived control, individuals' belief in their ability to prevent the health threat, should be added as a construct to the model (Figure 4). Although frequently used to investigate adherence in chronic conditions the HBM has been criticised for focusing solely on conscious processing of information (intentional non-adherence) (Ogden, 2012) and ignoring subconscious (or unintentional) non-adherence. The HBM implies that health-behaviours occur based in a single time-point cost-benefit conscious decision rather than an ongoing decision making process which is more likely relevant in long-term condition adherence to maintenance therapies (Horne & Weinman, 1998).

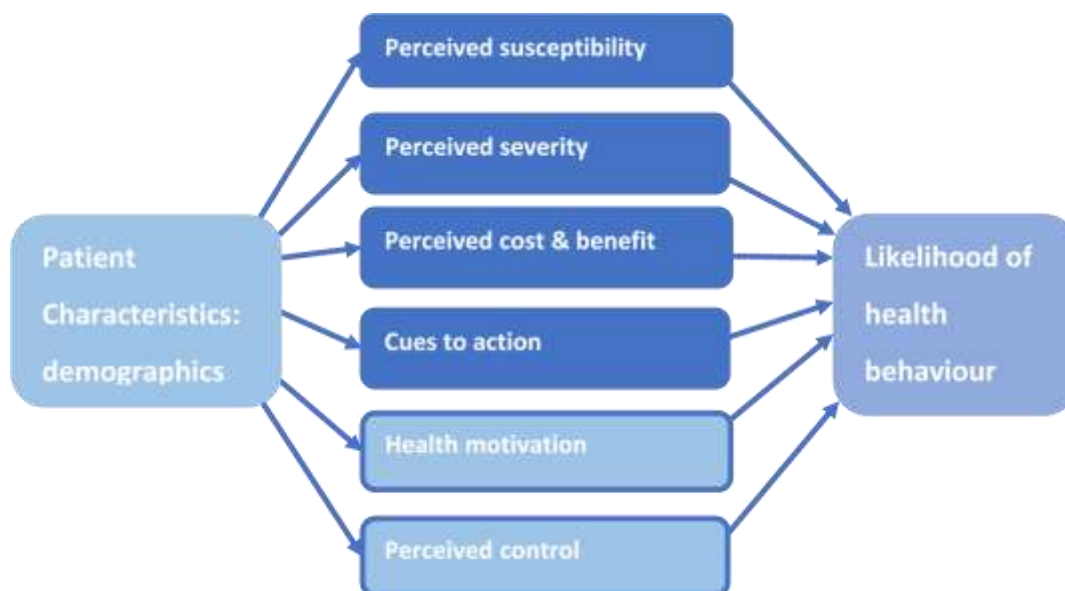


Figure 4: The Health Belief Model adapted from Ogden (2012)

One of the first empirical tests of the HBM in illness was in paediatric asthma with mothers of children taking theophylline (an oral treatment for asthma as described in Chapter 1) (Becker et al., 1978). Adherence to theophylline was measured by both subjective, parental report and objective, theophylline levels in the blood. The results supported the components of the HBM as both subjective and objective adherence significantly correlated with each component with the HBM. However, this study was a cross-sectional qualitative study so it cannot confirm causality of the relationship or that the relationship would hold over time.

More recent work based on the HBM that have investigated adherence in asthma are studies from Apter et al. (2003) and De Smet et al. (2006), both of which are described in the Holmes et al. (2014) review. Apter et al.(2003), conducted in adults with moderate/severe asthma,

was a cohort study which investigated adherence to ICS using a model that incorporates the HBM. The study measured adherence using an electronic monitor (MDILog), an objective measure of adherence, attached to the ICS medication. The cohort study found that less fear of side-effects of ICS and stronger beliefs in ICS benefit were associated with higher adherence (measured by the EMD). These findings support idea that attitudes are important in determining adherence behaviour, however no specific components of the HBM were highlighted. The results support the idea that beliefs in the medications benefits and fear of adverse events were associated with adherence behaviour (Apter et al., 2003). These findings are more in line with the Necessity and Concerns Framework (NCF (Horne & Weinman, 1999) (see 3.2.6) than the HBM.

De Smet et al. (2006) used adult routine insurance claims data to measure adherence across multiple controller medications (theophylline; chromoglycate and nedocromil and inhaled, oral, and injectable corticosteroids). The cross-sectional questionnaire study used an adapted version of a HBM based questionnaire, validated in diabetes (Given, Given, Gallin, & Condon, 1983) to measure beliefs and a self-report questionnaire (Brooks et al., 1994) to measure adherence to any asthma controller medication. The findings of this study showed moderate relationships between the HBM questionnaire statements and self-reported adherence. However, there are some limitations in this study which need to be considered prior to firm conclusions being drawn. Firstly, only one measure of adherence was used to measure all types of controller medication. It is likely that beliefs and therefore adherence will vary for different types of medication and therefore different drug classes should be measured separately (Wu et al., 2015). More recent studies focus on a single medication per measurement of adherence for accuracy (Normansell, Kew, & Stovold, 2017). Secondly, adherence was measured using insurance claims which can only highlight complete non-adherence (if no prescriptions are collected) rather than accurate adherence levels. Thirdly, this study was again a cross-sectional study and therefore causality cannot be confirmed between the HBM constructs and adherence behaviour. Fourthly, the HBM questionnaire used was minimally adapted from the original questionnaire which was validated in a population of patients with diabetes. The authors state this limitation in the paper and highlight the need for a specifically developed and validated HBM questionnaire to further investigate specific asthma related beliefs. Although diabetes and asthma may share similarities in that they are long-term conditions with the responsibility for medication taking falling heavily on the patient (Taylor et al., 2014), the diseases differ both in the nature of

their primary controller medications (inhaled corticosteroids for asthma and injectable medication for diabetes) and in their flexibility of their regimen.

Although the Holmes et al. (Holmes, Hughes, et al., 2014) review found that the HBM was the most frequently used theoretical model in the review of adherence interventions in long-term conditions only two included studies were in asthma. One study supported the use of the HBM but had concerning limitations in terms of its methodology (self-report for multiple medications within one questionnaire and limited adaptation of a HBM based questionnaire for the target patients); (De Smet et al., 2006). The second study supported some domains of the HBM (Apter et al., 2003), but the findings were more aligned to another psychological framework, the NCF (Horne & Weinman, 1999), rather than the HBM. A study by the originators of the HBM did show support for the model in its investigation of adherence to theophylline in children (Becker et al., 1978). However, this study focused only on theophylline which is now a largely obsolete treatment which has a severe side-effect profile (Joint Formulary Committee, 2019) and is a different class of medication (not an inhaled treatment) to ICS which are now the mainstay of asthma management, and the focus of this PhD. Although the HBM has some support in its ability to explain adherence to asthma medication within previous literature the factors of the model are not all supported. Indeed, the HBM lacks specificity as it refers to general benefit and risks and therefore has been criticised in its ability to be tested (Ogden, 2012). These criticisms of the HBM are supported by the above observations in the outlined adherence in asthma literature. The more recent research exploring treatment beliefs has expanded on these general terms for adherence behaviour with more specific constructs related to underlying beliefs about medicines: the necessity of the medication and patient's concerns about medication (both medications as a class and the specific medication in question)(Horne & Weinman, 1998, 1999).

### *3.2.1.2 Theory of Planned Behaviour (TPB)*

The TPB (Ajzen, 1988, 1991) is a progression of a previously developed model, the Theory of Reasoned Action (TRA (Ajzen & Fishbein, 1980; Fishbein & Ajzen, 1975)). These social psychology theoretical frameworks both describe the relationship between attitudes and behaviour. Attitudes are defined in the TRA "a disposition to respond favourably or unfavourably towards an, object, person, institution or event" (Ajzen, 2005, p. 3), in the context of this thesis the event of taking an ICS inhaler. The TRA highlighted that attitudes consist (Ajzen, 1991) of two facets: the importance of subjective norms (the individuals' beliefs about the social world around them and pressures for their behaviours to be similar

to other peoples) in terms of actual beliefs and the evaluation of those beliefs. The TPB added to the TRA a dimension called behavioural control. Perceived behavioural control is the amount to which an individual believes they can carry out a behaviour based on both internal factors such as their skills, and external factors such as the opportunity to be able to perform the behaviour. The TPB therefore emphasised that attitudes towards a behaviour (positive or negative attitudes towards both the behaviour and the outcome of the behaviour), subjective norms and perceived behavioural control all lead to an individual's behavioural intention and that intentions then lead to behaviour. Intentions are defined as "plans of action in pursuit of behavioural goals" (Ajzen & Madden, 1986). The TPB also highlights that perceived behavioural control can influence behaviour in two ways. 1. It can mediate the relationship between behavioural intentions and behaviour or 2. It can jointly determine the behaviour with behavioural intentions (Figure 5). The first association is highly related to the concept of motivation whereas the second more direct association is related to actual behavioural control, or ability. For the second association between perceived behavioural control and behaviour to be accurate a patient must have experienced the behaviour previously to inform their judgement (Ryan & Carr, 2010) e.g. be aware that they have not had the ability to adhere in the past.

Although TPB has been used as the theoretical basis for research in several long-term conditions (Holmes, Hughes, et al., 2014) , TPB has only been used in asthma in one study (Lee, Pincus, & Williams, 2016). However, this study was in adults not children, and was focused on adherence to prescription pick-up of the medication (medication initiation; Chapter 2.1.1) rather than adherence to the medicine regimen itself (implementation) (Lee et al., 2016). The study was only in 27 adults with asthma and adopted a survey methodology. Authors found that, based on the TPB based questionnaire, the only belief that was significantly different between those who did and did not self-report picking up their asthma controller was the belief that using the inhaler was important. This could be considered a necessity belief – see section 3.2.6 below – and thus relates to the NCF. The authors conclude that intention did not appear to be enough to encourage prescription pick-up of controller inhalers in this population. More work is needed to investigate patient specific barriers in addition to beliefs in order to build more effective interventions (Lee et al., 2016). Overall, this small study did not support the dimensions of the TPB alone in increasing adherence in an asthma population. The authors advocate a joint approach focusing on both specific beliefs (rather than general attitudes as specified by the TBP) and more practical barriers/facilitators that may influence adherence.

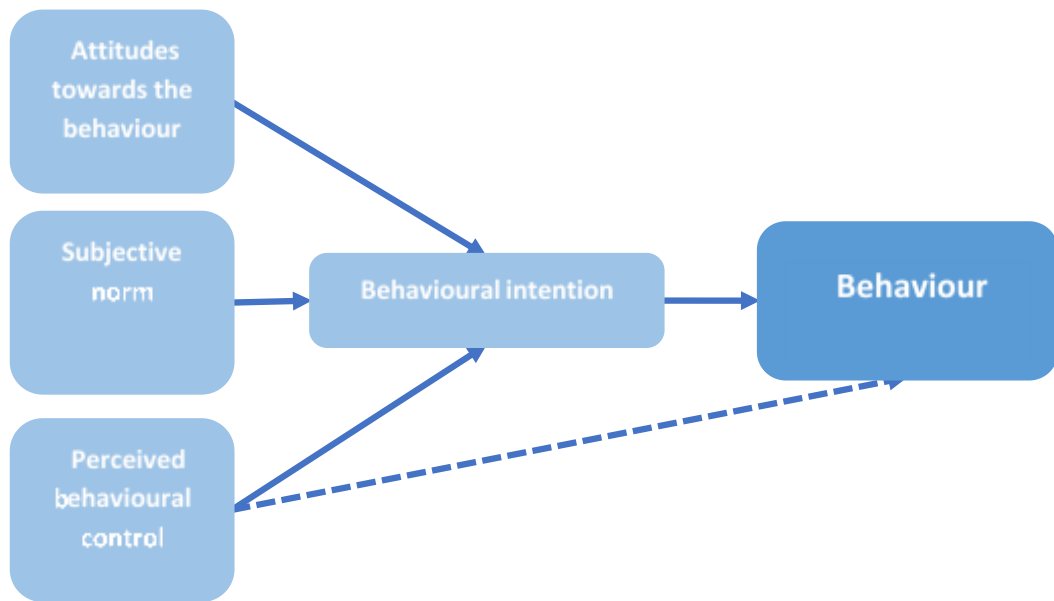


Figure 5: The Theory of Planned Behaviour adapted from Ajzen, (1988)

### 3.2.2 The Transactional Model of Stress and Coping (TMSC)

The TMSC (Folkman, 1984; Lazarus & Folkman, 1984) focused on the ability of an individual to deal with a potential stressor. Adherence to medication may be considered a stressor due to concerns about the medication including stigma related to adhering to the medication. The TMSC describes a two-stage appraisal process: firstly, the assessment of whether or not a potential stressor is actually stressful; secondly, whether they have the ability to cope with the stressor. The primary appraisal results in four responses: 1. The stressor is irrelevant; 2. Benign and positive; 3. Harmful and a threat, 4. Harmful and a challenge. Depending on the second appraisal (the individual's ability to cope with the stressor), one of four responses occur: 1. Action; 2. Information seeking; 3. No action; 4. Developing coping mechanisms to deal with the stressor (Hamilton-West, 2011; Ogden, 2012) (Figure 6).

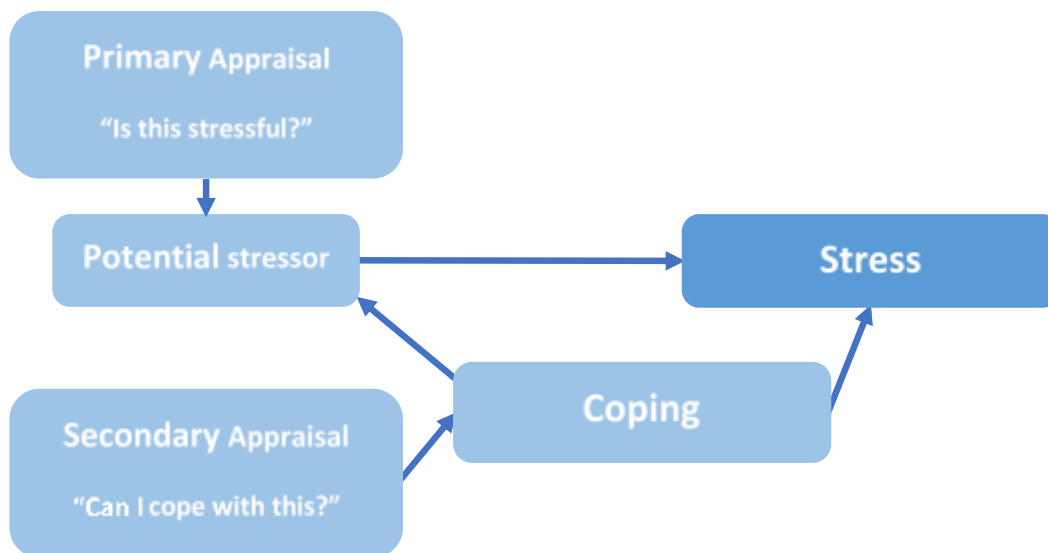


Figure 6: The Transactional Model of Stress and Coping adapted from Hamilton-West (2011) and Ogden (2012)

The TMSC has been used in various studies investigating adherence in Human Immunodeficiency Virus (HIV) but has not been used to explore adherence in asthma (Holmes, Hughes, et al., 2014). HIV is known to historically carry stigma as a sexually transmitted disease (Turan et al., 2017) and therefore diagnosis is often a stressful event and often leads to denial and non-adherence (Rao et al., 2012). No adherence studies in asthma have applied the TMSC. Although asthma can also be stigmatising (Pearce et al., 2018), particularly in some parts of the world such as South America and Nigeria (Lenney et al., 2018), it is a common condition globally and diagnosis of asthma often comes as a relief to parents (Cashin, Small, & Solberg, 2008) and children as opposed to a significant source of stress. Asthma, similarly to other chronic conditions, such as diabetes (Fernandes et al., 2007), is likely to be less stigmatising and therefore be less of a stressor than a diagnosis of HIV and therefore the TMSC this PhD will not use this model to exploring adherence to ICS in asthma.

### 3.2.3 Social Support Theory

Social support theory in adherence introduced the idea that the level of social support available is associated with non-adherence. Simoni et al. (2002) hypothesised that the relationship would be mediated by self-efficacy, negative affect states (depressive symptomology) and regimen knowledge (Figure 7). They hypothesised that self-efficacy would be a mediating factor leading from social support to lower non-adherence; that



regimen knowledge would be associated as mediators with lower and higher non-adherence respectively. However, Simoni et al. (2002) found that their hypothesis regarding regimen knowledge was not supported. The original study of this theory in HIV adherence also used self-report adherence as the outcome and found that the most common reasons patients gave for not adhering to their medication was forgetfulness, a factor that is not considered by the proposed model (Simoni et al., 2002).

Social Support Theory (Simoni et al., 2002) has only been used in studies targeting adherence to HIV (e.g. (Simoni, Frick, & Huang, 2006; van Servellen & Lombardi, 2005) and not in studies targeting adherence in in asthma. There was also traditionally a vast difference in the treatment burden for patients with asthma taking ICS compared to those with HIV (twice daily treatment maximum in asthma versus up to 20 tablets a day in early HIV therapy (Bangsberg, Ragland, Monk, & Deeks, 2010)) therefore there was a greater need for treatment social support in those with HIV. The concept of social support is relevant for children with asthma as parents are likely to help support children with the practicalities of taking their medicine (e.g. providing the medication and reminding them to take their medication) however, adherence to ICS is likely to be less related to regimen knowledge (a domain not supported by the testing of the model) and negative affect states. For these reasons Social Support Theory was not believed to be a useful model in exploring determinants of adherence in children with asthma within this PhD.

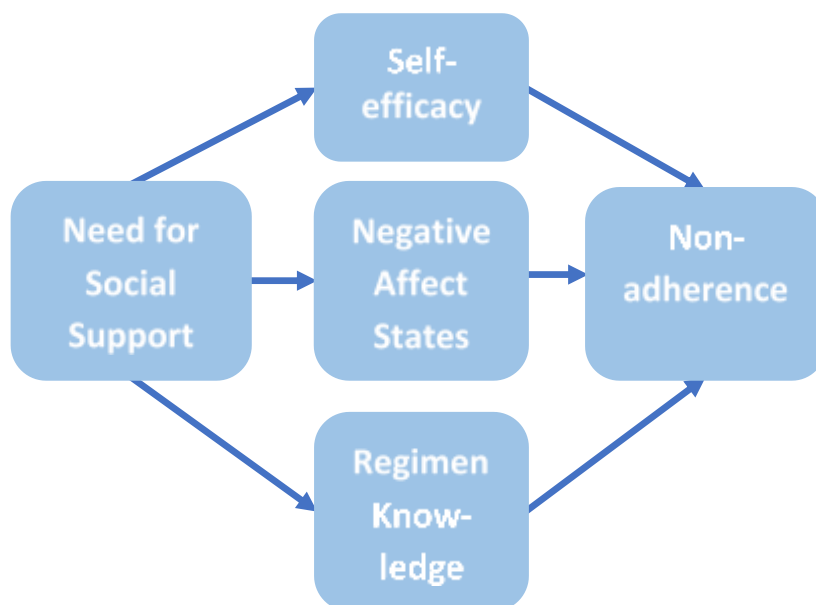


Figure 7: Social Support Theory adapted from Simoni (2002)

### 3.2.4 Self-Determination Theory (SDT)

The SDT (Deci & Ryan, 1985) is an approach for explaining human motivation. Often motivation is broken down into internal and external motivation. Internal motivation being motivation for a behaviour because the behaviour is rewarding in and of itself for example taking your inhaler because you think it will help you. External motivation is whereby the person is motivated by some external factor for example being given money as a reward for take your inhaler. The SDT however is a macro theory of motivation which outlines the process by which external motivation becomes internalised to create autonomous behaviour without the presence of the extrinsic motivation. The SDT proposes that extrinsic and intrinsic motivation are not binary and are in fact on a continuum. The theory suggests that the more internalised the motivation for the behaviour becomes the more persistent and easily maintained the behaviour will become (Prestwich, Conner, & Kenworthy, 2017).

Deci et al.'s (1985) SDT (Figure 8) outlines three basic human needs that are necessary for motivation to become internalised: autonomy, competence and relatedness. Autonomy is defined as the need for an individual to feel that their actions are their own choice and not influenced by external interference, that they are in control of their own behaviour. Competence refers to the need to feel able and capable to control the outcomes from your behaviour. Finally, relatedness refers to the need to feel close, have trust in, cared for and caring of other people. For internalisation of motivation to take place these three basic psychological needs must be met and maintained to increase the likelihood of the given behaviour.

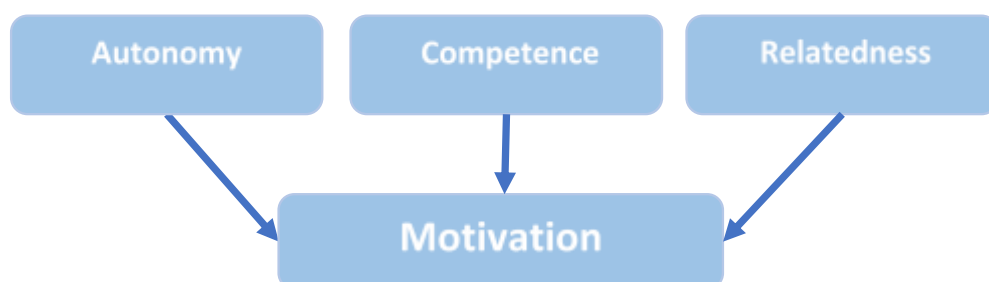


Figure 8: Self-Determination Theory

Two studies have used the SDT in a paediatric asthma population (Bruzzeese, Carcone, Lam, Ellis, & Naar-King, 2014; Gustafson, Wise, et al., 2012). Bruzzeese et al. (2014) conducted a mixed method research study investigating adherence in urban African American

adolescents with asthma. Adherence was measured by self-report using the Family Asthma Management System Scale (FAMMS) interview, with both the adolescent and their caregiver, and beliefs were self-reported using both validated and non-validated scales to measure the SDT constructs. Using multivariate analysis, the study concluded that only family routine was a significant predictor of adherence. The authors suggested that although the individual SDT components were correlated with adherence, family routine was more predictive of adherence than individual SDT components in this group of African American Adolescents with asthma (Bruzzese et al., 2014). Family routine is not a construct covered within SDT and therefore this study supports a role for additional constructs, related to more practical facilitators to adherence. Gustafson et al. (2012) conducted a study in children with asthma. The intervention study, in children aged 4-12 years old, was an online Comprehensive Health Enhancement Support System (CHESS) and was based on SDT. The online CHESS system was designed to provide information, social support, and skill-building tools for self-management of the disease, in this case asthma (Gustafson, Wise, et al., 2012). Adherence was measured using a composite score of self-report diaries and prescription refill rate. The authors concluded that social support mediated the effect of the intervention on asthma control, as assessed by the Asthma Control Test (ACT). However, the components of SDT were not specifically measured within the study and no significant differences between adherence, within or between the groups were found (Gustafson, Wise, et al., 2012). The use of the SDT as a theoretical model in asthma was not supported in either the Bruzzese et al. (2014) nor the Gustafson et al. (Gustafson, Wise, et al., 2012). Family routine and social support were found to be important components of these studies which are more related to practical factors (ability, see 3.3.1) as opposed to the specific psychological needs outlined by the SDT. The SDT may also not be appropriate for understanding and intervening in motivation for medication taking in children as the basic need for autonomy may be difficult to fulfil due to the need for support from their parents.

### **3.2.5 The Common-Sense Model of Self-Regulation (CSM)**

The CSM (Leventhal, Nerenz, & Steele, 1984) was the first theory to outline illness related behaviours within the context of illness as opposed to preventative health behaviours. The theory is based on the principle that individuals have implicit common-sense beliefs and emotions about their illness which play a key role in influencing health-related behaviours. (Leventhal et al., 1984) describe this set of beliefs as illness representations or personal models of illness and defined them in a theoretical model (Figure 9). These illness

representations are influenced by both concrete experience of their illness (such as an asthma attack and past experiences of asthma) and abstract information (such as knowledge from other sources e.g. their doctor or a leaflet). The patients' concrete experience is not always coherent with the abstract information, for example their common-sense model not fit with the medical model being provided. They propose that illness representations drive the selection of patients' coping procedures (adaptive or maladaptive) which must fit (according to their common-sense model of illness) with their representation of the health threat. Patients coping procedures are then appraised for their success or failure in light of their illness representation and amended accordingly (Leventhal et al., 1992; Ogden, 2012). Leventhal et al. (1992) proposed that the emotional and cognitive (illness representations) processes take place in parallel but influence each other. Based on patient interviews with patients with a variety of illnesses Leventhal et al. (1992), theorised that a person's illness representation is created based on five distinct (Figure 9) but related key perceptions of:

1. the identity of the illness (the medical diagnosis and the symptoms of the illness)
2. the cause of the illness (biological or psychosocial)
3. the control/curability of the illness (can the illness be treated or cured and are the outcomes of the illness controllable)
4. the consequences the illness may have (effects of the illness on their lives e.g. physical and/or emotional)
5. the expected time-line of the illness (e.g. long-term condition or acute condition)

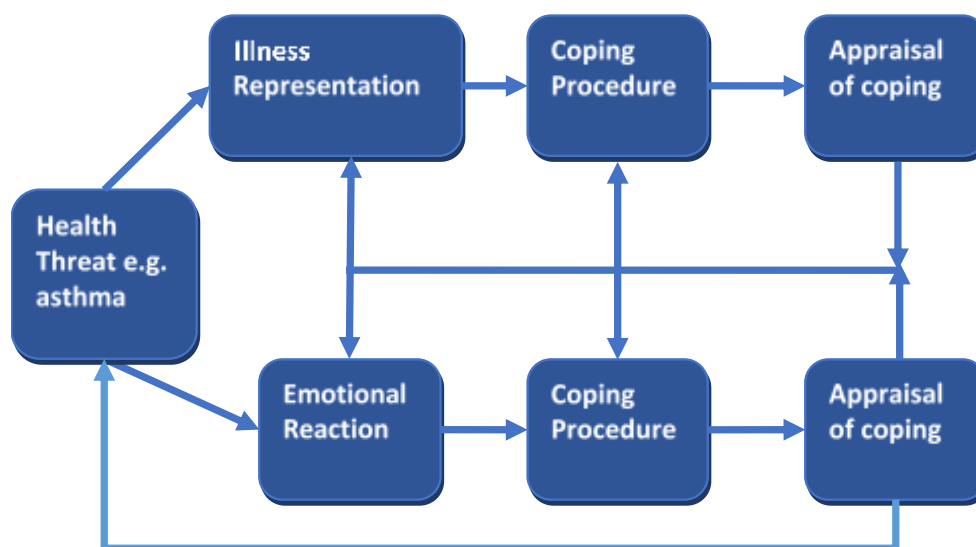


Figure 9: Simplified Common-Sense Model of Illness Representations adapted from Ogden (2012)

Leventhal's model is based on the premise that patients approach their illness (a health threat) in an attempt to problem-solve as they would any other problem to self-regulate their behaviour in order to resume the status-quo (Leventhal et al., 1992; Ogden, 2012). Consistent with models of problem solving the CSM represents three stages: Interpretation of the health threat (including illness representations and emotional reactions); Coping (behaviours to try to overcome the health threat and regaining normality) and Appraisal (evaluating the usefulness of the coping behaviour in overcoming the problem). The model is dynamic as the process will continue until a satisfactory coping procedure has been established to re-establish original health (or in the case of asthma complete asthma control). This is one of the only dynamic theoretical models that highlights the ongoing processes underpinning health behaviour. The CSM's explanatory value has been tested in a random-effects meta-analysis including 254 studies which had applying the model in over 50,000 participants (Hagger, Koch, Chatzisarantis, & Orbell, 2017). Hagger et al. (2017) supported the models' direct effects of illness representations and indirect effects mediated by coping on illness outcomes. The authors concluded that the CSM's effect was not moderated significantly by the type of study design or context, study quality or illness group. This meta-analysis also concluded, from a sub group of studies investigating adherence (n=18), that treatment beliefs have unique effects on illness outcomes, and they highlighted their importance for future developments of the CSM.

### **3.2.6 The Extended Common-Sense Model (e-CSM)**

The Common-Sense/Self-Regulatory Model focuses on illness representations in relation coping strategies. Horne et al. (1997) postulated that individuals treatment representations may be more proximal determinants of adherence related illness outcomes.

#### *3.2.6.1 Treatment representations*

Treatment representations are formed of two types of beliefs about medicine: general and specific beliefs about medicine. General treatment beliefs are beliefs about pharmaceutical treatment as a class of medication, whereas specific beliefs are about a particular prescribed medication (Horne & Weinman, 1999).

##### *3.2.6.1.1 General Beliefs about Medicines*

These treatment specific necessity and concern beliefs are influenced by wider general beliefs about medicine (social representations) (Horne & Weinman, 1999). Patients are often

sceptical or even fearful of pharmaceuticals perceiving them to be harmful, overprescribed and unnatural (Horne & Weinman, 1999). These set of beliefs about medicines form a patient's "pharmaceutical schema" meaning how the individual organises their ideas about medicines (Horne, Cooper, Wileman, & Chan, 2019). Negative pharmaceutical schema are influenced by wider concerns about science (Calnan, Montaner, & Horne, 2005). The individual's pharmaceutical schema influences the processing of the specific medications benefits and harms and therefore effects consequential adherence behaviour (Horne, 2017). For example, in experimental studies individuals with more negative pharmaceutical schemas are more likely to attribute symptoms as a side-effect of a drug as oppose to a symptom if the condition or other unrelated bodily sensation (Heller, Chapman, & Horne, 2015) and less likely to accurately recall side-effects (Heller, Chapman, & Horne, 2017).

#### 3.2.6.1.2 Specific Beliefs about a Medicine

Specific beliefs are influenced by pharmaceutical schemas with negative pharmaceutical schemas being associated with greater specific concerns about a particular medication and with increased doubts leading to decreased personal necessity for the treatment (Chapman, Horne, Chater, Hukins, & Smithson, 2014; Clatworthy et al., 2009; Watkinson, Chapman, & Horne, 2017). Specific beliefs about a medicine are categorised as the patients' perceptions about the personal need for the specific treatment (necessity) and the concerns about the medication (concerns). Although necessity beliefs are influenced by beliefs about the treatment efficacy, necessity beliefs are not efficacy beliefs. For example, we may believe that a treatment is effective but that we do not need it for our condition or that we need a treatment but believe that the current treatment is not effective. Necessity beliefs are perceptions related to the personal need for the treatment. These beliefs are also influenced by the experience of the condition (Horne & Weinman, 2002) and by the symptoms actually experienced versus those expected. Examples of necessity related statements are: "without my inhaler I would be very ill" or "I rely on my inhalers a lot".

Concern beliefs generally highlight something negative such as a fear of side effects e.g. "I worry about the steroids in my inhaler" or "I don't want to become over reliant on my inhaler". Concern beliefs are related to the costs that the individual feels will come with taking the treatment. One key area of concern that is often reported by patients is side-effects (both short and long-term) e.g. that ICS use will result in weight gain (Hand & Bradley, 1996) and more general worries e.g. that the patient may get bullied about using their inhaler. However, side-effects are not the only type of concern belief. Patients may have

concerns about future side-effects, negative impacts on their lives such as dependence on medication (Horne, 2006, 2017), they may face stigma from the people around them (Katz et al., 2013) or about more practical aspects such as the cost of medication (Laba et al., 2019). When patients are deciding if they are going to take their medication, they may ask themselves two questions: “How much do I need this treatment?” and “How much can I get away with not taking this treatment?” This process is implicit rather than explicit and patients themselves may not know they are conducting this process until they are asked to explore these beliefs.

#### 3.2.6.1.2.1 The Necessity and Concerns Framework

The Necessity Concerns Framework (NCF) was developed to explain the key treatments beliefs influencing adherence behaviour (Horne & Weinman, 1999). Horne, Weinman and Hankins (1999) used principal components analysis to identify that patients’ decisions about whether or not to take a medication related to their perceived personal necessity for the treatment and their concerns about the treatment. In several studies and across various conditions, necessity beliefs have been found to be correlated with high adherence and concerns with poor adherence (Horne & Weinman, 1999; Ponieman, Wisnivesky, Leventhal, Musumeci-Szabo, & Halm, 2009). Many patients are faced with the necessity vs. concerns dilemma and have to decide which outweighs the other in relation to their medicines. The behavioural outcome from the treatment beliefs (i.e. medication taking) depends on the balance between the perceived pros and cons (i.e. necessity and concerns of treatment). For example, if the patient has frequent symptoms and poor asthma control but is rarely hospitalised then necessity beliefs may be moderately high. However, the child or parents may have concerns related to ICS and growth and so the patient may not take their inhaler despite the moderately high necessity (De Simoni, Horne, Fleming, Bush, & Griffiths, 2017; Desager, Vermeulen, & Bodart, 2018; Pearce et al., 2018). The CSM was extended to include treatment representations including emotional responses to treatment and coping procedures related to treatments (the extended-Common Sense Model (e-CSM; Figure 10) (Horne, 2003).

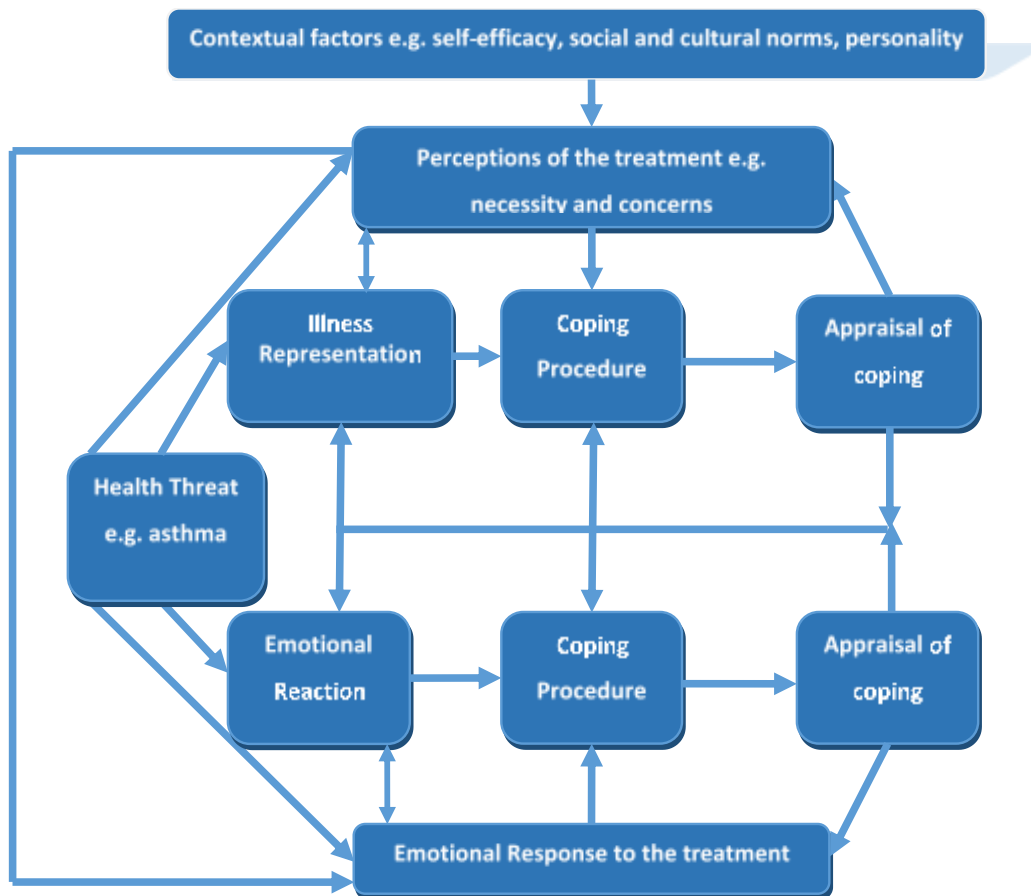


Figure 10: The extended-Common Sense/Self-Regulatory Model including the NCF (adapted from Horne (2003))

### 3.2.6.2 Evidence Supporting the e-CSM and NCF

The CSM and e-CSM have been explored in several studies exploring outcomes in asthma (including adherence) but these have often been in adults or in parents of children (Kaptein et al., 2008). The CSM and illness beliefs have often been explored by quantitative methodologies and are more often carried out via primary care or in those with mild to moderate asthma. This represents a research gap for patients with more severe asthma; as such, this PhD will explore illness and treatment beliefs using qualitative methodology in children and young people with problematic asthma who are seen within tertiary care (see Chapter 6:).

Leventhal et al.'s (1992) theory has been tested on multiple populations using a questionnaire developed specifically to test each construct in the CSM. The Illness Perception Questionnaire (IPQ) (Weinman, Petrie, Moss-Morris, & Horne, 1996) was developed to measure beliefs about illness which is comprised of five scales related to the



five components of the CSM, as outlined above (Identity, Cause, Timeline, Control and Consequences (Leventhal et al., 1992). Several versions of the IPQ have now been developed and validated in multiple patient groups including in adults with asthma (IPQ, Weinman et al. (1996); IPQ-Revised, Moss-Morris et al. (2002) and The Brief Illness Perception Questionnaire (B-IPQ) Broadbent, Petrie, Main, and Weinman (2006).

The first empirical test of the e-CSM explored non-adherence to preventer medication in adolescents and adults with asthma (Horne, 2002). The regression analysis revealed that both illness beliefs and treatment beliefs were predictive of adherence measured by validated self-report tools (IPQ, MARS, and BMQ). Treatment beliefs accounted for 17% of the variance in adherence, illness beliefs accounted for 13%, demographic variables accounted for 6% of the variance and clinical factors accounted for no variance in adherence scores (Horne, 2002). As treatment beliefs are more proximal to treatment behaviours e.g. adherence it is not surprising that structural equation modelling revealed the relationship between illness beliefs and adherence to be mediated largely by treatment beliefs, particularly necessity beliefs (15% of the variance in adherence). The e-CSM has been supported by Klok et al. (2013) paediatricians in the Netherlands, as a framework for exploring paediatric respiratory disease with a view to improving adherence and asthma control (Klok, Kaptein, & Brand, 2013).

The Necessity and Concern Framework has been the focus of two large meta-analyses in adults with long-term conditions, including asthma, which summarises work from 94 studies using the NCF via the Beliefs about Medicine Questionnaire (BMQ) (Foot, La Caze, Gujral, & Cottrell, 2016; Horne et al., 2013). The BMQ is a validated questionnaire that operationalises the NCF and measures both specific and general medication beliefs (the BMQ is fully described in Chapter 7.2.1). Horne et al. (2013) showed that across studies higher adherence was associated with higher treatment necessity beliefs (OR = 1.742, 95% CI [1.569, 1.934],  $P < 0.0001$ ) and lower treatment concern beliefs (OR = 0.504, 95% CI: [0.450, 0.564],  $p < 0.0001$ ) (Horne et al., 2013). This relationship was stable across studies conducted in different countries, with different adherence outcomes and studies with varying sample sizes. Studies in asthma in particular found that necessity beliefs related to adherence more often than concerns.

The meta-analysis of Foot et al. (2016) supports the results of the Horne et al. (2013) study. They found that higher necessity beliefs were correlated with higher adherence ( $r=0.17$ ) and

that higher concern beliefs were associated with lower adherence ( $r=-0.18$ ). Foot et al (2016) also stratified the results by disease group and found that patients with asthma had the strongest correlation between necessity beliefs and adherence ( $r=0.33$ ) when compared to other disease groups. The relationship between concern beliefs and adherence was similar across all disease groups. A more recent study has also confirmed these results in asthma: Brandstetter et al. (2017) found that patients with higher necessity beliefs were three times as likely to be completely adherent (OR 2.97, 95% CI 1.54–5.73) compared to those with lower necessity beliefs.

Few studies have explored treatment and illness representations in children with asthma. Klok, Kaptein, Duiverman and Brand (2012) used the B-IPQ as an outcome measure in a paediatric asthma study exploring parental illness representations in young children with asthma. The study measured adherence to ICS, using Smartinhaler™, in patients aged 2-6 years old and explored their parents' illness and medication beliefs. The median adherence for the group over a three-month monitoring period was extremely high 92 (IQR=76– 97%) and was associated with high necessity scores and low general perceptions of harm, measured by the BMQ (see 3.2.6), but not the individual items of the B-IPQ. This study supports treatment representations more proximal relationship to adherence than illness representations as theorised by the NCF (Horne, 2003; Horne & Weinman, 1999; Horne et al., 1999) and the extension of the CSM (e-CSM) for understanding adherence behaviour.

Most studies investigating treatment beliefs in children with asthma and their relationship with adherence have used parental BMQ or qualitative outcomes. Although this is logical for younger children who cannot understand or complete the questionnaire unassisted, parental report has limitations as they are not always the beliefs of the child. Indeed, high parental concern beliefs (measured by the BMQS) have been shown to be significantly correlated with poor adherence ( $p<0.05$ ) where necessity beliefs were not, in a study of young children (3-7 years) with persistent asthma (Conn et al., 2005). Parental high necessity scores have been shown to be correlated with adherence (measured by a Smartinhaler™) in a group of children aged 2-12 (median adherence= 84% (IQR= 70–92%)) (Klok, Kaptein, Duiverman, & Brand, 2015). In contrast child reported necessity beliefs (measured using a Turkish adaptation of the BMQ) have been correlated with respiratory clinical severity ( $r = -0.43$ ,  $p = .036$ ) (Yilmaz, Eroglu, Ozalp, & Yuksel, 2012). Within this study although parental and child concern beliefs were significantly associated they were only moderately correlated ( $r = 0.53$ ,  $p = .009$ ) (Yilmaz et al., 2012). Although parental treatment beliefs are clearly an important

determinant of adherence and are useful in younger children, given the lack of correlation between older child and parental beliefs highlighted in the adherence literature, it may be more accurate to focus on the child's own beliefs, providing they are old enough to read and write, as they are likely to be most proximal to the child's adherence behaviour. Moreover, this may be more appropriate than asking parents as fifty percent of children aged 11 have been shown to manage their asthma treatments independently with little or no supervision from their parents (Orrell-Valente, Jarlsberg, Hill, & Cabana, 2008).

### **3.3 Frameworks Underpinning Behaviour to Inform Interventions: A Summary of Research to Date**

#### **3.3.1 An Approach to Adherence: The Perceptions and Practicalities Approach**

The Perceptions and Practicalities Approach (PAPA) is a simple framework of the “minimal ingredients” needing to be targeted in order to understand adherence behaviour within an individual (PAPA, Figure 11(Horne, 2001)). PAPA was developed specifically for use in informing the development and evaluation of adherence interventions as many previous interventions targeted practical determinants of unintentional non-adherence with limited success. PAPA postulates that a patients' motivation to take their treatment and their ability to take their treatment must be targeted by taking account of individuals perceptions about treatment and illness (e-CSM) and practical barriers to taking their treatment. PAPA highlights that each individual will have a different combination of perceptual and practical barriers, therefore interventions need to be adapted and tailored to the individual to meet their requirements (Horne, 2005). This approach should adopt a non-judgemental approach and has been adopted by the National Institute for Clinical Excellence adherence guidelines (NICE). The NICE guidelines were developed for health professionals to help them to support patients in their decisions around medication and in their medication use (National Collaborating Centre for Primary Care UK, 2009). It is a simple approach for healthcare professionals to understand and implement.

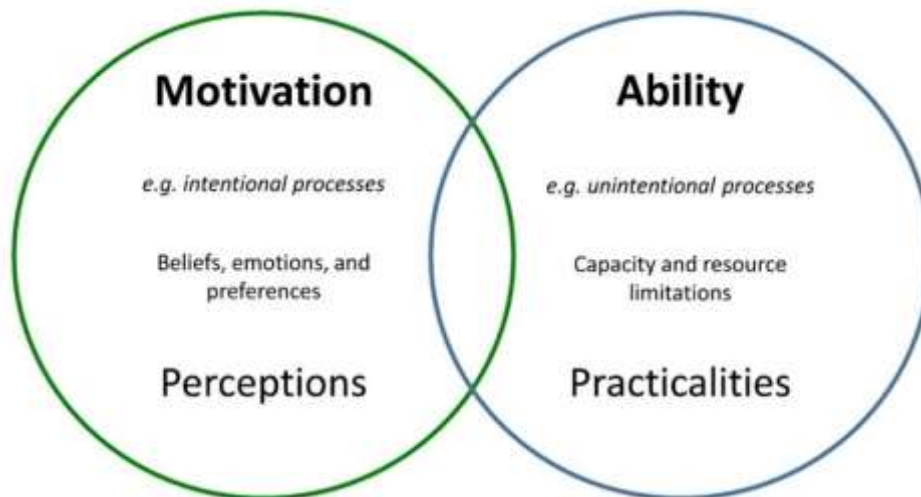


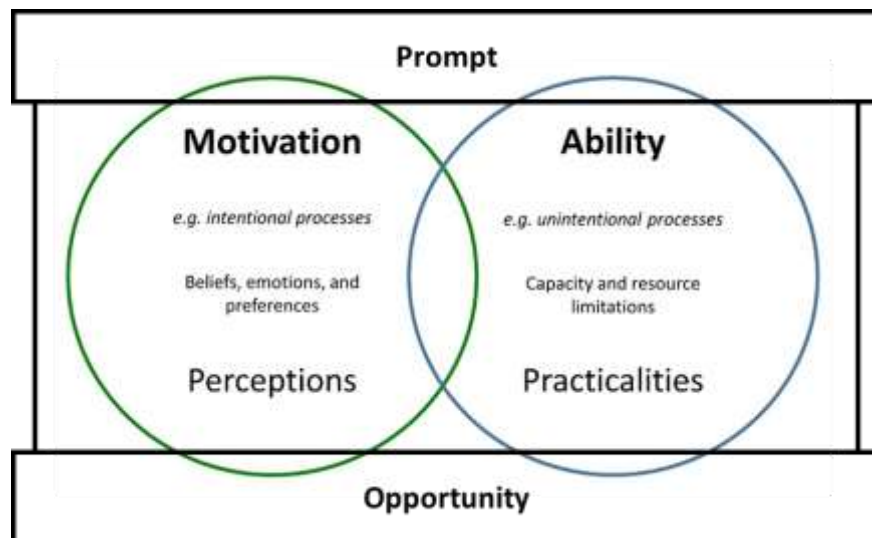
Figure 11: The Perceptions and Practicalities Approach adapted from Horne (2001)

PAPA focuses on two questions “Does the patient have the ability to take a medication due to potential barriers e.g. paying for prescriptions, having to collect a repeat prescription on time and being able to take the inhaler appropriately (ability/unintentional non-adherence)?” and “do they have the motivation to take the medication”. Motivation may influence an individuals’ ability to take the medication and vice versa which is why the concepts overlap within the figure (Horne, 2001). For example, if you do not consider a medication to be necessary you may be more likely to forget to take the medication or not build it into your daily routine. Similarly, the easier a medication is to take the greater motivation a patient may have to take it.

### 3.3.1.1 Opportunity and Prompts

The approach highlights the need for interventions to target internal (intrinsic) patient factors including the patient’s perceptions about the illness and their perceptions about the medication (e-CSM) as these influence their intention to adhere to their medication regimen (motivation/intentional non-adherence). Motivation and ability are influenced by factors extrinsic to the individual. Both the Motivation- Opportunity- Abilities model (Thøgersen, 1995) and the Capability, Opportunity, Motivation and Behaviour model highlight this extrinsic factor as the construct “opportunity” (COM-B; see section 3.3.2.2). Similarly, Fogg’s behavioural model (2009) highlights an external construct now labelled prompt (previously triggers) which is described in a similar way to opportunity and theorised to influence both motivation and ability (Fogg, 2009). Clearly there are overlaps between each model. The

PAPA approach also highlights the importance of external (extrinsic) factors such as environmental or health-care system related factors and prompts in explaining adherence. However, the PAPA approach focuses on the individual and postulated that extrinsic factors effect adherence via enhancing or decreasing motivation and/or ability (Horne et al., 2019).



COM- Figure 12: PAPA Including Prompts and Opportunity adapted from (Horne, 2001; Horne et al., 2019) B

(Michie, van Stralen, & West, 2011) and PAPA (Figure 12(Horne, 2001; Horne et al., 2019) consists of similar overarching constructs. The constructs capability and motivation within COM-B are similarly described by the PAPA approach as practicalities and perceptions respectively. However, capability as described by COM-B combines both psychological and physical capability (3.3.2.2) which in PAPA is split between the psychological and physical constructions (perceptions and practicalities). Similar to motivation within the COM-B mode,l PAPAs definition of motivation relates to both intentional (decision-based) motivation to adhere (or not) and unintentional (automatic or unconscious) adherence (or not). The key difference between the models is related to the COM-B construct of opportunity. Opportunity was not originally included in the PAPA, as stated above, as it was developed to explain an individual’s behaviour from an intrinsic perspective whereas COM-B does not prioritise one perspective over another (individual, group or social).. In order to optimise adherence PAPA suggests that focusing on the individual is the most affect way to begin understanding adherence behaviour and building intervention content as motivation and

ability are the most proximal components to behaviour and may vary considerably on an individual basis.

### 3.3.1.2 *Habit formation and the PAPA*

Where a patients' motivation and ability to conduct the behaviour (i.e. adherence) are high and there are no external barriers to conducting the behaviour, medication taking routine can be established and maintained. This could, be for example, for those that feel the medication is important keeping it in a visually prominent position and anchored to another routine behaviour. One common location and time for asthma medication is in the bathroom and visible when an individual brushes their teeth. However, when motivation (including treatment necessity) diminishes, routines are likely to suffer if they have not yet been well established and developed into habits. Habits are formed by repetition of a behaviour (e.g. medication taking) within a specific context (e.g. the bathroom) resulting in the context cueing the behaviour. Habits are formed as a result of a learned association between behaviour and the situational cue (Wood & Neal, 2009). This mental association then allows the behaviour to be performed in the specific context without awareness or cognitive effort. Habit is experienced as an impulse to conduct a behaviour and is defined as a cognitive-motivational process (Gardner, 2015). For example, if adherence is erratic due to patients' belief that the treatment is only necessary when they are experiencing symptoms (Halm, Mora, & Leventhal, 2006) and if the habit is not fully embedded, which takes approximately 66 days (Range= 18-254 days (Lally, Van Jaarsveld, Potts, & Wardle, 2010), then habit may be impeded.

Despite, the ability of health behaviours to be performed and maintained without cognitive awareness being challenged by some (Ajzen, 2002; Maddux, 1997), research has been conducted to explore the role of habit in adherence to medication. Habit formation has been shown to be important in adherence in patient groups including adult patients with asymptomatic hypertension (Phillips, Leventhal, & Leventhal, 2013). In this longitudinal study using regression analyses, Phillips et al. (Phillips et al., 2013) concluded that habit strength (measured by the Self-Report Habit Index (SRHI; (Verplanken & Orbell, 2003)), plus some additional items tailored to the study) was the greatest predictor of long-term medication adherence in the hypertension population overall and of unintentional non-adherence. The authors also concluded intentional non-adherence were predicted by patient's experience/illness coherence (Phillips et al., 2013). Although this study's methodology has strength in that it is not cross-sectional in design there is one important limitation which the authors

themselves highlighted. The participants adherence showed little variance and overall participants were very adherent. As a result, the concepts of habit and intentional adherence cannot be differentiated. A sample with varying levels of adherence would enable the concepts to be distinguished between (Phillips et al., 2013). Gardner (2015) also commented on this stating that studies exploring habit often focus on behaviours that have underlying congruent habits and intentions for example exploring habit in adherent patients who have high necessity and low concern beliefs towards their ICS treatment. Studies measuring non-congruent habit and intentions in health research have been called for to adequately differentiate between the two processes, conscious decision making and habit (Gardner, 2015; Phillips et al., 2013).

Durand et al. (2018) have supported the work of Phillips et al. (2013) in a group of patients with resistant hypertension. They too concluded that habit strength was the most predictive factor for medication adherence in patients with hypertension. Although this study recruited a larger sample than Phillips et al. (2013) in an attempt to recruit participants with more variable adherence, the participants were also highly adherent. Despite using one of the most well-validated self-report tools to measure indicators of automaticity, indicative of habit (the Self-report Behavioural Automaticity Index (SRBAI), (Gardner, 2015), this study was less rigorous in design due to its cross-sectional nature which explored past adherence. Gardner (2015) also criticise studies exploring habit using past behaviour as true habit is a cognitive-motivation process and cannot be distinguish from non-habit behaviour.

A more recent systematic review study also found habit to be a key factor in medication adherence in several chronic conditions including pulmonary disease (Conn & Ruppap, 2017). Although the sample size limited generalisation a recent study in cystic fibrosis (Hoo et al., 2019) overcomes many of the limitations of previous explorations of the role of habit in adherence. Hoo et al. (Hoo et al., 2019) recruited participants with differing levels of adherence (both high and low) and found in a prospective (3 month) study habit (measured by the (SRBAI, (Gardner, 2015) to be the strongest predictor of adherence to nebulisers. However, the authors highlighted the need for both non-conscious motivation (e.g. habit) and conscious motivation (e.g. treatment beliefs) to be considered in developing effective future adherence interventions.

In asthma specifically, higher motivation for a correct inhaler technique has been linked to ease of learning when training patients on inhaler technique. The training was most effective in patients who were motivated to practice the technique, potentially increasing their habit and increasing their ability to take the medication (Ovchinkova, Smith, & Bosnic-Anticevich, 2011).

#### *3.3.1.3 Self-efficacy and PAPA*

Although it is not explicitly measured within this PhD, self-efficacy is related to PAPA including illness and treatment perceptions (Hilliard, Eakin, Borrelli, Green, & Riekert, 2015)(Figure 11) and also practicalities. Self-efficacy is related to both concerns about treatment (Horne et al., 2019) and practical barriers to adherence. If someone has fewer concerns about adhering to their medication and fewer practical barriers to doing so they are likely to have high self-efficacy and therefore to be more adherent. However, if the patient has low personal necessity for treatment this may outweigh the other factors. Indeed, research in adherence has shown self-efficacy to be an important indicator of adherence behaviour, but treatment necessity beliefs to be important in explaining in non-adherent behaviour (Lotsch et al., 2015).

#### *3.3.1.4 Evidence for the use of PAPA in adherence*

PAPA has been previously used as framework (e-CSM and practicalities) to explore determinants of adherence (Clark, Gould, Tobias, & Horne, 2016; Jamison, Sutton, Mant, & De Simoni, 2018) and to retrospectively categorise intervention content (Mes et al., 2018) in order to develop appropriate intervention content. Chapman et al. (2015) set out to validate the PAPA in a cohort of patients non-adherent to antiepileptic drugs. Over 1000 participants took part in the cross-sectional survey study which analysed the utility of the PAPA using multiple logistic regression analyses. The study supported the importance of the two key elements of PAPA, perception (both necessity and concern beliefs) and practicalities, in explaining non-adherent behaviour (Chapman et al., 2015).

PAPA has also been recently used to both explore determinants of non-adherence to inhalers in adolescents with asthma, within a qualitative forum based analysis (De Simoni et al., 2017) and to retrospectively code adherence intervention content within a systematic review and meta-analysis in adults with asthma (Mes et al., 2018). Both studies support the use of PAPA for adherence in patients with asthma with Mes et al. (2018) concluding that interventions in line with PAPA were more effective.



### 3.3.2 An Approach to Behaviour Change

#### 3.3.2.1 Theoretical Domains Framework

The theoretical domains framework (TDF) (Michie et al., 2005) was created, due to considerable overlap between the theoretic frameworks, to synthesise all the domains that are relevant for changing behaviour which have been specified in health psychology theoretical frameworks. A group of 30 health psychologists were involved in the consensus meetings. From these meetings 33 psychological theoretical frameworks were summarised comprising of 128 constructs. The consensus process concluded that 12 domains were important in our ability to explain behaviour. These were: (1) knowledge, (2) skills, (3) social/professional role and identity, (4) beliefs about capabilities, (5) beliefs about consequences, (6) motivation and goals, (7) memory, attention and decision processes, (8) environmental context and resources, (9) social influences, (10) emotion regulation, (11) behavioural regulation, and (12) nature of the behaviour. The TDF was updated as a more thorough investigation of the content validity was conducted in 2012 to validate the original findings using Discriminant Content Validation and Fuzzy Cluster Analysis (whereby each data point can belong to more than one cluster) (Cane, O'Connor, & Michie, 2012). Based on the results of the study, the TDF was updated to contain 14 domains: (1) Knowledge, (2) Skills, (3) Social/Professional Role and Identity, (4) Beliefs about Capabilities, (5) Optimism, (6) Beliefs about Consequences, (7) Reinforcement, (8) Intentions, (9) Goals, (10) Memory, Attention and Decision Processes, (11) Environmental Context and Resources, (12) Social Influences, (13) Emotions and (14) Behavioural Regulation.

The TDF has been widely used, including recently in respiratory disease, as the basis for qualitative work exploring the determinants of non-adherence including in cystic fibrosis (Arden, Drabble, O'Cathain, Hutchings, & Wildman, 2016) and bronchiectasis (McCullough et al., 2015) however it has not be used to investigate adult or paediatric asthma.

The TDF was not developed for a specific type of behaviour change (e.g. adherence) as it was developed from all psychological theoretical frameworks rather than regarding a specific behavioural target. It has been suggested that theoretical models of behaviour change are likely to be more explanatory and therefore useful when their content is developed with a specific behaviour as a target (Craig et al., 2013), which in this case that would be adherence. The TDF, although useful for exploring determinants of adherence, is not a model or

approach for developing interventions alone and has had limited previous application to asthma and therefore will not be the basis of this thesis.

3.3.2.2 The Capability Opportunity Motivation-Behaviour (COM-B) model

The Capability Opportunity Motivation- Behaviour model (COM-B; (Michie et al., 2011); Figure 14) was developed to explain behaviour change using concepts derived from the TDF. COM-B is “the hub” of the behavioural system developed by Michie et al. (2011) and named the Behaviour Change Wheel (Figure 13). The Behavioural system comprises COM-B in the centre, encircled by intervention functions (e.g. education or modelling etc.) and then by policy categories (e.g. legislation or guidelines etc.) (Michie et al., 2011). The model gives no greater emphasise to the individual, group or environmental perspective unlike the PAPA which focuses on the experience of the individual.

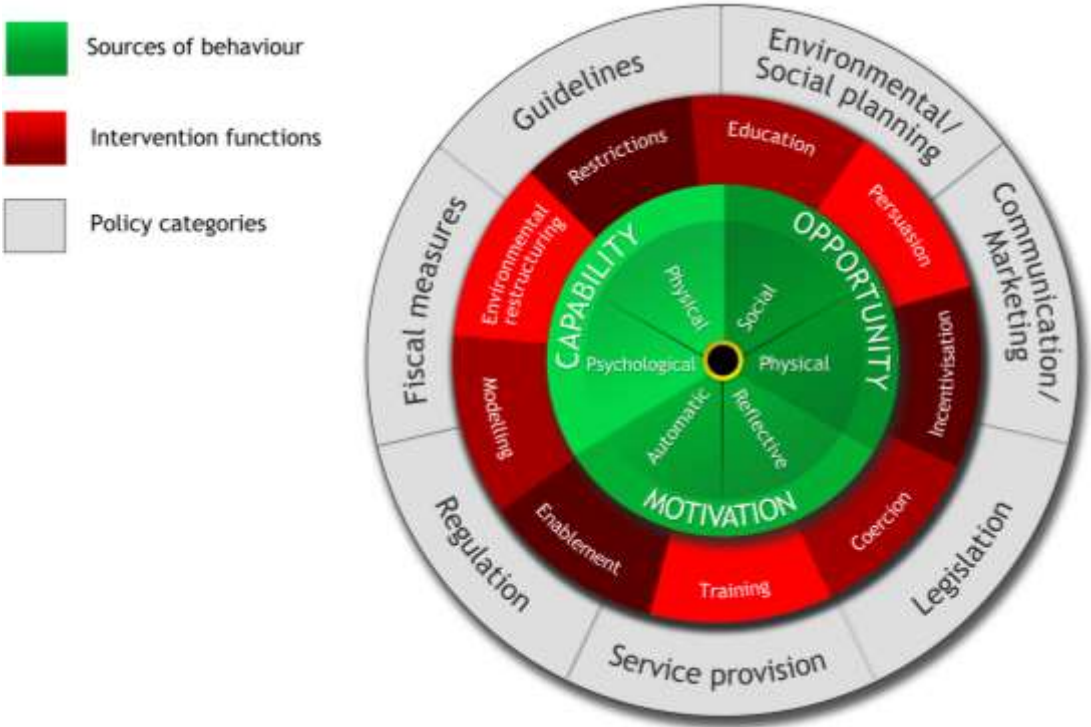


Figure 13: The Behaviour Change Wheel from Michie et al. 2011

COM-B is made up of three key concepts capacity, opportunity and motivation (Figure 13 and Figure 14,). Capability is described as an individual’s capability to change both physically and psychologically and includes having the skills and knowledge necessary to perform the behaviour. Opportunity is defined as external factors that prompt or influence the performance of the behaviour and are more contextual. Opportunity includes both social

opportunity such as family and cultural upbringing and physical opportunity such as the healthcare setting and environment. Motivation is described as anything that motivates behaviour including conscious analytical decision making and more automatic, habitual behaviour and emotional responding. The authors state that this is both a framework to explain behaviour and to help to develop interventions and policy to change a given behaviour.

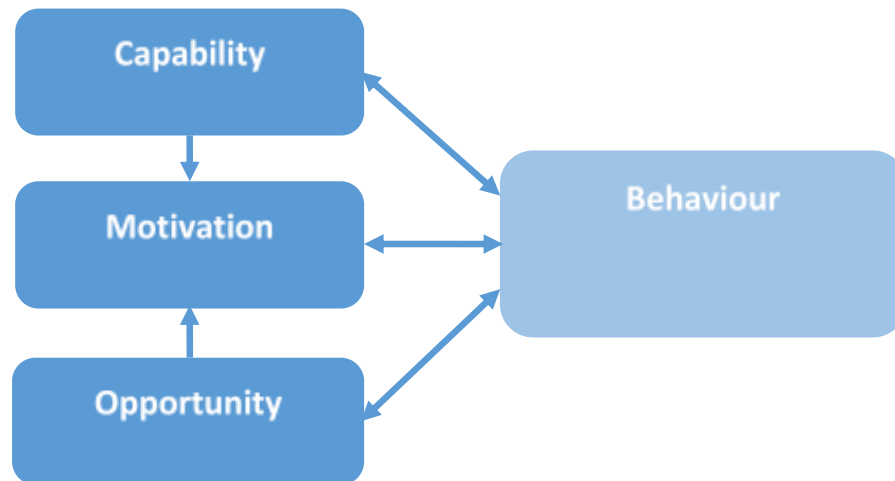


Figure 14: The COM-B model: a framework for understanding behaviour (Adapted from Michie et al. (2011))

COM-B has been used as a framework for qualitative analysis in recent studies of non-adherence in long-term conditions (Arden et al., 2016; Ritschl et al., 2018). Arden et al. (2016) used COM-B to understand patients adherence to nebulisers in interviews with a group of adult patients with Cystic Fibrosis (a chronic respiratory condition). Although the interview topic guide was based on the TDF, COM-B was used as a framework to explore and interpret the results of the study. The work by Arden et al. (2016) supported the use of the TDF and COM-B as the findings were mapped to the concepts of capability, opportunity and motivation. Qualitative work by Ritschl et al. (2018), who also mapped their findings to the COM-B model, supports the use of COM-B in exploring factors relevant to non-adherence in Rheumatoid Arthritis in adults. The COM-B model has also been used, retrospectively, to explore intervention content within a literature review summarising interventions for adherence to long-term anticoagulation medication (Abdou, Auyeung, Patel, & Arya, 2016). The exploratory review by Abdou et al. (2016) present the findings related to the dimensions

of the COM-B model, with related recommendations for assessing and addressing non-adherence in this population.

Although COM-B has been used within some research within the field of adherence (Jackson, Eliasson, Barber, & Weinman, 2014) it has not been previously used in adherence research in adults or children with asthma. Both PAPA and COM-B are comparable overarching frameworks for use intervention development. Given the origins of PAPA in adherence research and the proposal that theoretical models are more likely to be explanatory when their content is specific to the behaviour being explored (Francis, O'Connor, & Curran, 2012) PAPA including the e-CSM will be used to explore adherence within this PhD.

### *3.3.2.3 Behaviour Change Techniques*

Once the appropriate framework of behaviour change has been selected, the specific intervention components need to be chosen. A set of agreed behaviour change techniques (BCTs), techniques that can be used to influence an individual's behaviour, have been developed. The set of BCTs are theory-driven and up until the late 1990s were not catalogued or defined in any systematic way (Bartholomew, Parcel, & Kok, 1998). Abraham and Michie (2008) conducted extensive work to define a set of BCTs for three main purposes: for use in retrospectively applying to intervention content; for systematically recording intervention content and for use prospectively for developing future intervention. The BCT taxonomy (v1) contains 93 hierarchically- clustered techniques grouped within 19 categories (see Appendix 1) and was developed by 14 experts in a Delphi-type exercise (Michie et al., 2013). This group of BCTs, named the BCT taxonomy, are intended to enable more transparent reporting of intervention content to aid reviews of research, replication of research, implementation of effective intervention and creating stronger behavioural medicine science. Previously and unlike other science, a "black-box" phenomenon was experienced whereby researchers were unclear what intervention content was being used.

BCTs have been used in a plethora of research in a variety of behaviour change areas over the last decade including in chronic disease populations targeting adherence (Crawshaw, Auyeung, Ashworth, Norton, & Weinman, 2017; Joost, Dorje, Schwitulla, Eckardt, & Hugo, 2014; Mes et al., 2018). Joost et al. (2014) conducted an intervention in kidney transplant patients aimed at increasing adherence to immunosuppressant medication. The intervention team used the BCT (v1) taxonomy to build their intensified pharmaceutical care (IPC) intervention content. Sixteen of the 93 behaviour change technique clusters were used.

Although this was not an RCT so conclusions of efficacy cannot be confirmed, the IPC group had significantly greater adherence (measured with a pill bottle EMD) compared to the control group (standard care) post intervention (Joost et al., 2014).

BCTs can also be retrospectively coded to enhance the understanding of study content within systematic review and meta-analysis. Mes et al. (2018) explored BCTs as part of a systematic review and meta-analysis to investigate interventions targeting adherence to ICS in adults with asthma. The authors concluded that the number and type of BCTs did not determine effectiveness. However, the authors did state that intervention content was not always adequately described to allow for accurate BCT coding. Indeed, Crawshaw et al. (2017), in a review investigating adherence in acute coronary syndrome, stated that no included studies (n=23) explicitly used the behaviour change taxonomy when describing their intervention content. Although Crawshaw et al. (2017) were able to code 32/93 BCTs within the included studies the data were insufficient to ascertain which if any BCTs were associated with effectiveness of the adherence interventions.

Clearly BCT coding is a useful tool to explore beyond the components of a chosen model to establish appropriate tools to use/ or that have been used in an intervention. Although this taxonomy has been published for a little over a decade there is still a need for researchers in this field to incorporate BCTs into their intervention development, associated protocols and their published articles to use the full potential of the taxonomy. This PhD will use BCTs for the first time to explore adherence to ICS in children with asthma.

The previous sections have discussed existing research in asthma and adherence in children. Several gaps exist particularly in the field of problematic severe asthma that remains an under-researched area of asthma. Specifically, most research that exists focuses on mild-moderate asthma, and primarily in adults rather than a paediatric population. Specifically, research investigating illness and treatment beliefs in paediatric asthma often rely on self-report and parental report and do not explore patterns of non-adherence using objective adherence measurements.

## Research Aims and Objectives

The four key aims in this PhD are:

- 1) To identify potentially modifiable factors related to non-adherence in children with problematic asthma
- 2) To identify potential ways to target the modifiable factors to support optimal medication use
- 3) To adapt the BMQ, to highlight key modifiable factors relevant to adherence behaviour for the specific target population, for future development of a screening tool
- 4) To outline features that need to be considered when developing an intervention to increase adherence to ICS in children with severe asthma

There are five core objectives arising from these aims:

- 1) Identify previously conducted adherence interventions and explore factors which relate to their efficacy, in particular how effective they were, what BCTs they used and using the PAPA framework to explore features of effective and ineffective interventions.
- 2) To identify patterns of non-adherence using previously collected Smartinhaler™ data which can inform adherence intervention development.
- 3) To explore potentially modifiable factors related to non-adherence using qualitative interviews with non-adherent young people (12-17 years old). This study will explore both the patterns of non-adherence identified in the previous study and newly emerging data.
- 4) To develop and test an adaptation of the BMQ incorporating practical adherence barriers for use in young people (12-17 years) within tertiary care.
- 5) To create recommendations for the development of a PAPA-based intervention.

## Chapter 4: **Systematic Review: What are the Most Effective Aspects of Interventions for Adherence to Preventative Medication in Children with Asthma?**

### **4.1 Introduction**

Most children with asthma can achieve good disease control with maintenance low dose ICS, which are effective at preventing a large proportion of asthma hospitalisations and deaths (Suissa & Ernst, 2001). However, some children remain poorly controlled despite being prescribed high dose ICS treatment. Poor adherence has been associated with poor asthma control, severe attacks and hospitalisations in children with asthma (Engelkes, Janssens, de Jongste, Sturkenboom, & Verhamme, 2015; Williams et al., 2011).

According to the World Health Organisation (WHO.) if the mortality rates of the countries included in the review were the same as Sweden (with the least asthma related deaths) 6198 deaths per year could have been prevented globally in 0-14 year olds. The Global Initiative for Asthma reported that underuse of self-management (including treatment) is one patient-specific barrier to reducing the burden of asthma (Masoli, Fabian, Holt, Beasley, & Global Initiative for Asthma, 2004). Similarly, the UK National Review of Asthma Deaths stated that 67% of asthma deaths were avoidable, of which one of the most important avoidable contributors was poor ICS adherence in the month and/or year before death (Royal College of Physicians, 2014).

Many interventions have been developed to address the issue of poor adherence in children, with varying effectiveness. In order to implement appropriate adherence interventions a greater understanding of the effective components of interventions is needed including investigation of the context, channel of delivery and content of the interventions. A recent systematic review suggested that interventions to improve adherence to ICS can be effective, but did not identify what factors were important for effectiveness nor were they focused on children (Normansell et al., 2017). The Medical Research Council advocate basing all complex interventions on a theoretical framework (Craig et al., 2008) however many interventions are still developed without this basis. Prestwich et al. (2015) highlight the importance of using psychological theory in intervention development to promote changes to behaviour and to understand why some interventions work compared to others

No previous systematic reviews in paediatric asthma have explored the use of conceptual frameworks, or the BCTs (see Chapter 2 for further details) used within adherence interventions. This systematic review aims to identify the adherence interventions conducted in children with asthma, and to explore the factors influencing their effectiveness. Specifically, the review will synthesise randomised control trials investigating interventions in children with asthma which targeted adherence to ICS verses usual treatment or basic education control group; and secondly, to identify high validity studies and explore them in terms of method of asthma diagnosis used, adherence measurement tool used, risk of bias, context, channel of delivery and content including identifying to what extent interventions were informed by the PAPA, and which BCTs were used within the interventions.

## **4.2 Methods**

### **4.2.1 Search Strategy**

PubMed, Embase, PsychINFO, Medline, Web of Science, and International Pharmaceutical Abstracts databases were searched systematically from the date of database inception until 27<sup>th</sup> June 2018 to identify relevant literature. MeSH, Emtree and truncated terms were used where applicable (Table 2). Key search terms used were: asthma, child, Intervention, adherence and randomized. “Asthma” rather than “problematic severe asthma” was chosen to widen the search, as narrowing specifically to problematic severe asthma would yield too few papers to draw conclusions from. All authors were contacted via email or, if not reachable via this route, by ResearchGate messaging for further details about the studies.



Table 2: Database Search Terms and Dates

Database Title	Dates searched	Search Terms and combinations
Embase	1974 to 2015 December 01	Child AND Asthma AND Intervention study AND patient compliance AND randomized
PsycINFO	1806 to November Week 4 2015	Asthma AND children AND intervention AND (randomised OR randomized) AND treatment compliance
Pubmed		((((adherence) AND children) AND Randomised control trial) AND asthma) AND intervention
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)	1946 to Present	Asthma AND child AND intervention study AND patient compliance AND randomized
Web of science all databases		(intervention OR intervention study) AND randomised control trial AND patient compliance AND asthma AND (child OR infant OR adolescent)
International Pharmaceutical Abstracts (Ovid)		(Adherence OR patient compliance) AND asthma* AND child AND (Intervention OR Intervention Study) AND (randomised control trial or randomized control trial)

#### 4.2.2 Study selection

Christina Pearce (CP) and Tracy Jackson (TJ) reviewed the abstracts, followed by the full texts against the inclusion/exclusion criteria. Where differing opinions arose for inclusion/exclusion of the study a third, opinion was sought (Professor Rob Horne). Inclusion criteria were based on the Participant-Intervention-Comparison-Outcome-Study Design (PICOS) framework. Articles were included where the full text was written in English, where the population of interest was patients aged 0-18 years old with a diagnosis of asthma (including a GP or specialist diagnosis, or self-reported). Although preschool children should not be diagnosed with asthma studies often include younger children in their recruitment range and therefore this inclusion criteria helped to avoid missing relevant articles. If they do not meet the diagnostic criteria for asthma this will be highlighted later in the chapter in the section regarding reliability of the criteria for asthma diagnosis. Any interventions that focused on adherence to ICS with at least one outcome measure of adherence and used a randomised control trial (RCT) design were included. The comparison group in the included studies were either treatment as usual or basic education arms. Studies were excluded if they did not meet the above criteria or if they were an RCT comparing two medications only, or where the majority of participants were not in 0-18 age group (e.g. the mean age of participants was over 18 years or only adults were recruited).

#### 4.2.3 Data Extraction and Synthesis

Following full-text review Christina Pearce and Tracy Jackson (also a PhD student in health psychology) then extracted details of (Table 3) study characteristics (e.g. setting, number of participants, diagnostic criteria, intervention and control content, outcome of interest); Effectiveness; Risk of Bias; BCTs; Target of the BCTs; relationship to PAPA (Chapter 3.3.1, Figure 11). Behaviour change techniques were independently coded by CP and TJ for each intervention any differences were discussed until consensus was reached. The Data extraction plan was developed based on the Cochrane resources for reviewers document (13a Good practice data extraction form (Effective Practice and Organisation of Care (EPOC), 2015).

Table 3: Data Extraction Table

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
Baren et al. (2006).	Nine Emergency Departments chosen for geographical and patient diversity	Patient with asthma aged 2 to 54 years 384 participants were randomised: A=126 B=126 C=132	Current asthma exacerbation including a new diagnosis of asthma made by the emergency physician.	For groups B and C (interventions), a 5-day course of prednisone and two transportation vouchers for travel to and from the PCP were provided.	Usual care- Group A patients served as control subjects and received usual discharge care from the treating physician.	Regulation, Pharmacological support	Both child and parent	Level 1: Practicalities only	Secondary outcome- Self Report
Burgess et al. (2010)	A paediatric asthma clinic from an outer metropolitan general hospital, Queensland Australia	Children diagnosed with asthma ages 6-14 years old with uncontrolled asthma despite prescribed preventive medication. I=14, C=12	Not stated- assumed by a paediatric doctor at the hospital	The parent and child were informed that the Smartinhaler would "count" the number of doses dispensed. All children were reviewed monthly for 4 months. Smartinhaler data were shared with the child, parent, and physician during the consultation for those	Both groups were provided with preventive medication (fluticasone or fluticasone/salmeterol); loaded into a validated electronic monitoring device, Smartinhaler. The control group received the same care as the intervention group except the feedback and	Shaping knowledge; instruction on how to perform a behaviour; Feedback and monitoring; monitoring of others with feedback on behaviour; Regulation, pharmacological support;	Both child and parent	Level 3: personalised asthma education and asthma management plan designed collaboratively with the parent and child	Primary outcome- Electronic monitoring

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
				allocated to the intervention group. These data were incorporated in the management plan for the coming month. When suboptimal adherence was identified, adherence barriers were discussed with the patient within a tailored feedback discussion. Consultations involving feedback focused on positive outcomes and discussions about non-adherence were non-judgemental.	discussions around the Smartinhaler adherence data.	Goals and planning; goal setting (behaviour); Associations, prompts/cues; Reward and threat, non-specific reward			
Canino et al. 2016	Independent Provider Associations (clinics) subcontracted by the dominant	Children were eligible if they had poor asthma control and were ages 5-12 years old.	Through their health records equivalent to primary care but also classed as	Physician education was addressed by adapting the content from the Physician Asthma Care Education (PACE) program [25]. Similar	Both study, Arms 1 and 2, used an evidence-based asthma intervention called CALMA.	Shaping knowledge; instruction on how to perform the behaviour	Both child and parent	Level 2: Information not tailored - the education was "administered" to them	Secondary outcome-

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
	insurance company serving San Juan metropolitan area of Puerto Rico.	404 children were enrolled.	persistent asthma by their insurance claims.	to the PACE program, physicians in the CALMA-plus intervention were offered training in three interactive seminars lasting an hour and aimed at enhancing their clinical skills to diagnose, manage and treat asthma according to the NAEPP guidelines.					
Chan et al. (2015).	Regional emergency department New Zealand	Patients aged 6-15 years old. 220 participants were randomly assigned. 110 to each group,	Patients with a diagnosis of acute asthma who were prescribed treatment with twice-daily ICS (checked on their medical records).	All patients were switched to fluticasone propionate inhaled treatment and if on combined treatment- fluticasone propionate and salmeterol xinafoate. Intervention group- SmartTrack with audio-visual enabled.	Control- SmartTrack with audio-visual disabled.	Feedback and monitoring, others monitoring with awareness; Regulation, pharmacological support; Associations, prompts/cues	Child	Level 1: Practicalities only	Primary outcome- Electronic Monitoring

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
Chatkin et al. (2006).	Clinical Setting Brazil- presumable primary care, 15 states	12 years plus inclusion. 293 patients- 271 included in the study. Control- 131 Intervention- 140 Control group- 16.6 years +- 44.4 SD Intervention group- 15 years +-43.3	Moderate or severe persistent asthma, according to GINA criteria and Brazilian guidelines. Patients were selected by their physicians in their own clinical setting as having asthma based on clinical and spirometry evidence.	Telephone based asthma education every two weeks with a focus on adherence. A trained nursing student delivered the 10 min telephone calls to the child which involved basic facts about asthma, the role of medication, and the importance of adherence to treatment and also instructions for taking rescue actions.	Patients received an initial and final telephone call- the same as the intervention group. Both groups received free Salmeterol/ fluticasone x 3 packages.	Regulation, Pharmacological support; Associations: prompts/cues; Natural consequences: information about health consequences	Child	Level 3	Primary outcome Discus dose counter
Garrett et al. (1994)	New Zealand (South Auckland) An asthma education centre was set up in the	2-55 years old with asthma. 500 patients went into the prospective study. Education	They were diagnosed as having asthma by the attendant physician in the	Education programme run by two nurse specialists and a group of respiratory physicians established the service. Community	Usual care.	Shaping knowledge: instruction on how to perform the behaviour; Shaping knowledge:	Both child and parent	Level 3: tailored to area and staff ethnicity	Secondary outcome- Prescription refill

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
	community near a free specialist-run hospital-based asthma clinic	group= 251 Control group= 249 High proportion Mauri and Pacific Islander (some European)	emergency room.	health workers with similar ethnicities to the target audience provided the education programme. The work was tailored and included inhaler technique training and information about what causes asthma.		information about antecedents			
Guendelman et al. (2002)	Outpatient hospital clinic	Inner-city children aged 8-16 years old (mean 12 years old) diagnosed with asthma by a physician. 134 participants consented.	Diagnosed by a physician as having persistent asthma using NHLBI guidelines.	Heathy Buddy connected to the home phone and can be programmed to present questions and information on a screen and to record responses. These are sent each day by the nurse coordinator and the answers are reviewed the following day. Question content was 10 questions about asthma symptoms,	All children received a standardized teaching session regarding peak flow meters and inhaler technique. It also covered how to get the most of their medications and health services and the green-yellow-red zoning info. All participants received a \$20 incentive. Comparison group: A standard asthma diary for monitoring	Feedback and monitoring-feedback on behaviour, self-monitoring of behaviour; Association; prompts/cues	Child	Level 3: tailored feedback and messages	Secondary outcome- Parental/caregiver self-report

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
				peak flow readings, use of medications and of health services and functional status such as school attendance and activity limitation. Immediate tailored feedback is given. In addition, asthma facts and trivia (changed daily) were presented to enhance learning.	symptoms, recording peak flow, medication use and restricted activity.				
Gustafson et al. 2012)	Managed health care organisations in Wisconsin, Madison and Milwaukee, USA.	305 Patient dyads were enrolled, 301 were assigned to control or intervention, Control= 153 and Intervention= 148. 127.153 completed in the control group and 132 of 148 completed in	Diagnosis of asthma or wheeze and prescribed asthma controlled medication and poor medication adherence; defined as having missed one medication refill or	CHESS-CM is a year-long intervention including an eHealth program (CHESS) and a monthly telephone call to a parent from an asthma nurse case manager (CM). CHESS modules provide information, adherence strategies, decision-making tools, and support services in attractive, easy-to-use formats.	All participants, regardless of study condition, received a call from the project manager 1 week after randomization to see how things were going. They also received with their mailed surveys at 3, 6, 9, and 12 months a packet of educational materials about asthma control, child development, parenting,	Goals and planning, problem solving; Social support, unspecified; Feedback and monitoring, self-monitoring of behaviour, monitoring of others with feedback on behaviour	Both child and parent	Level 3: tailored information and support	Secondary outcome- Self-report and Prescription refill



Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
		the intervention group. (4-12 years old)	having ED visits because of poor asthma control.	CHES provided tailored feedback and links to salient CHES content and other interactive tools. Children received simplified information in game and audio-visual formats, as well as social support via a peer discussion group and personal stories. Monthly case management calls to the parent assessed the child's asthma, medication adherence, and psychosocial challenges, and provided relevant education and support.	and community resources. Parents and children returned to the clinic or community centre for an exit interview that included taking the same measures used at the intake appointment.				
Hederos et al. (2005).	Primary care and the regional hospital-referrals	60 parents of children 3 months-6 years old given a diagnosis of	Had been given a diagnosis of asthma in our region 1-2	Ninety minute meetings in a group setting with parents were help 3 times weekly meetings soon	Each family received basic information about asthma and its treatment and info on environmental control	Shaping knowledge, instruction on how to perform a behaviour;	Both child and parent	Level 1: Perceptual	Primary outcome- Parental-report Verified adherence-canister weight

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
		Asthma- and the children. Mean age of participants Intervention- 28 months (2 years 4 months) and control- 26 months (2 years 2 months)	months earlier	after diagnosis. Three paediatricians, three nurses and two psychologists were involved in these sessions. They elicited main worries, taught about asthma and asked what does asthma mean to you? Subjects that were covered were: medical information, treatment possibilities, family relationships related to chronic illness, preventative measures, prognosis, experiences and outcome.	at their first visit to the clinic. They also received a written action plan.	Natural consequences: information about health consequence			
Jan et al. (2007).	Paediatric Allergy and asthma clinic at National Cheng Kung University Medical	6-12 year olds who had been diagnosed with persistent asthma following the GINA	Were diagnosed as having persistent asthma following the GINA clinical	An internet-based multimedia asthma education and monitoring system: Blue Angel for Asthma Kids. In this setting, patients were	Asthma education as part of their usual care; verbal information and a booklet with written asthma diary.	Feedback and monitoring, self-monitoring of behaviour and feedback on behaviour;	Both child and parent	Level 3	Primary outcome- Self-report and dose counter

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
	Center, Tainan, Taiwan	guidelines. 164 patients and their care-givers. Control group- 76 Intervention group-88	practice guidelines.	able to complete the electronic asthma diary and record symptoms, need for rescue medication, and PEF values. The Internet tool's action plan comprised a three-color warning system accompanied by a written treatment plan. Physicians then feedback to patients by e-mail or telephone to adjust doses or continue as usual.		Associations: prompts/cues			
Julious et al. (2016)	Primary care general practices in the UK	Children with asthma registered at a GP of school age 4-16 years old. All children had to have been prescribed asthma	GP diagnosed asthma	For the intervention, a letter sent from a GP to the parents/carers of children with asthma reminding them to maintain their children's medication and collect a prescription if they	Usual care with no letter sent to them in July to remind them to pick up medication.	Regulation, pharmacological support; Associations: prompts/cues	Parent	Level 1: Perceptual only	Primary outcome- Prescription refill

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
		medication within the last year.		are running low. It also advised that, should their child have stopped their medication, it should be resumed as soon as possible.					
Morton et al. (2017)	Outpatients' hospital clinics in Sheffield and Rotherham in the UK.	6-16 year old children with asthma who had been taking regular ICS with poorly controlled asthma (ACT score 1.5+). Participants were on either seretide or symbicort. 90 participants were recruited Sheffield=81 Rotherham=9.	Doctor diagnosed	Smart inhalers were attached to their regular inhalers. Participants were told this would record the time and date of the actuation of the inhaler. At clinic visits the previous 3 months data were downloaded. This data was then reviewed with the parents and child. Open non-judgmental discussions were held about the adherence rates, barriers were identified and if necessary personalised	Inhaler technique was checked in both arms by a qualified nurse and they received a brief asthma education session emphasising the importance of taking ICS regularly. Smart inhalers were attached to their regular inhalers. Participants were told this would record the time and date of the actuation of the inhaler but that the data would not be reviewed.	Shaping knowledge, instruction on how to perform a behaviour; Feedback and monitoring, others monitoring with awareness, feedback on behaviour (and reminders); Goals and planning, problem solving/coping planning; Associations, prompts/cues	Both child and parent	Level 3: tailored to identify and address barriers to individuals and reminders for forgetfulness.	Secondary outcome- Electronic monitoring

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
				strategies for improvement were devised. Devices were also set to play reminders at certain times (different for the week and weekends). The reminder played for 5s every minute for 15 minutes or until actuation.					
Mosnaim et al. (2013).	Three primary care practices at Rush University Medical Centre in Chicago, Illinois.	11-16 year old African American and Hispanic adolescents with persistent asthma. Those with 48% or less adherence were recruited (poor adherers). 68 were randomised I=34, C=34; 5 week follow-up	An outpatient visit to Rush University Medical Center with asthma listed as a diagnosis code for that visit, and a prescription for daily ICS.	The intervention group received coping peer group sessions led by a social worker in 1-4 and 6-9 weeks. The facilitator was training in Motivational Interviewing, asthma education and behaviour change therapy and had a topic guide. Participants discussed barriers to taking daily ICS and	All participants received spacers, peak flow meters and education on both. Those in the control group met individually with the research assistant in weeks 1-5 and 6-9. The research assistant did not encourage adherence. The control group received music on an iPod shuffle with content promoting adherence to their daily	Social support (general); Goals and planning, problem solving/coping planning; Self-belief, self-talk; Associations: prompts/cues	Child	Level 3: Authors stated based on social cognitive theory.	Primary outcome- Electronic monitoring Also self-report

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
		(I=29, C=28) 10 weeks (I=29 C=29)		strategies to overcome them. After each session patients recorded 2-4 messages gleaned from the discussions that encouraged each other to take the ICS. These messages were the played along with music tracks on the iPod shuffle.	ICS medications and these were developed and recorded by asthma doctors rather than by participant.				
Stergachis et al. 2002	Community based pharmacist in an urban setting. Two pharmacies were affiliated with public health clinics predominantly serving low-income clients, six located in hospitals or clinics, 9	32 pharmacies Intervention=14 pharmacies Control=18 pharmacies. Participants were aged 6-17 and were receiving medication refills for asthma medications no less than every 6 weeks and who had at	Patients were receiving either oral theophylline daily or oral or inhaled beta agonists more than twice daily or ICS for asthma daily.	Pharmacist intervention 8 hours in person group education session. PEAK was guided by the AirWise patient education and self-management program and by the principles of pharmaceutical care. Over 1 year pharmacists were expected at every refill to: establish a relationship with the	Usual care did not receive other contact or training and were instructed to provide their usual care.	Regulation, Pharmacological support; Shaping knowledge, instruction on how to perform a behaviour	Child	Level 2: tailored and looking for any drug related problem.	Secondary outcome- Adherence measurement not described

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
	affiliated with large retail chains and 6 independent pharmacies. United States- Washington.	least a three month history of medication use. Intervention= 153 and control= 177		patient; collect relevant patient data; assess the patient for potential or actual drug related problems; prioritise and make a plan for resolving the DRP and implement the plan and follow-up. Content included queries and counselling about disease progression; medications; symptom management; early warning signs; triggers; lung function; environmental control and independence as well as demonstration of inhaler technique.					
Teach et al. (2006).	Emergency department of an urban	12 months-17 year olds attending the	Physician-diagnosed asthma and a	The intervention was based on the health belief model and	Received an asthma education booklet but	Feedback and monitoring,	Both child	Level 3	Secondary outcome- Parental report

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
	paediatric medical centre called Children's National Medical Center, Washington, USA.	ED for an unscheduled visit.	primary discharge diagnosis of asthma from the emergency department.	promoting self-efficacy. Each session required 60-90 minutes education in three domains- asthma self-monitoring and management; environmental modification and trigger control and linkages and referrals to ongoing primary care. Individualised medical action plan were created and devices were provided. The educator then gave copies of everything to the family including the asthma action plan and made a follow-up appointment within primary care for them within 4 weeks.	no specialised follow-up.	self-monitoring of behaviour; Regulation, pharmacological support; Shaping knowledge: instruction on how to perform a behaviour; Natural consequences: information about health consequences	and parent		



Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
van Es, et al. (2001)	Six out-patient clinics: 2 academic teaching hospitals; 1 specialist asthma centre; 3 district hospitals.	11-18 years attending secondary school. 112 adolescents took part. 58 in the intervention group and 54 in the control group.	Asthma diagnosed by a physician and daily treatment prescribed by a paediatrician.	The Patients also discussed: disease characteristics, triggers for airway obstruction and treatment objectives and PEF from the 2 weeks prior to the appointment. The specially trained asthma nurse discussed asthma with the patients using drawings and written information. Inhaler techniques was discussed and demonstrated and additional written information was given to the parents about pulmonary conditions and medications. The session was patient centred. They also attended 3 group sessions (4-8	Usual care from their paediatricians. Appointments every 4 months and no visits to the asthma nurse.	Shaping knowledge, instruction on how to perform a behaviour; Social support, unspecified; Goals and planning- problem solving/coping planning; Natural consequences: information about health consequences	Both child and parent	Level 2: not tailored	Primary outcome- Self-report

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
				participants) once a week after the nurse appointments. Participants discussed coping and role-played difficult situations under the supervision of the same asthma nurse. Discussions included: communicating with your doctor, talking with peers about having asthma; attitudes towards asthma, asthma medication and refusing to accept a cigarette. The fourth visit took place to review all aspects of the preceding visits.					
Vasbinder et al. (2016)	Hospital outpatient clinics in the Netherlands	209 outpatient children (4-11 years old). 108 in the intervention, 111 in the	Doctor-diagnosed asthma for over 6 months and who visited	Real-time medication management (RTMM) (electronic monitoring device attached to the inhaler measuring	RTMM without text messages (an EMD attached to the inhaler)	Feedback and monitoring, others monitoring with awareness no	Both child and parent	Level 2: targeted practicalities only (forgetfulness) and tailored	Primary outcome- Electronic monitoring data

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
		control group- 10 excluded from ITT analysis (7=I; 3=C). Clinically stable patients.	the outpatient clinic in the past 12 months (using ICS).	what time and how often doses were taken) with short SMS reminders when a dose was at risk of omission. These were sent to parents and children when a dose had not been recorded within 15 minutes of planned administration time.		feedback on behaviour; Goals and planning, commitment; Associations, prompts/cues			
Wiecha et al. (2015)	Boston community health centres; the Boston Medical Centre and other practices in the area.	21 in the control group and 37 in the intervention group. Children aged 9-17 with persistent asthma. At 6 months: control= 14 intervention= 28 Median age in the intervention was 12 (8-16) and for the	Diagnosed by their primary care doctor with persistent asthma.	The web-based interactive asthma education and monitoring system was based on social cognitive theory and eHealth theoretical models and included education, self-monitoring and rewards. Participants used the website to report their medication which was reviewed every two months by a	The control group received an asthma education manual; peak flow meter and usual care from tier physicians.	Feedback and monitoring, self-monitoring of behaviour, feedback on behaviour; Shaping knowledge, instruction on how to perform a behaviour; Information about antecedents; Reward and threat, material	Both child and parent	Level 3: Tailored feedback regarding adherence.	Secondary outcome- Electronic monitoring

Citation	Setting	Participants	Diagnosis of Asthma	Intervention	Control	BCTs	BCT target (Child, Parent, Both child and parent)	Intervention components PAPA	Outcomes of interest
		control was 14 (7-17) at baseline.		paediatric specialist and nurse and feedback was given via an online discussion board. The education online included video explanations of asthma and why it develops, how to mitigate impact on activities, use of controller and rescue medications, triggers, smoking, pets, action plans, and peak flow meters. Completion of each function earned points, which were redeemable for gift card.		incentive (behaviour); Social support: social support (unspecified); Natural consequences: information about health consequences & salience of consequences			

#### 4.2.3.1 *Intervention content*

The data extraction form also included sections specifically relevant to the research questions for this PhD such as to what extent the intervention is informed by the Perception and Practicalities Approach and also which Behaviour Change Techniques the intervention used. BCTs were coded using BCT taxonomy V1 app (Appendix 1(Michie et al., 2013) for consistency with the terms used. The taxonomy (Michie et al., 2013) includes 16 behaviour change topics with descriptions and subgroups under each BCT topic totally 93 BCTs. Both the wider topic and the narrower BCT were recorded. Intervention content was also coded for the PAPA as follows: Level 1 (intervention only targeted perceptions or only practicalities and not tailored); Level 2 (both perceptions and practicalities targeted but not tailored or one component (perceptions or practicalities) and tailored) and Level 3 (both perceptions and practicalities targeted and tailored to the individual).

#### 4.2.3.2 *Risk of bias*

Risk of bias (RoB) was assessed independently using the Cochrane Risk of Bias Handbook (Higgins et al., 2011) by two reviewers (Amy Chan and Christina Pearce) and the Covidence platform ([www.covidence.org](http://www.covidence.org)) to record coding decisions and consensus discussions. The RoB score was based solely on the adherence outcome. Each study was scored across five domains as outlined by Cochrane: selection bias; performance and detection bias, attrition bias and reporting bias across size domains, and was scored as either low, high or unclear risk for each study. Authors were contacted for clarification when information relating to domains seemed unclear.

#### 4.2.3.3 *Study reliability*

To ascertain which interventions were truly effective the reliability of the studies needs to be considered. As this review focused on asthma and adherence, the author team looked at two key areas related to reliability of the findings: how asthma diagnosis was made in the study and the objectivity of the adherence measurement. Both diagnosis and adherence measures can range from being subjective to objective, therefore considering the reliability of the approaches used is key for determining study reliability. Through multidisciplinary team discussions (including respiratory physicians, pharmacists and a health psychologist) a coding hierarchy that considered the reliability of the asthma diagnosis and adherence measurement used was created and applied to the specific studies within this review (Table 4). Although other validated tools have been used to assess quality such as the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool (Ryan R & Hill

S.H, 2016) the authors felt that there were several crossovers between RoB, the reliability scores, the 3Cs of Behaviour Change approach (described below) and in particular, the indirectness section of the GRADE tool and based on the aim of this review the reliability measurements would be more useful when considered with RoB

Table 4: Hierarchy of Asthma Diagnosis and Adherence Measurement Outcome

<b>Reliability of a True Diagnosis of Asthma</b>	
Reliable	Using objective clinical measurements (e.g. spirometry)
	Emergency department diagnosis
Less Reliable	Using a guideline e.g. GINA, BTS, SIGN, NHLBI
	Outpatient specialist physician diagnosis
Not Reliable	Primary care record of asthma and a prescription of ICS
	Primary care record of asthma
	Self-report of asthma
	Parental report of asthma
<b>Objectivity of the Adherence Measurement</b>	
Objective	Directly Observed Therapy
	Electronic monitoring device with microphone
	Electronic monitoring device with time and date
	Dose counter or Canister weight (does not differentiate time or date)
	Prescription Refill
Not Objective	Self-report
	Parental Report

Based on the RoB, the reliability of the asthma diagnosis, and the objectivity of the adherence measurement, the most reliable and least biased studies were used to ascertain what components constituted an effective intervention. Previous literature suggests that when

considering how to create the ideal adherence interventions three areas should be optimised to increase study effectiveness: the content (including the theory used in this case PAPA), channel of delivery and context as proposed by the 3Cs of Behaviour Change (Horne, 2012). The 3Cs of Behaviour Change (Horne, 2012) was also applied to this review.

Studies were summarised by a narrative synthesis which uses text to describe, summarise and to critically explore similarities and differences between studies (Lisy & Porritt, 2016). Meta-analysis was not conducted due to the wide study heterogeneity in terms of setting, asthma diagnosis criteria, and outcome measures used. The study protocol is published on PROSPERO ([https://www.crd.york.ac.uk/prospero/#searchadvanced\(ref:CRD42016029213\)](https://www.crd.york.ac.uk/prospero/#searchadvanced(ref:CRD42016029213))).

## **4.3 Results**

### **4.3.1 Search Results**

Two systematic searches were conducted one at the beginning of the PhD and one as an update (2<sup>nd</sup> December 2015 and 27<sup>th</sup> June 2018). The first literature search retrieved 80 articles. Duplicates were found through both an Endnote search and manual checks resulting in six articles being removed. Based on abstract screening 48 articles were excluded and a further eight papers were excluded based on the full text. The main reasons for exclusion were: study design not an RCT; medication adherence not included as an outcome; trial compared medications or was conducted in an adult population. Eighteen studies were therefore remaining for inclusion in the systematic review; see full PRISMA diagram (Figure 16). The second update to the literature search retrieved 172 articles in total. An additional nine were identified from other sources. Six duplicate articles were removed before abstract screening. Based on abstract screening, 149 papers were excluded and a further eight papers were excluded based on the full text. The number and reasons for exclusions remained the same as in the first search as did the included studies. Eighteen studies were included in the narrative synthesis (Baren et al., 2006; Burgess et al., 2010; Canino, Shrout, Vila, Ramirez, & Rand, 2016; Chan, Harrison, et al., 2015; Chatkin, Blanco, Scaglia, Wagner, & Fritscher, 2006; Garrett et al., 1994; Guendelman, Meade, Benson, Chen, & Samuels, 2002; Gustafson, M, et al., 2012; Hederos, Janson, & Hedlin, 2005; Jan et al., 2007; Julious, Horspool, et al., 2016; Morton et al., 2017; Mosnaim et al., 2013; Stergachis et al., 2002; Teach et al., 2006; van Es et al., 2001; Vasbinder et al., 2016; Wiecha et al., 2015); see full PRISMA diagram (Figure 15).

#### 4.3.2 Inclusion/Exclusion agreement between reviewers

Agreement between reviewers was explored using the data from the first systematic search. Coder agreement was calculated using Kappa Measure of Agreement in SPSS. Kappa agreement was initially 0.37,  $p < 0.0005$  with 74 reviewed studies. This level of agreement was classed as poor and was due to differences in interpretation of the inclusion/exclusion criteria for the population aspect of the studies between the reviewers. Following discussion and amendment of the criteria for the population inclusion criteria the reviewers separately reviewed the articles for a second time. After amendments were made the Kappa agreement score was 0.51 with a significance level of  $p < 0.005$ . The Kappa agreement score still only indicated moderate agreement between the coders. However, once discussed the second reviewer noted some errors in their coding given our previous discussions and amendments to the population criteria. The Kappa score was then recalculated and was 0.87,  $p < 0.0005$  (very good agreement) which was deemed acceptable. All further disagreements were discussed with the second reviewer and a third party, Professor Rob Horne until a consensus was reached. The included studies were finalised via a telephone meeting and 57 texts were excluded from the study, leaving 18 remaining papers for inclusion in the qualitative synthesis (Figure 15). Second coding was not conducted for the second update to the systematic search as the coders had perfected the inclusion/exclusion criteria and therefore the few uncertainties that did arise were discussed and agreed upon within the supervisor team.



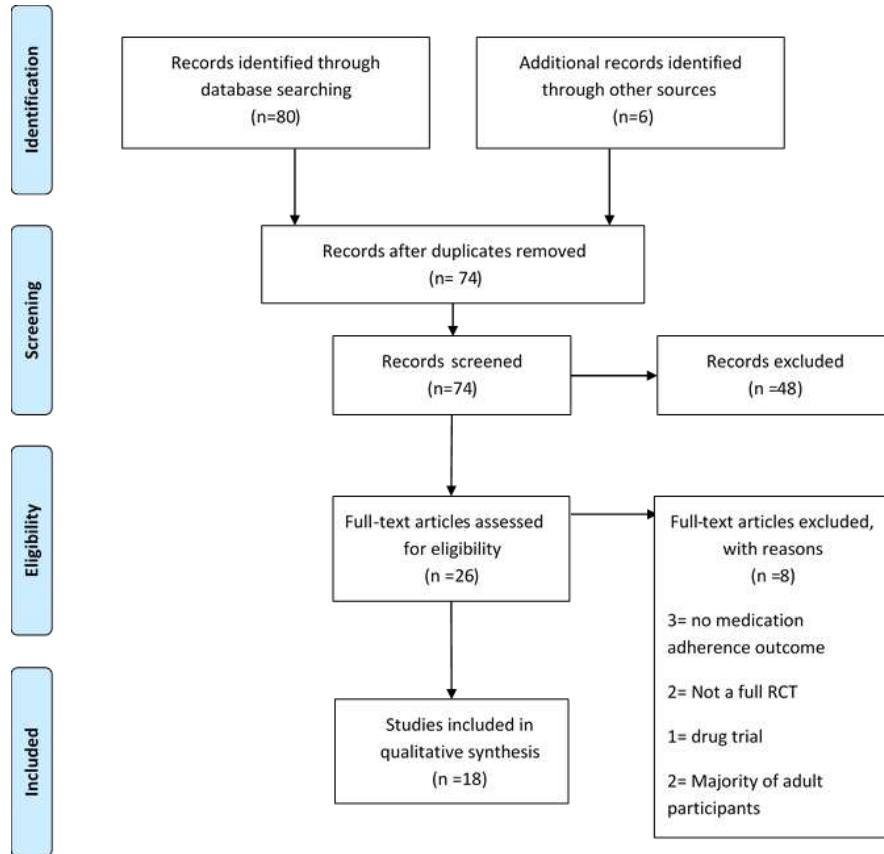


Figure 16: PRISMA flow diagram showing the first systematic search

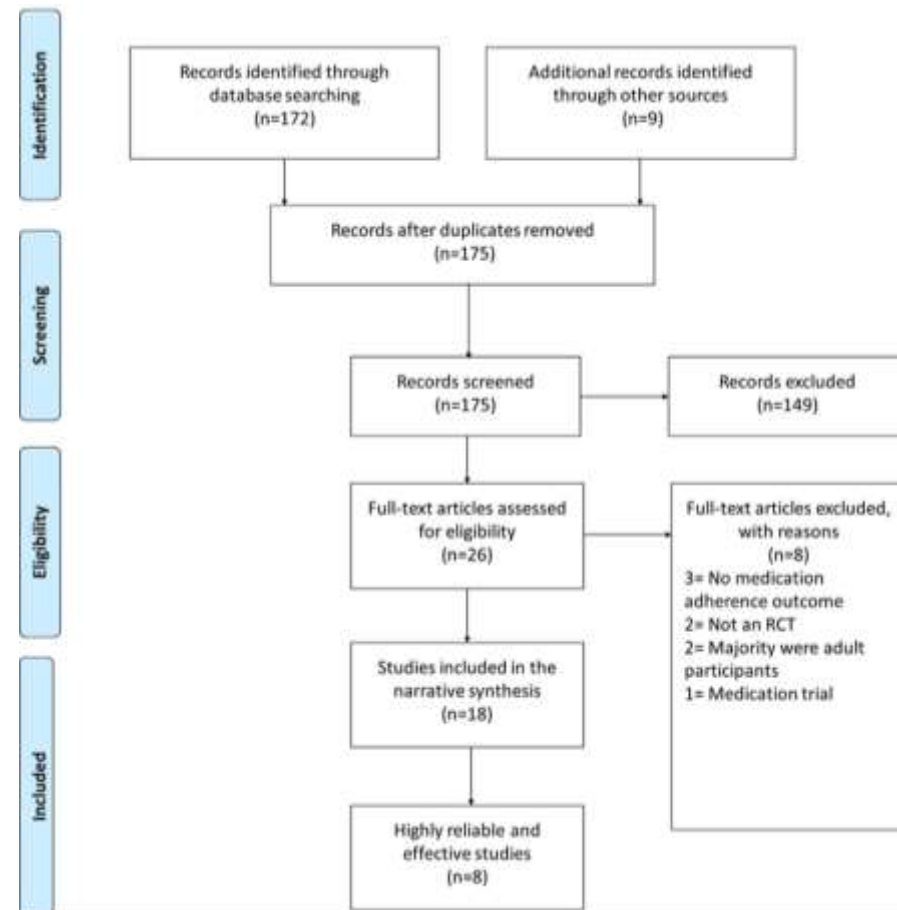


Figure 15: PRISMA flow diagram showing the second systematic search

### 4.3.3 Narrative Synthesis of Results

#### 4.3.3.1 Study characteristics

##### 4.3.3.1.1 Effect on adherence

Only half of the interventions (9/18) showed significant improvement in adherence in the intervention groups compared to the control groups (Burgess et al., 2010; Chan, Harrison, et al., 2015; Chatkin et al., 2006; Garrett et al., 1994; Guendelman et al., 2002; Julious, Horspool, et al., 2016; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016)(Table 5).

Table 5: Results for the adherence outcome

Study	Adherence  Primary or Secondary outcome of interest	Effect on Adherence  *=statistically significant  Adherence data (e.g. mean / median) are shown along with indicator of data spread (e.g. SD, CIs). Data not shown in this table are absent due to a lack of reporting.	Statistical significance  *=statistically significant
Baren et al. 2006	Secondary	Median adherence was 34% in the control group versus 36% in the pooled adherence group.	P=0.66
Burgess et al. 2010	Primary	Mean adherence percentage  Intervention=79%  Control= 57.9%	P<0.01*
Canino et al. 2016	Secondary	Odds ratio with 95% confidence interval  0.299 (-0.537, 1.134)	P=0.39
Chan et al. 2015	Primary	Median 84% in the Intervention group (10th percentile 54%, 90th percentile 96%), compared with 30% in the control group (8%, 68%)	p<0.0001*
Chatkin et al. 2009	Primary	Percentage of patients with adherence over 85% was 51.9% in the control group and 74.9% in the intervention group adherence	p=0.001*

Study	Adherence  Primary or Secondary outcome of interest	Effect on Adherence  *= <b>statistically significant</b>  Adherence data (e.g. mean / median) are shown along with indicator of data spread (e.g. SD, CIs). Data not shown in this table are absent due to a lack of reporting.	Statistical significance  *= <b>statistically significant</b>
Garrett et al. 1994	Secondary	No quantitative data reported	P<0.0005*
Gustafson et al. 2012	Secondary	Composite adherence score (Mean and SD)  Control= 73.54% (47.81)  Intervention=69.80% (26.96)  Pharmacy refill  Control= 56.86% (27.14)  Intervention= 58.44% (26.68)	P= 0.65          P=0.35
Hederos et al. 2005	Primary	In the control group 30% had low adherence compared to 8% in the  Intervention group (based on VAS scores)  Verified mean adherence was 94% in the intervention group compared to 72% in the control group	P=0.015*   P=0.06
Jan et al. 2007	Primary	Mean difference in the control group at 12 weeks was a decline of 40.2% compared to a decline of 20.3% in the intervention group.	P<0.05 in favour of the intervention group

Study	Adherence  Primary or Secondary outcome of interest	Effect on Adherence  *= <b>statistically significant</b>  Adherence data (e.g. mean / median) are shown along with indicator of data spread (e.g. SD, CIs). Data not shown in this table are absent due to a lack of reporting.	Statistical significance  *= <b>statistically significant</b>
Julious et al. 2017	Primary	Adjusted OR 1.43, 95% CI 1.24- 1.64*	
Morton et al. 2017	Secondary	Median adherence for the Intervention group was 70% vs 49% for the control group	P<0.001*
Mosnaim et al. 2013	Primary	Median percentage adherence with IQR (Q1 and Q3)  Intervention= 18.8 (5.4, 24.2) Control=16.1 (7.14, 19.6)  Intervention= 7.1 (0.9, 21.4) Control= 14.3 (5.4, 21.4)	Outcome measured at 5 and 10 weeks  5 weeks= p=0.534  10 weeks p=0.929
Stergachis et al. 2002	Secondary	No quantitative results reported	
Teach et al. 2006	Secondary	3 months= Adjusted RR 2.37 (95% CI, 1.83-3.04)  6 months= Adjusted RR 2.03 (95% CI, 1.57-2.62) *	
Van Es et al. 2001	Primary	Mean difference percentage adherence and SD	Bonferroni corrections used and authors reported results not significant (however

Study	Adherence  Primary or Secondary outcome of interest	Effect on Adherence  *= <b>statistically significant</b>  Adherence data (e.g. mean / median) are shown along with indicator of data spread (e.g. SD, CIs). Data not shown in this table are absent due to a lack of reporting.	Statistical significance  *= <b>statistically significant</b>
		7.8% (1.6) Intervention versus 7.3% (1.8) Control  7.7% (2) Intervention versus 6.7% (2.3) Control	adjusted statistics not reported)  Time 1= p=0.14  Time 2=p=0.05
Vasbinder et al. 2016	Primary	Mean adjusted result= 12% (95% CI 6.7-17.7%) *	
Wiecha et al. 2015	Secondary	Mean change since baseline  Intervention= 11.2% increase  Control=4.4% decrease	P=0.46

Footnote: Abbreviations: SD= Standard Deviation; OR= Odds Ratio; RR= Relative Risk, IQR= Interquartile Range

#### 4.3.4 Reliability of the study findings

Although half of the studies were reported as effective at increasing adherence the study reliability varied widely (Table 6). A wide range of criteria were used for the diagnosis of asthma and therefore the patient sample included in each study was heterogeneous. Where reported, most diagnoses were based on guidelines such as GINA, National Heart, Lung, and Blood Institute (NHLBI) (Chatkin et al., 2006; Guendelman et al., 2002; Jan et al., 2007) or a physician diagnosis plus a prescription for ICS (Chan, Harrison, et al., 2015; Gustafson, M, et al., 2012; Mosnaim et al., 2013; Stergachis et al., 2002; van Es et al., 2001; Vasbinder et al., 2016) (50%, 9/18). Just under half (44%, 8/18) reported using an asthma diagnosis given by the emergency department physician (Baren et al., 2006; Canino et al., 2016; Garrett et al., 1994; Teach et al., 2006), where patients asthma symptoms will have been observed by physicians first hand, or by diagnosis from medical records (Hederos et al., 2005; Julious, Horspool, et al., 2016; Morton et al., 2017; Wiecha et al., 2015). In one study the method of diagnosis of asthma was unclear (Burgess et al., 2010).

Adherence measurement varied with studies using objective and subjective measures. Based on the above coding hierarchy of objectivity of adherence measurements (Table 4), most studies used more objective measurements (Burgess et al., 2010; Chan, Harrison, et al., 2015; Chatkin et al., 2006; Julious, Horspool, et al., 2016; Morton et al., 2017; Mosnaim et al., 2013; Vasbinder et al., 2016; Wiecha et al., 2015) or both objective and subjective measures (Gustafson, M, et al., 2012; Hederos et al., 2005; Jan et al., 2007). Six of the studies used subjective measurements of adherence only (Baren et al., 2006; Canino et al., 2016; Garrett et al., 1994; Guendelman et al., 2002; Teach et al., 2006; van Es et al., 2001) and one was unclear (Stergachis et al., 2002). Based on the risk of bias, reliability of asthma diagnosis and objectivity of the adherence measurement within each study the reliability of the evidence can be summarised (Table 6).

Table 6: Study reliability

Risk of Bias	Study Reliability		
	Not Reliable	Moderately Reliable	Highly Reliable
Low risk		Baren et al. (2006) Teach et al. * (2006) Julious et al. * (2016)	Chatkin et al. * (2006) Chan et al. * (2015c)
Moderate Risk	Canino et al. (2016) Van Es et al. (2001)	Gustafson et al. (2012) Jan et al. (2007) Garrett et al. * (1994) Burgess et al. * (2010)	Morton et al. * (2017) Vasbinder et al. * (2016)
High risk	Stergachis et al. (2002)	Hederos et al. (2005) Guendelman et al. * (2002) Mosnaim et al. (2013) Wiecha et al. (2015)	

\*significantly effective at increasing adherence in the intervention group



#### 4.3.4.1 *Risk of Bias*

##### 4.3.4.1.1 Risk of bias within studies

Only a few studies were considered low risk (Baren et al., 2006; Chan, Harrison, et al., 2015; Chatkin et al., 2006; Julious, Horspool, et al., 2016; Teach et al., 2006), with most being considered moderate risk (Burgess et al., 2010; Canino et al., 2016; Garrett et al., 1994; Gustafson, M, et al., 2012; Jan et al., 2007; Morton et al., 2017; van Es et al., 2001; Vasbinder et al., 2016). Five studies were considered high risk (Guendelman et al., 2002; Hederos et al., 2005; Mosnaim et al., 2013; Stergachis et al., 2002; Wiecha et al., 2015) (Table 6 and Figure 17).

##### 4.3.4.1.2 Risk of Bias across Studies

The main risk of bias was due to performance bias. Overall, risk of bias was low for most studies in terms of selection bias (random sequence generation and allocation concealment); detection bias (blinding of outcome assessment) and reporting bias (selective reporting bias). Attrition bias (incomplete outcome data) was frequently unclear or high risk (Figure 17).

#### 4.3.4.2 *Reliability of the evidence*

Based on the risk of bias, reliability of asthma diagnosis and objectivity of the adherence measurement within each study the reliability of the evidence can be summarised (Table 6). The most reliable studies (i.e. moderate or high reliability based on asthma diagnosis and adherence measurement criteria) and low/ moderate RoB are discussed in more detail below. Eight of the eleven studies in this category were effective at increasing adherence (Burgess et al., 2010; Chan, Harrison, et al., 2015; Chatkin et al., 2006; Garrett et al., 1994; Julious, Horspool, et al., 2016; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016) and three were ineffective (Baren et al., 2006; Gustafson, M, et al., 2012; Jan et al., 2007). The following section compares the eight effective studies with the three ineffective studies within this high reliability group. Of those studies which reported effectiveness for increasing adherence, only one study was not considered to be in the high reliability group.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Baren 2006	+	+	+	+	+	+
Burgess 2010	?	?	+	+	+	+
Canino 2016	+	?	+	+	+	+
Chan 2015	+	+	+	+	+	+
Chatkin 2009	+	+	+	+	?	+
Garrett 1994	?	?	+	?	+	+
Guendelman 2002	?	+	+	+	?	+
Gustafson 2012	+	+	+	+	+	+
Hederos 2005	+	+	+	+	+	+
Jan 2007	?	+	+	?	+	+
Julious 2016	+	+	+	+	?	+
Morton 2017	+	+	+	+	+	+
Mosnaim 2013	+	+	+	+	+	+
Stergachis 2002	+	+	+	+	+	+
Teach 2006	+	+	+	+	?	+
vanEs 2001	+	+	+	+	?	+
Vasbinder 2016	+	+	+	+	+	+
Wiecha 2015	?	?	?	+	+	+

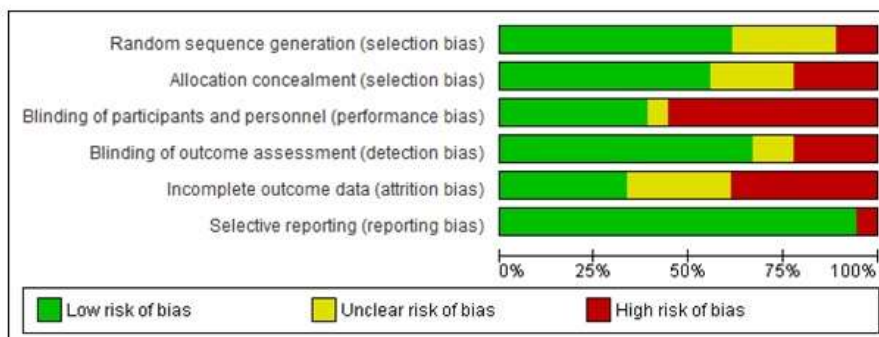


Figure 17: Risk of bias

#### 4.3.4.3 *Components of effective interventions*

This section will summarise the findings of this systematic review on the basis of the 3Cs of Behaviour Change in order to critically appraise the effectiveness of the components within the most reliable intervention study evidence.

##### 4.3.4.3.1 Context

The eight effective studies were conducted in Brazil (Chatkin et al., 2006); New Zealand (Chan, Stewart, et al., 2015; Garrett et al., 1994), Australia (Garrett et al., 1994); the USA (Teach et al., 2006), the UK (Julious, Horspool, et al., 2016; Morton et al., 2017) and the Netherlands (Vasbinder et al., 2016). The ineffective studies were conducted in the USA (Baren et al., 2006; Gustafson, M, et al., 2012; Mosnaim et al., 2013; Wiecha et al., 2015), Taiwan (Jan et al., 2007) and Sweden (Hederos et al., 2005). In terms of setting several studies took place in an emergency care setting (Chan, Stewart, et al., 2015; Teach et al., 2006), primary care (Chatkin et al., 2006; Julious, Horspool, et al., 2016), hospital outpatients (Burgess et al., 2010; Morton et al., 2017; Vasbinder et al., 2016) and in the community (Garrett et al., 1994). The ineffective studies took place in: emergency care (Baren et al., 2006), the community (Gustafson, M, et al., 2012) and hospital outpatients (Jan et al., 2007). There are no data regarding whether or not the intervention used a no-blame approach (Horne, 2012) but three of the studies tailored intervention content to specific patient needs (Burgess et al., 2010; Chatkin et al., 2006; Garrett et al., 1994) whereas only one of the ineffective studies were tailored to the patient (Jan et al., 2007).

##### 4.3.4.3.2 Channel (Delivery Vehicle)

Five of the high quality effective studies used technology to deliver the intervention including using EMDs (Burgess et al., 2010; Chan, Stewart, et al., 2015; Morton et al., 2017; Vasbinder et al., 2016), the telephone (Chatkin et al., 2006) and an SMS-based system (Vasbinder et al., 2016). Two of the ineffective studies used technology to deliver the intervention via a website and monthly telephone calls (Gustafson, M, et al., 2012) and via the internet alone (Jan et al., 2007). Different health care practitioners were involved in the interventions. Effective studies involved Pharmacists (Chan, Stewart, et al., 2015; Vasbinder et al., 2016), nurses (Burgess et al., 2010; Chan, Stewart, et al., 2015; Chatkin et al., 2006; Garrett et al., 1994; Morton et al., 2017), specialist physicians (Burgess et al., 2010; Garrett et al., 1994; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016), community health workers (Garrett et al., 1994) and researchers (Vasbinder et al., 2016). In one study (1/8), the only channel was a letter sent from the patients' GP (Julious, Horspool, et al., 2016)

to the parents of the child with asthma. The ineffective studies used limited contact with any health care practitioner (Baren et al., 2006), nurse (Gustafson, M, et al., 2012; Jan et al., 2007) and physician (Jan et al., 2007).

#### 4.3.4.3.3 Content

4.3.4.3.3.1 Summary of perceptions and practicalities targeted by adherence interventions  
Of the eight effective highly reliable studies (Table 7), five met the criteria for Level 3 (63%; (Burgess et al., 2010; Chatkin et al., 2006; Garrett et al., 1994; Morton et al., 2017; Teach et al., 2006) The three other effective high reliability studies were categorised as Level 1 or Level 2 with two focusing on practical factors only (Chan, Stewart, et al., 2015; Julious, Horspool, et al., 2016) and one targeting practicalities in a tailored way (Vasbinder et al., 2016). Of the high reliability studies only three were not effective- two were categorised as Level 3 (Gustafson, M, et al., 2012; Jan et al., 2007) and one was categorised as Level 1 (Baren et al., 2006).

Only one effective study was classified as low reliability which was categorised as Level 3 (Guendelman et al., 2002). The ineffective low reliability studies were either classed as Level 1 (no tailoring) (Hederos et al., 2005), Level 2 perceptual only (Stergachis et al., 2002; van Es et al., 2001), or both but not tailored (Canino et al., 2016) or Level 3 (Mosnaim et al., 2013; Wiecha et al., 2015). Therefore, only four studies (4/18) using Level 3 PAPA were not effective, two of which were classed as low reliability studies. Overall only 29% (2/7) of high reliability studies using Level 3 of the PAPA did not result in effective studies.

Table 7: PAPA Categorisation and Reliability

<b>PAPA</b>	<b>Highly Reliable (11/18)</b>	<b>Low Reliability (7/18)</b>
Level 1 = Targeting only one factor, either perceptual or practical, and not tailored	Julious et al. (2016)* Chan et al. (2015)* Baren et al. (2006)	Hederos et al. (2005)

Level 2 = Targeting either perceptual and practical factors in a tailored intervention or both perceptual and practical factors but not tailored	Vasbinder et al. (2016)*	Canino et al. (2016) van Es et al. (2001) Stergachis et al. (2002)
Level 3 = Targeting both perceptual and practical factors in a tailored intervention	Chatkin et al. (2006)* Garrett et al. (1994)* Burgess et al. (2010)* Morton et al. (2017)* Teach et al. (2006)* Gustafson et al. (2012) Jan et al. (2007)	Mosnaim et al. (2013) Wiecha et al. (2015) Guendelman et al. (2002)*

\* Significant effect reported for increasing adherence in the intervention group compared to the control

#### 4.3.4.3.3.2 Summary of Behaviour Change Techniques used

Relevant to the age of the participants the BCTs most often targeted both parent and child with the aim (primary or secondary outcome) of improving the child's adherence to ICS. Only in one instance did the BCT pharmacological support target only the parent in the form of a letter to encourage the parent to pick-up the child's ICS prescription (Julious, Horspool, et al., 2016). Four further studies specified that the interventions targeted the child specifically (Chan, Stewart, et al., 2015) and these were often with older children (Chatkin et al., 2006; Mosnaim et al., 2013; Stergachis et al., 2002).

##### 4.3.4.3.3.2.1 Reward and Threat

Reward and threat, material incentive (behaviour) was used by one effective study (Burgess et al., 2010). A tailored goal was set for adherence and a reward was received when this goal was shown to be met with EMD data (a Smartinhaler™). For extracted examples of each behaviour change technique see Table 8.

#### 4.3.4.3.3.2.2 *Associations- prompts/cues*

The BCT Associations- prompts/cues, meaning reminders, were used in 6/8 (75%) of the effective interventions (Burgess et al., 2010; Chan, Stewart, et al., 2015; Chatkin et al., 2006; Julious, Horspool, et al., 2016; Morton et al., 2017; Vasbinder et al., 2016) compared to two (25%, 2/8) that did not use prompts (Garrett et al., 1994; Teach et al., 2006).

#### 4.3.4.3.3.2.3 *Feedback and Monitoring*

Five of the effective high validity intervention studies (63%, 5/8) used feedback and monitoring in their interventions (Burgess et al., 2010; Chan, Stewart, et al., 2015; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016) and three studies (38%, 3/8) did not use this BCT (Chatkin et al., 2006; Garrett et al., 1994; Julious, Horspool, et al., 2016).

#### 4.3.4.3.3.2.4 *Pharmacological Support*

Pharmacological support was used within five (63% 5/8) of the effective interventions (Burgess et al., 2010; Chan, Stewart, et al., 2015; Chatkin et al., 2006; Julious, Horspool, et al., 2016; Teach et al., 2006) and was not used in three effective studies (38%, 3/8) (38%, 3/8) (Garrett et al., 1994; Morton et al., 2017; Vasbinder et al., 2016). This often involved providing free medications in countries where medications were not free and providing a longer-term supply when the medications were free.

#### 4.3.4.3.3.2.5 *Shaping knowledge*

Shaping knowledge instruction on how to perform a behaviour had mixed results. This BCT was used in four of the effective high reliability studies (50%, 4/8) (Burgess et al., 2010; Garrett et al., 1994; Morton et al., 2017; Teach et al., 2006) and was not used in the other four (50%, 4/8) (Chan, Stewart, et al., 2015; Chatkin et al., 2006; Julious, Horspool, et al., 2016; Vasbinder et al., 2016).

Shaping knowledge information about antecedents was used in one effective study (Garrett et al., 1994) and one ineffective low reliability study (Wiecha et al., 2015).

#### 4.3.4.3.3.2.6 *Natural Consequences*

Information about health consequences had mixed results. This BCT was used in two of the eight studies (25%, 2/8) (Chatkin et al., 2006; Teach et al., 2006). It was also used in two effective but low reliability studies (Hederos et al., 2005; van Es et al., 2001). Van Es et al. (2001) and Hederos et al. (2005) both used parental self-report of adherence however, when

corrected statistically for multiple comparisons (using Bonferroni correction) or using a verified adherence measurement (objective measurement) the findings were not statistically significant.

Salience of consequences was only used within one low reliability ineffective intervention (Wiecha et al., 2015). When the authors conducted sub-group analysis of the high-risk group <75% adherence the intervention was effective however this was post-hoc and not included in the analysis plan.

#### *4.3.4.3.3.2.7 Goals and Planning*

Goals and planning BCTs were also found to be mixed, within 2/8 high reliability studies (25%) finding problem solving/coping planning effective (Burgess et al., 2010; Morton et al., 2017). Burgess et al. (2010) also used goal setting (behaviour) and was the only study in the review to use this specific BCT. However, three studies 3/18 (17%), which were of low validity uses problem solving/coping planning but were ineffective (Gustafson, M, et al., 2012; Mosnaim et al., 2013; van Es et al., 2001).

#### *4.3.4.3.3.2.8 Social Support*

Social support was found to be general or unspecified and was not found to be an effective technique in any of the 4/18 studies (22%) that used it (Gustafson, M, et al., 2012; Mosnaim et al., 2013; van Es et al., 2001; Wiecha et al., 2015). Only one of the studies was within the high reliability category and it was not effective (Gustafson, M, et al., 2012). The low reliability studies were all based on social cognitive theories (Mosnaim et al., 2013; van Es et al., 2001; Wiecha et al., 2015) and were ineffective interventions.

#### *4.3.4.3.3.2.9 Self-Belief*

Self-belief, in particular self-talk, whereby a person is encouraged to talk positively either aloud or silently before or during the desired behaviour e.g. about adherence, was used in one low reliability ineffective intervention study (Mosnaim et al., 2013) . Mosnaim et al.'s (2013) recorded patient self-talk around adherence and put them on an MP3 for the patient to listen to. Self-belief messages did not change adherence over and above messages from a doctor recorded on the device within this study (Mosnaim et al., 2013).

Table 8: Examples of the Coded Behaviour Change Techniques

Behaviour Change Technique	Examples of BCTs used in Effective Interventions
Reward and Threat	“developing a target adherence rate and an associated reward, increasing supervision by the parent, or linking improved adherence with a desirable outcome such as better sporting performance” Burgess et al. 2010
Association: prompts/cues	“the real-time feedback provided by the device, since the reminder only ceased when the correct dose was taken or after 15 min, with the screen displaying the date and time of the most recent dose taken.” Chan et al. 2015
Feedback and monitoring	“Open, non-judgemental discussions were held about the adherence rate, barriers identified and, if necessary, personalised strategies for improvement were devised.” Morton et al. 2017  “...and receive immediate feedback on their decisions and behaviours...” Guendelman et al. 2002
Regulation: Pharmacological support	“We provided participants with fluticasone propionate inhaled treatment.” Chan et al. 2015  “your child should continue to take their asthma medication as prescribed by their GP or practice nurse. If your child has stopped taking their medication over the summer holidays it is important to start it again as soon as possible.” Julious et al. 2017
Shaping Knowledge: Instruction on how to perform a behaviour	“The child’s use of their spacer (holding chamber) was assessed by a trained asthma nurse.” Burgess et al. 2010  “provided any necessary device teaching (metered-dose inhaler, spacer, diskus, compressor, nebulizer)” Teach et al. 2006
Shaping Knowledge: Information about antecedents	“The aim of the community health centre programme was to educate patients in basic pathophysiology of asthma, (b) definition and avoidance of triggers, (c) how asthma medications work...” Garrett et al. 1994  “The education online included video explanations of asthma and why it develops, how to mitigate impact on activities, use of controller and rescue medications, triggers, smoking, pets, action plans, and peak flow meters...” Wiecha et al. 2015



## 4.4 Discussion

### 4.4.1 Summary of the evidence

This chapter summarises what has been published about effective interventions to increase adherence in children with asthma, considering the reliability of the studies and whether the behaviour change framework and techniques were used in a clinically meaningful way. Previous reviews of adherence interventions in adults and children have shown that only half of interventions are effective at increasing adherence (Normansell et al., 2017). In line with previous literature, this systematic narrative review found that only half of the included studies (9/18) were effective at significantly increasing adherence (Burgess et al., 2010; Chan, Stewart, et al., 2015; Chatkin et al., 2006; Garrett et al., 1994; Guendelman et al., 2002; Julious, Horspool, et al., 2016; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016). However, this review then went further to explore the crucial factors for an effective intervention to increase adherence.

Of the 9 studies that were effective, 8 were considered high reliability (Burgess et al., 2010; Chan, Stewart, et al., 2015; Chatkin et al., 2006; Garrett et al., 1994; Julious, Horspool, et al., 2016; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016). By comparing the effective and reliable studies (8/18) (accurate asthma diagnosis, objective adherence measure and low/moderate RoB) to the unreliable or ineffective studies this review enables tentative conclusions to be drawn for the development of future interventions. There appeared to be no difference between high reliability studies that were effective or not, in terms of the intervention context (such as country or healthcare context). However, within the high reliability group (8/18) all the interventions conducted in a primary care setting were effective, although the small numbers included in this review (n=2) prevent firm conclusions from being drawn. Two of the three high reliability but ineffective studies were not tailored to the patient group (Baren et al., 2006; Gustafson, M, et al., 2012). This highlights the importance of tailoring as it has been well reported that tailoring is associated with more effective interventions (Nunes et al., 2009).

The findings of this review support the use of technology as a channel to deliver the intervention including EMDs for measuring adherence and website and telephone calls for delivering the interventions. Based on this review healthcare practitioner type is not as important as the use of face-to-face contact while providing digital interventions. This finding supports a previous recent review based on digital interventions in long-term

conditions (Lycett, 2017). Healthcare professionals or researchers planning an adherence intervention should therefore consider the amount of contact alongside digital interventions as a key component to future effectiveness.

In terms of content, five out of the seven reliable effective interventions were coded as Level 3 (Burgess et al., 2010; Chatkin et al., 2006; Garrett et al., 1994; Morton et al., 2017; Teach et al., 2006). Three high reliability and effective studies did not meet the criteria for Level 3 PAPA (Chan, Stewart, et al., 2015; Julious, Horspool, et al., 2016; Vasbinder et al., 2016). Overall only two of the highly reliable studies based on Level 3 PAPA did not result in effective interventions (Mosnaim et al., 2013; Wiecha et al., 2015). The two studies had high risk of bias and involved limited face-to-face contact with a healthcare professional.

PAPA is easy to apply when developing an intervention because it simply highlights the effective minimal ingredients for change in adherence. This review found that currently developed interventions in this area largely neglect the role played by patient beliefs about asthma and ICS. Research shows that these are often important determinants of non-adherence in adults (Chapman et al., 2015; Mes et al., 2018) and there is emerging evidence of relevance in the paediatric population (Yilmaz et al., 2012): in terms of parental beliefs (Conn et al., 2005; Klok, Kaptein, Duiverman, et al., 2015) and adolescent beliefs (De Simoni et al., 2017; Pearce et al., 2018). Patients' perceptions that are of particular importance are beliefs about their personal need for treatment (even in the absence of symptoms) and concerns about steroids. These issues are important because necessity and concern beliefs may be a precursor to adherence as they influence the motivation to adhere to the treatment (Foot et al., 2016; Horne et al., 2013).

The most common BCTs used in effective interventions within the review were association-prompts/cues (e.g. reminders) (Burgess et al., 2010; Chan, Stewart, et al., 2015; Chatkin et al., 2006; Morton et al., 2017; Vasbinder et al., 2016); feedback and monitoring (Burgess et al., 2010; Chan, Stewart, et al., 2015; Morton et al., 2017; Teach et al., 2006; Vasbinder et al., 2016); pharmacological support (Burgess et al., 2010; Chatkin et al., 2006; Teach et al., 2006); shaping knowledge instruction on how to perform a behaviour (Burgess et al., 2010; Garrett et al., 1994; Morton et al., 2017; Teach et al., 2006) and information about antecedents (Garrett et al., 1994). Each BCT was found to be most effective as part of complex interventions when tailored to the patient. It is currently unknown how many and what combination of BCTs are likely to increase the effectiveness of an intervention. Equally,

few BCTs of the 93 listed within the BCT taxonomy (v1) were used, or could be coded, within the included interventions. However, this review is the first to show that certain BCTs are important to consider when developing a tailored intervention for increasing adherence in children with asthma.

#### 4.4.2 Strengths and Limitations

Due to the heterogeneity of the data, limited availability of author's raw data and the small number of eligible studies a meta-analysis was not possible. Only three studies would have been able to be included but there were significant differences between study methodologies such as the setting of the intervention and the adherence outcome measures used (Canino et al., 2016; Chan, Stewart, et al., 2015; Vasbinder et al., 2016).

This systematic review focuses on adherence as an outcome as opposed to clinical health outcomes as unlike within the adult literature, few studies in paediatric asthma include both adherence and clinical outcomes. Focusing on adherence therefore allowed a greater number of studies to be synthesised. Ideally intervention studies should have an objective reliable clinical outcome as well as an adherence outcome to account for any inaccuracies of the adherence measurement and for those patients that may have low adherence despite good control (likely over-medicated). However, unlike in some other conditions, adherence to ICS has been shown to be highly correlated with objective clinical outcomes (Murphy, A, et al., 2012) and therefore the use of adherence as a primary focus for this review is useful as a proxy for a clinical outcome.

The majority of the interventions had moderate risk of bias which was increased by the high level of performance bias which is common in behavioural interventions. This is due to the lack of ability to blind patients and personnel to the purpose of the study, however, many of the studies tried to counteract that using deception (where ethically permitted). This included objective electronic monitoring devices and additional measurements to distract from the adherence data collection. The studies often had low selection and detection bias but as the lack of adherence to modern recommended reporting guidelines such as CONSORT (Turpin, 2005) was often high, as was reporting bias, and attrition information was either unclear or high. This review therefore recommends using objective methods of measuring adherence, and also for the diagnosis of asthma, alongside blinding which may help to increase the reliability of future intervention findings.

One further limitation is not excluding interventions where the diagnosis of asthma reported was not rigorous, for example where primary care medical records were used to identify those with asthma but where the prescribing of ICS was not used as a criterion or where a physician diagnosis was given without objective measurement of asthma. Future intervention studies should ensure the children recruited really have a reliable diagnosis of asthma and objective measurements of adherence so the true effectiveness of the interventions can be determined (Pearce & Fleming, 2018). Therefore, this review considered the reliability of the evidence for both the diagnosis of asthma, the measurement of adherence and the risk of bias of the studies in the focused narrative review of the literature and in drawing conclusions.

#### 4.4.3 Conclusions

This systematic review shows that half of all interventions that have been carried out to increase adherence to ICS in children with asthma have been effective. In studies that were effective psychological theory can be helpful in evaluating the reasons behind their effectiveness including assessing the content of the interventions. Using the PAPA framework, we found that targeting perceptual and practical factors around non-adherence in a tailored approach was more effective than a non-PAPA approach or using partial PAPA (targeting both perceptions and practicalities but without a tailored approach). We also identified the most frequent BCTs used in effective interventions, which were Reward and Threats (Practical), Prompts/cues (Practical), Feedback and Monitoring (Perceptual), Pharmacological support (Practical) and Shaping knowledge (Perceptual). These were particularly effective when used in a complex, tailored intervention. However, several studies were poorly reported, lacking detail on how an asthma diagnosis was made, how adherence was measured, whether or not blinding of the participants was conducted, attrition bias and limited available data on the context of the interventions making BCT coding and also replication of the context difficult. Future work should focus on addressing these issues as well as using high reliability diagnosis and adherence measurement tools to increase the reliability of an effective or ineffective intervention result.

This chapter has evaluated previous literature to explore the content of effective interventions to increase ICS adherence in children with asthma. It was not possible to conduct a systematic review with patients with problematic asthma from a tertiary care setting as so few studies have been conducted in this group of patients. Therefore, it was

important that this PhD then focused on exploring the specific content for the intervention including the determinants of nonadherence for this group. As Chapter 2 highlighted objective measures such as EMD are indicated as one of the most reliable measurement tools for adherence to ICS and therefore the remaining chapters used Smartinhaler™ EMDs to measure adherence. As Chapter 3 and 4 have shown tailoring is extremely important in developing an effective intervention and therefore the following chapter will explore patients' patterns of ICS use to begin to understand how ICS are being used and whether based on these there are different groups of patients that we could target within a tailored intervention. Chapter 6 will then lead on from this work in qualitatively exploring these patterns with patients along-side questions related to their perceptual and practical barriers for adherence to ICS.

### **5.1 Introduction**

Although previous studies have used EMDs to monitor adherence, the adherence data have been used as an outcome to compare patients' adherence levels following an intervention rather than to investigate the underlying behaviours or patterns of non-adherence. EMDs may be useful in investigating patterns of adherence in children as they allow researchers to collect detailed inhaler use data. Patients give different reasons for non-adherence, and not all patients behave in the same way therefore patterns in EMD adherence data may give insights into these behaviours.

Exploring patterns of adherence is important as previous research has highlighted several temporal factors which relate to adherence in asthma in adults and within other conditions. These factors include: decreased effect of adherence monitoring (Hawthorne effect) over time (Konstantinou, 2012), a preference for lower dosing frequency (Chapman et al., 2017), poor routine related to forgetfulness (Holley et al., 2017) and seasonal variations such as lower adherence in the summer holidays (Julious, Horspool, et al., 2016; Turi et al., 2018). Patterns of use may also vary with asthma severity and with a comorbidity that is closely related to asthma such as atopy (Newby et al., 2014). These factors have often been discovered through qualitative research but patterns of adherence have not been explored quantitatively through EMD data within this population. Furthermore, even when participants know they are being monitored adherence remains sub-optimal in the majority (Jochmann et al., 2017). There are many reasons for poor adherence and understanding these is important in order to develop effective interventions and tailor these to the individual.

This study sought to analyse patterns of non-adherence during a period of electronic monitoring to explore differences between patients' adherence behaviour. This study is novel as it aimed to use previously collected Smartinhaler™ data to explore patterns of adherence behaviour in ICS use in children who have problematic asthma. Subsequently, these patterns were explored with non-adherent patients within a qualitative study. Six key hypotheses were tested:

1. That adherence will reduce significantly over the period of electronic monitoring due to a diminishing Hawthorne effect

2. That there will be different clusters of adherence behaviour over time including a group of high and low adherers
3. That nonadherence will increase at the weekends compared to during the school week related to a lack of routine
4. That children will take their inhaler once or more a day more often than as prescribed
5. That children's adherence will differ across the months and seasons of the year
6. That severe therapy resistant asthma patients will have different patterns of adherence to those with difficult and more moderate asthma.

## 5.2 Methods

### 5.2.1 Study design and Study Population

This study was a secondary analysis of Smartinhaler™ data collected as part of a prospective observational cohort study (Jochmann et al., 2017) which recruited children from the outpatient department of the Royal Brompton Hospital, a tertiary care hospital. Data were collected from patients between August 2015 and February 2016.

All of the participants were diagnosed with asthma at the Royal Brompton Hospital (RBH) on one or more of the following criteria:

- Documented bronchodilator reversibility ( $\geq 12\%$ )
- Recorded evidence of spontaneous variation in FEV<sub>1</sub> ( $\geq 12\%$ ) in the past year
- Airway hyper-responsiveness confirmed by direct or indirect challenge tests

Patients were between 5-17 years of age and were recruited as either having severe therapy resistant asthma (STRA), difficult asthma (DA) or mild-moderate asthma. STRA and DA were defined as previously described in Chapter 1.5. Mild-moderate asthma was defined as patients having a prescribed dose of  $\leq 250\text{mcg FP}$  or  $\leq 400\text{mcg BUD}$  (or equivalent) per day and only taking one (or no) additional controller medication. Asthma control in the mild-moderate group was either well or partially controlled according to GINA guidelines (GINA., 2012). Children in the DA or STRA groups had been assessed using the RBH difficult asthma protocol. The protocol involves nurse home visits and visits to the patient's school as well as hospital based clinical tests to assess severity, adherence, psychosocial factors and environmental factors relevant to the patient's asthma control (Bracken et al., 2009; Sharples et al., 2012). Those classified as DA were found to have modifiable reasons for poor adherence whereas those with STRA had ongoing poor control despite attention to the basics of asthma management (such as adherence). For further clinical information

regarding the sample please see the original published article (Jochmann et al., 2017). The primary study was approved by the NRES Ethics Committee London-Westminster.

All children attended a baseline visit where a Smartinhaler™ (Adherium, New Zealand) adherence monitoring device was fitted to their preventer inhaler after their inhaler technique was checked by a specialist nurse. Patients were followed up at the end of the 8-16 week monitoring period and their adherence data were downloaded from the Smartinhaler™ microchip. Daily adherence was calculated by assessing the percentage of controller medication taken in relation to the number of doses prescribed. This was a number from zero to a maximum of 100% for each day with over-doses excluded. Mean percentage adherence of the daily figures were used for some of the analysis e.g. mean monthly adherence and mean day of the week adherence. Good adherence was defined as >80% of the prescribed doses taken (actuated). These definitions are consistent with previous work with EMD in asthma (Chan, Stewart, et al., 2015; Jochmann et al., 2017; Morton et al., 2017) (see Chapter 2:).

Participants and their parents were told that the Smartinhaler™ would record the total number of actuations per day. Patients were not deceived in any way and were also informed that the doctors and nurses would download and look at their data when they returned to clinic. The data for this secondary analysis were collected over a period of up to 200 days within a previous study (Jochmann et al., 2017)(see the results section for further details 5.3).

### **5.2.2 Statistical Analysis**

The sample size was opportunistic, since there were no published data to inform a power calculation. I assessed missing data including missing data patterns and the normality of the data was checked Sapiro-Wilk Normality test. All statistical tests were carried out using IBM SPSS statistics version 22. The adherence data were not normally distributed so nonparametric analyses were conducted where possible and medians and interquartile ranges reported. Generalised linear models and cluster analyses assume a normally disturbed data set, however, as the data had no extreme outliers these analyses were conducted consistent with advice from the AUKCAR statistician, Dr Christopher Newby.



The following analyses were undertaken:

### 5.2.3 Adherence over the monitoring period

To test hypothesis one that adherence will reduce significantly over the period of electronic monitoring data for each month of the monitoring period were compared using Friedmans test. Wilcoxon signed-rank test was then used as a post-hoc test of the difference between each of the three months. The first 12 weeks of monitoring were included and analysed as 4 week blocks.

### 5.2.4 Cluster analysis

To test hypothesis two that there will be different clusters of adherence behaviour over-time including a group of high and low adherers a factor and a two-step cluster analysis were conducted to explore patterns of non-adherence over time. First a principle components analysis was conducted to explore how the data points were correlated across time points. Factors with eigen values over one and components with a factor loading over 0.7 in the rotated component matrix were carried forward into the cluster analysis. The factors taken forward into the two-step cluster analysis were dummy variables that represent the data over time.

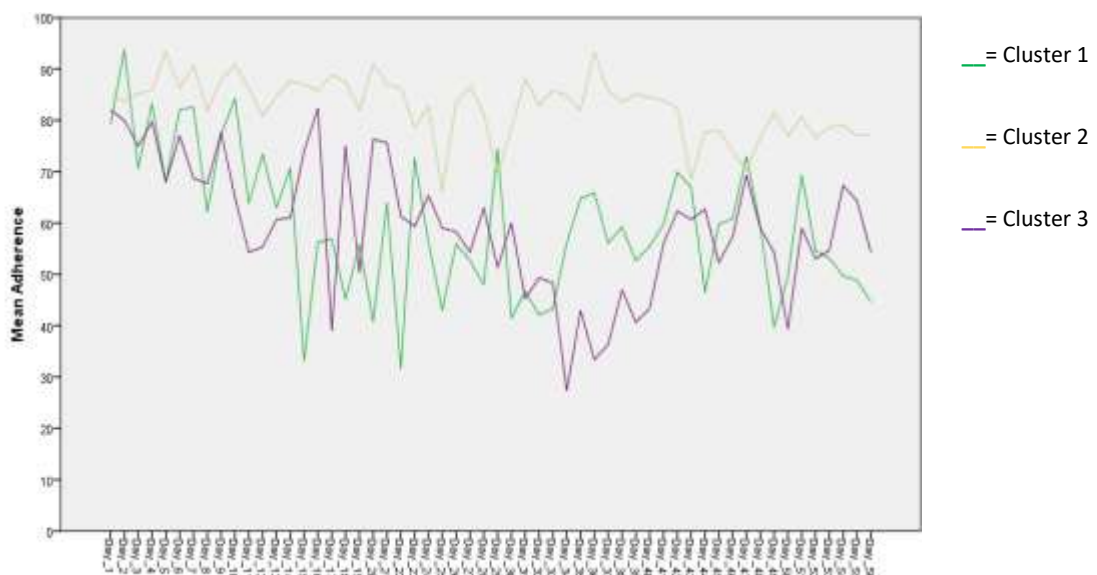


Figure 18: Cluster analysis all data

The initial factor analysis revealed only two factors that were considerably contributing to the variance in adherence over time. When these two factors were taken into a cluster

analysis only two clusters which were found: continual high adherence and continual low adherence with no temporal differences. Based on this initial exploration it became evident that all participants were behaving similarly at the beginning of the monitoring. The first 10 days of data were biasing the cluster analysis as there was little variance between participants percentage adherence within the first 10 days of adherence monitoring (high adherence across participants over the first 10 days of monitoring; (Figure 18) and therefore the first 10 days of data were removed. Data were included up to day 56 of adherence monitoring as the amount of data (where patients had differing end points for their period of electronic monitoring) reduced significantly after this point (days 11-56 of the adherence monitoring period were included). The factor analysis and cluster analysis were then repeated. The cluster model with the best cluster quality measured by the silhouette measure of internal cluster cohesion and external cluster separation will be reported. The closer this figure to one the stronger the cluster model (0.5-1 indicates a good cluster quality).Weekend versus weekday adherence

To test hypothesis three that nonadherence will increase at the weekends compared to during the school week mean adherence for each day of the week was calculated for each participant and then the adherence means for the days of the week (Monday-Sunday) were compared using the Friedman test. Then nights not preceding a school day (Friday-Saturday) were compared versus weekday (Sunday-Thursday data) adherence data were compared using Wilcoxon signed-ranks test. All 93 participants' data were included in the analyses.

#### **5.2.5 Once daily adherence**

To test hypothesis four that children will take their inhaler once or more a day more often than as prescribed data for ninety-two children who were prescribed twice daily ICS (n=1, prescribed once daily) were analysed. Each participant's data for all the days where they took at least one dose of their inhaler were summed. The sum was then transferred into a percentage based on the total number days collected per participant. The median adherence rates which have been gathered from the Jochmann et al. (2017) work were compared to the results for an at least once daily dose (see Table 10). Dichotomised groups were also compared for those that were 100% adherent against those that were not and those that were adherent or not using an 80% cut off point (in line with asthma adherence literature (McNally et al., 2009). The analyses were Wilcoxon signed-rank and non-parametric Fisher's exact test.

### 5.2.6 Seasonality and adherence

To test hypothesis five that children's adherence will differ across the months and seasons of the year an independent sample Kruskal-Wallis test was conducted to explore the difference in adherence between the months of the year and a separate analysis for the four seasons of the year. As participants adherence was monitored over different months of the year repeated measures analysis was not able to be conducted (the data not recorded appears as missing data).

### 5.2.7 Severity and adherence

To test hypothesis six that patients with severe therapy resistant asthma will have different patterns of adherence to those with difficult and more moderate asthma a Kruskal-Wallis test was conducted to explore differences between severity groups and adherence. Four severity groups were used to categorise patients' asthma severity by Jochmann et al. (2017) for the previous primary data analysis. Patients were categorised as having STRA when they had poor asthma controlled while prescribed high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids despite potentially modifiable factors previously being addressed (ERS/ATS definition)(Chung et al., 2014). Patients were categorised as having DA when they presented with poor control despite either previous or current high-dose ICS but were found to have modifiable factors which have not yet been addressed such as poor medication adherence, which could account for their poor control. Patients were categorised as having Mild/Moderate asthma when their asthma was partially or well controlled according to GINA (2012) while on a moderate dose of ICS and only one controller medication (including long-acting  $\beta$ -agonists, leukotriene receptor antagonists or theophylline). New referrals are patients that were newly referred to the hospital and had not been classified. The relationship between atopy and adherence was also tested using a Kruskal-Wallis test. Atopy was included in the analysis as it was hypothesised that those with atopy would be more likely to have hay fever (one type of atopy) and hence be more symptomatic (and thus adherent) over the hay fever season (spring/summer). A generalised linear model was then used to explore the relationship between adherence, severity atopy and the seasons.

## 5.3 Results

Useable data were available for 93 participants and are included in each of the following analyses. Monitoring data was for a mean of 92 (range=56-200) days. Participants mean age

was 11.9 years old (SD=3.1). Sixty-two participants were male (67%). Median percentage adherence was 74% (Range=21–99%). The sample included patients of different ethnicities. Fifty seven percent of the sample were White British, 17.2% were Black/African British, 15.1% were Asian, 6.5% were Mixed race (Caucasian/Black), 1% were Hispanic and 3.2% were categorised as other.

There was no significant difference in median percentage adherence over the whole monitoring period based on gender ( $p=0.32$ ) or ethnicity ( $p=0.17$ ). Age was not significantly correlated with adherence ( $r_s=-0.07$ ,  $p=0.32$ ).

### 5.3.1 Adherence over the monitoring period

As hypothesised a Friedmans test showed that adherence decreased over the three-month monitoring period ( $p<0.001$ ) (Figure 19) and a post-hoc Wilcoxon signed-rank test showed adherence to be significantly higher during the first month of monitoring (Median=78%, IQR=62.5-88.3) than in the second month of monitoring (Median=70%, IQR=50-88.3)  $p<0.001$ . There was also a significant reduction between month 2-3 (Median=67%, IQR=33.6-86.1)  $p=0.006$ .

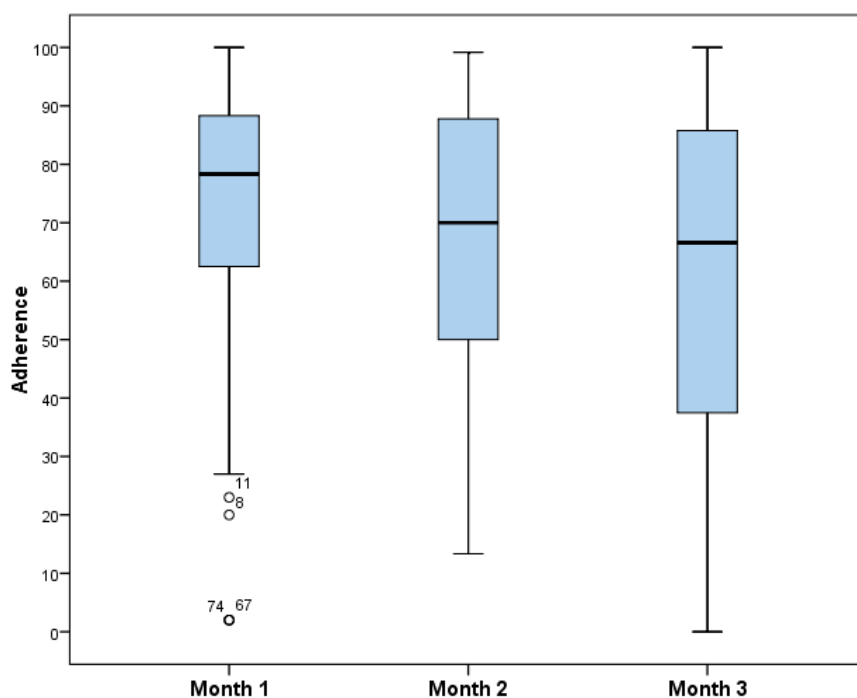


Figure 19: A box and whiskers plot of monthly adherence over the monitoring period showing median, IQR and outliers (outliers as ○)

### 5.3.2 Cluster analysis

The factor analysis revealed three factors with eigen values over one. Both the scree plot and the rotated components matrix confirmed that only two factors were relevant with a factor loading of over 0.7. The third factor only represented a small amount of variation across all the days and therefore was not included in the cluster analysis. As a result, only two independent factors were taken forward as dummy variables representing the data (11-56 days) into the cluster analysis. The Two-step cluster analysis including 93 participants' data revealed the model with the best fit had three clusters. The model showed good cluster quality with the silhouette measure of cohesion separation being 0.7. The three clusters were: (Figure 20):

1. Patients whose adherence began high but then dipped after a month for around 10 days and then increased again towards the end of the two-month monitoring period (Mean adherence=63%, SD=16). Nineteen percent of the participants were within this cluster
2. Patients whose adherence was consistently highest (adherence above 65%) across the monitoring period (Mean= 81%, SD=15). Fifty-six percent of the participants were within this cluster.
3. Patients whose adherence began high but then reduced to low adherence across the time period (Mean= 49%, SD=22). Twenty-five percent of the participants were within this cluster.

The cluster analysis hypothesis was partially supported in that a group of patients with higher adherence is evident. However, there was no one group whose adherence remained low from the start of the monitoring period to the end and the exploratory cluster analysis found two behavioural patterns related to lower adherence over time.

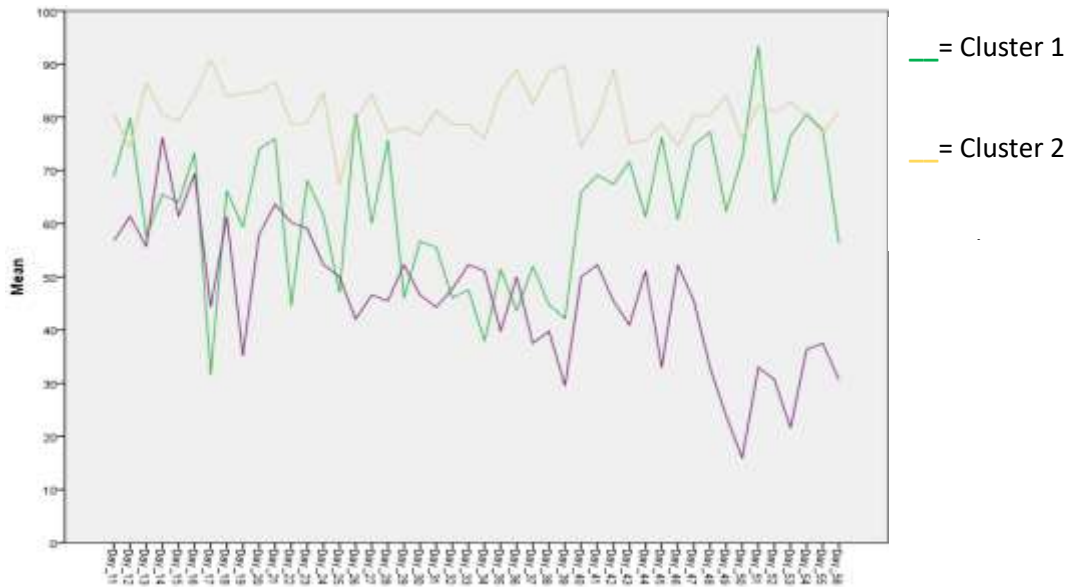


Figure 20: Adherence clusters based on daily mean adherence

### 5.3.3 Weekend versus weekday adherence

A Friedman’s test revealed no significant difference between daily adherence across days of the week ( $p=0.224$ ). This findings did not support the overall hypothesis related to weekend adherence however in line with the literature regarding the disruption of routine, there was a trend towards lower adherence on Friday and Saturday (Table 9 and Figure 22).

Table 9: Median and Interquartile Range for each day of the week

Day of the week	Median	Interquartile Range
Monday (1)	78.06	54.68- 90.0
Tuesday (2)	78.87	56.38- 89.23
Wednesday (3)	77.96	53.78- 88.54
Thursday (4)	77.18	55.14- 88.35
Friday (5)	66.43	48.66- 85.83
Saturday (6)	72.05	51.72- 84.12
Sunday (7)	73.97	57.69- 89.02

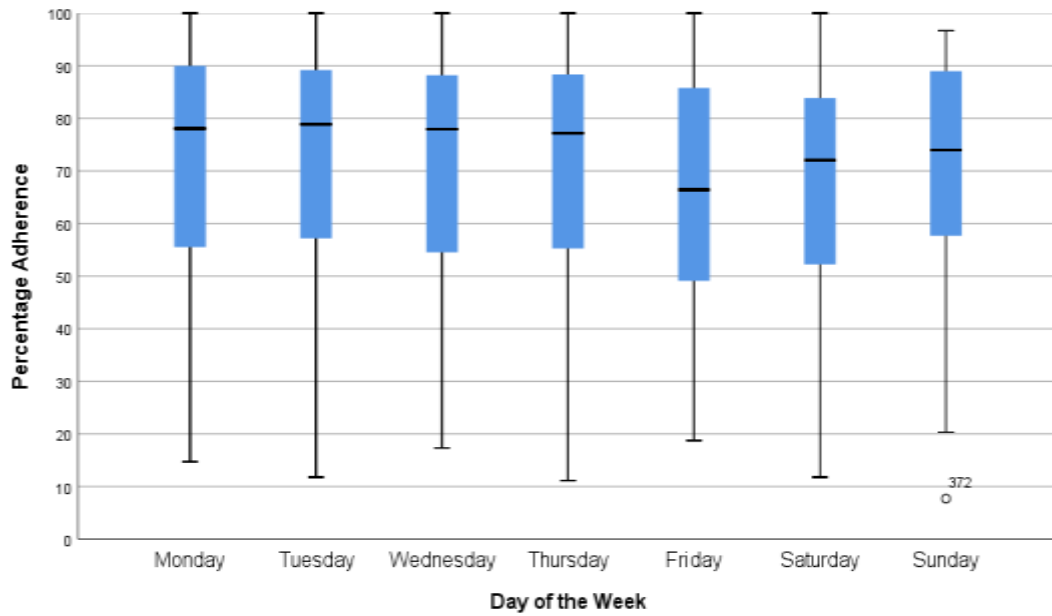


Figure 22: Box and whisker plot showing the percentage adherence for each day of the week

A post-hoc Wilcoxon-signed rank test was conducted which revealed a significant difference ( $p=0.006$ ) between two groups (Sunday to Thursday and Friday-Saturday (Table 9 and Figure 21) with Friday-Saturday having significantly lower adherence (Median= 68.37%, IQR= 50-84.5) when compared to Sunday-Thursday (Median= 77.27%, IQR=55.67-88.89).

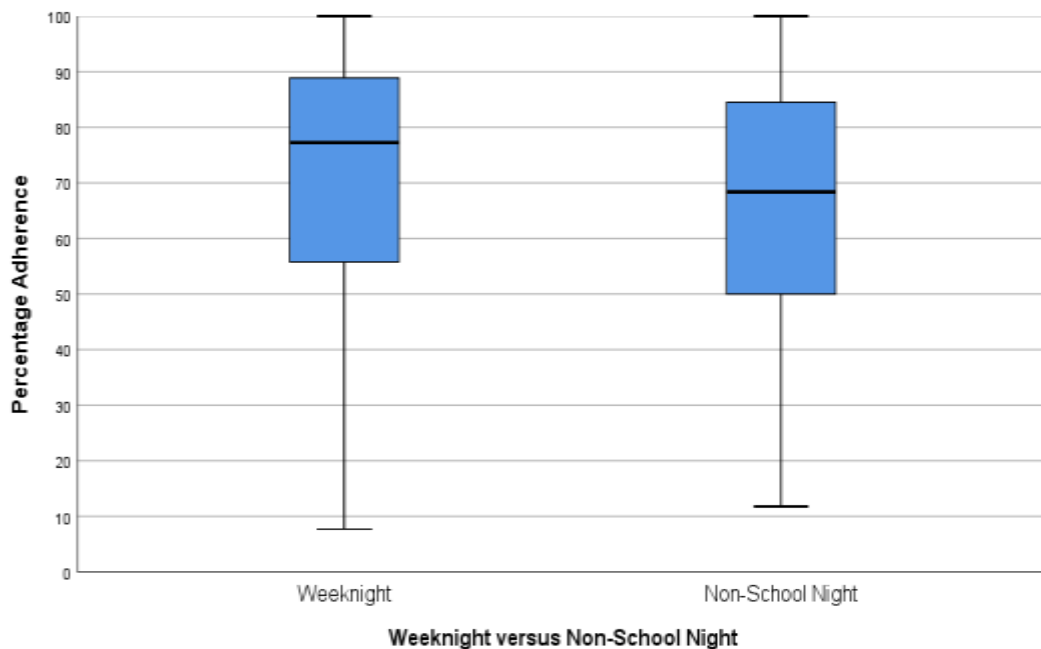


Figure 21: Box and whisker plot showing the percentage adherence for weeknights versus non-school nights

### 5.3.4 Once daily adherence

Data were analysed for a total of 92 participants as one patient was only prescribed once daily ICS and therefore excluded from this analysis. As hypothesised the Wilcoxon signed-rank showed a statistically significant difference between the two group medians ( $Z=-8.28$ ,  $p<0.001$ ) with adherence to at least a once daily dose being higher (Median=93%, IQR=76-98%) than adherence to their prescription (Median=74%, IQR=54-87%) (see Table 10). No patients took their inhalers exactly as prescribed every day but 11/92 patients took their inhaler at least once a day every day ( $\chi^2$ ,  $p<0.001$ ). Finally, using Fisher's exact test to investigate clinically relevant adherence cut-offs (which in asthma is more than 80%), 41% of patients were classified as good adherers from the adherence to prescribed dose group compared to 69% of patients who were able to take their inhalers at least once daily (80% or more of the time) ( $p<0.001$ ).

Table 10: Percentage adherence to ICS as prescribed compared to percentage of at least once a day use of ICS

Analysis	Adherence to "as prescribed" preventer inhaler	Analysis of at least once daily dose	Significance
Median and interquartile range adherence	74% (54-87%)	93% (76-98%)	$P<0.001$
Proportion of patients that took all their doses (100%)	0% (n=81)	12% (n=11)	$P<0.001$
More than 80% (adherence)	41% (n=38)	69% (n=63)	$P<0.001$

### 5.3.5 Seasonality and adherence

A Kruskal-wallis test revealed that there was no significant difference between the percentage adherence across the months of the year ( $p=0.67$ ) (Table 11).



Table 11: Monthly percentage adherence compared with a Kruskal-wallis test

Month	Median	IQR	Significance
January (1)	82.14	58.33 - 92.52	p=0.67
February (2)	77.87	50.00 - 88.73	
March (3)	67.00	45.00 - 87.10	
April (4)	74.09	51.56 - 88.96	
May (5)	84.66	58.29- 100.00	
June (6)	83.04	50.54 - 89.73	
July (7)	82.26	66.04 - 89.36	
August (8)	80.00	64.52 - 87.90	
September (9)	68.79	60.21 - 92.50	
October (10)	76.61	55.87- 95.16	
November (11)	75.00	56.04 - 87.50	
December (12)	72.97	48.65 - 87.99	

No significant difference was found in percentage adherence between the seasons (p=0.43). There was a trend towards adherence being highest in summer compared to winter, spring and autumn (Table 12 and Figure 23). These results did not support the hypothesis that there would be differences in adherence between the months and seasons of the year.

Table 12: Seasonal percentage adherence compared with a Kruskal-wallis test

Season	Median	IQR	Significance
Winter (1)	75.46	52.49 - 88.50	p=0.43
Spring (2)	64,85	55.16 - 85.37	
Summer (3)	80	68.29 - 87.98	
Winter (4)	76.27	59.95 - 88.67	

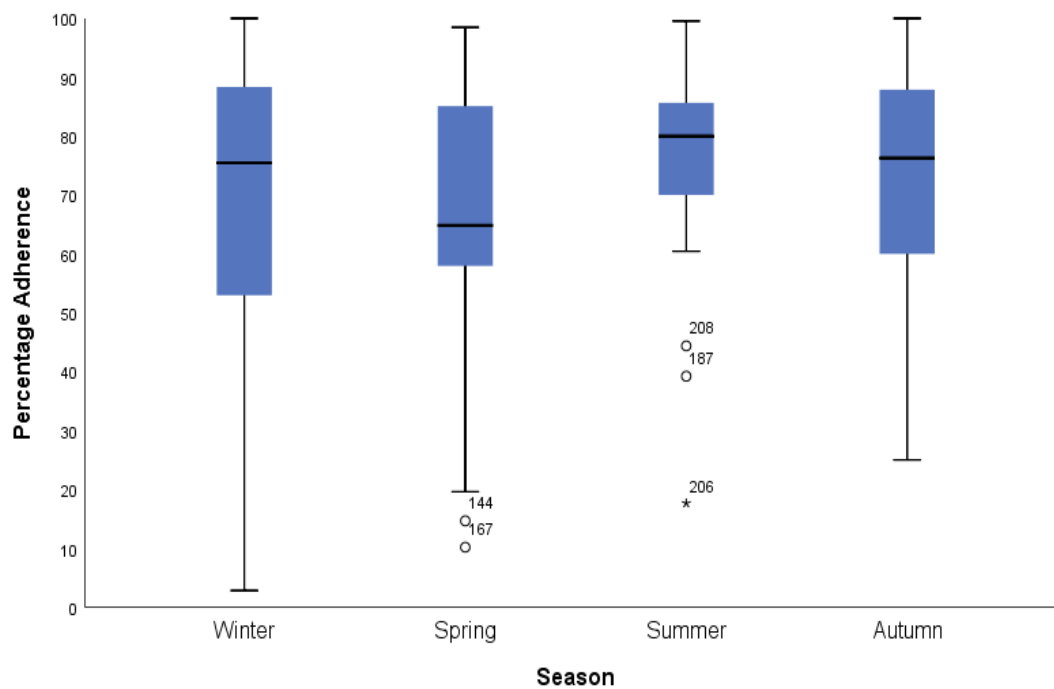


Figure 23: Boxplot of percentage adherence for each season

### 5.3.6 Severity, Atopy, Seasonality and Adherence

There was no significant difference found in adherence between the different severity groups ( $p=0.17$ ). Again, the hypothesis related to differences in adherence between severity groups was not supported. There was no significant difference found between atopy groups (atopy ( $n=89\%$  of patients) versus no atopy ( $n=11\%$  of patients) and seasonal adherence ( $p=0.99$ ).

In the exploratory generalised linear model (Figure 24) there was no significant interaction between atopy and severity of disease ( $p=0.53$ ). There was a significant interaction between the seasons, severity and adherence ( $p<0.001$ ). In spring there was significantly lower adherence than in autumn ( $p=0.03$ ) and patients with STRA had significantly worse adherence than those with difficult asthma ( $p<0.001$ ); mild/moderate asthma ( $p<0.001$ ) and new referrals ( $p<0.001$ ). There were significant interaction effects in spring with the three groups having significantly worse ( $p<0.001$ ) adherence in spring than those with severe therapy resistant asthma. In summer those with difficult asthma ( $p=0.02$ ) and those with

mild/moderate asthma ( $p=0.002$ ) had significantly better adherence than those with severe asthma

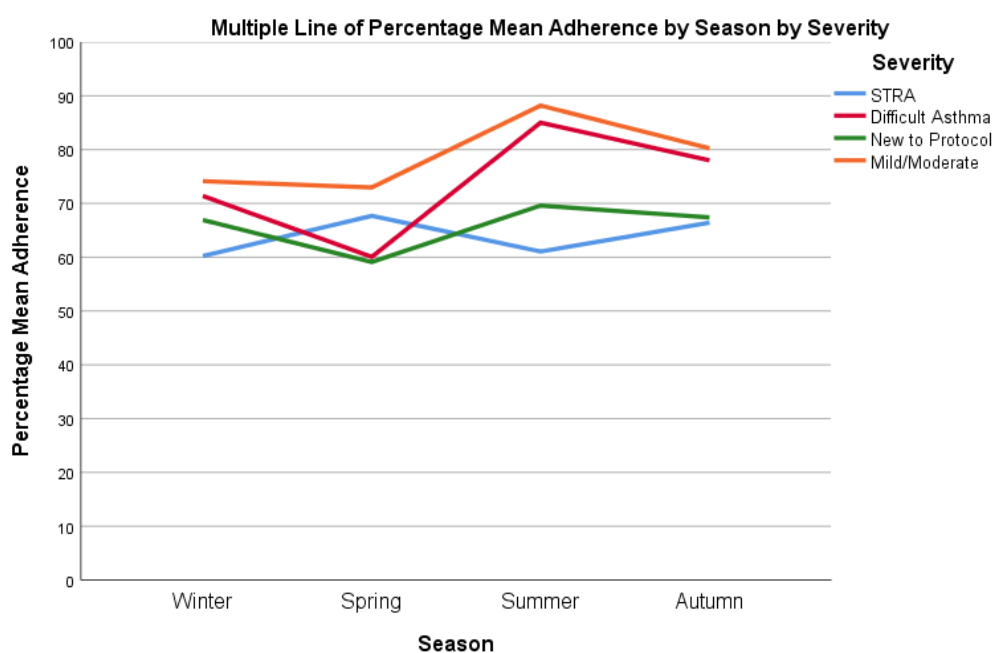


Figure 24: Seasonal effects on adherence with separate severity groups

## 5.4 Discussion

### 5.4.1 Main Findings

This is the first study to have extensively explored patterns of non-adherence to ICS in children with asthma using objective adherence electronic monitoring data. This is also the first study to quantitatively investigate adherence as a non-binary behaviour, recognizing that not all children with asthma are non-adherent in the same way. The results showed that in the cohort as a whole adherence decreased over time from the first to the third month of monitoring. Adherence was worse overall on non-school nights (Friday and Saturday) and more patients took their ICS doses once daily than as prescribed, twice daily. Seasonal differences were also found with patients having higher adherence during the summer than in spring, winter and autumn. Seasonal differences in adherence to ICS were influenced by severity of asthma, but not as hypothesized, by atopy. However, conclusions cannot be drawn in relation to atopy and adherence as the number of non-atopic patients was very small and therefore the analysis was not powered. Three clusters of adherence behaviour were also found within the data. These types of analysis are important in pediatric asthma as they allow us to explore relevant factors for consideration in personalised adherence interventions using objective data.

#### 5.4.2 Comparison with the literature

This study showed that even while being monitored patients' adherence is not optimized and that increases in adherence in response to adherence monitoring were short-lived as patients' adherence was found to reduce significantly over the monitoring period (without any feedback given). This finding is explained by the Hawthorne effect, a phenomenon whereby when individuals are monitored they modify their actions in line with the socially desirable behaviour (Adair, 1984) but with time they revert to previous behaviour. In this study it appears that participants take their inhalers more regularly when they know they are first being monitored but within a month the effect of being monitored declines and adherence levels fall towards their pre-monitored levels. However, even within the first month of adherence monitoring, arguably the time in which patients would be most motivated to adhere, median adherence in this population was 78% (IQR=62.5-88.3) and therefore in over half the cohort adherence was less than the <80% cut-off accepted as optimal.

This Hawthorne effect (Adair, 1984) has been noted in previous studies which monitored adherence to oral corticosteroids in patients with asthma (Konstantinou, 2012). Bender et al. (2008) found a significant decrease in adherence over time where feedback was not given. This corresponds to our study as feedback on adherence was not given until the end of the monitoring period when patients returned to clinic. Where previous studies in children with asthma have given feedback on adherence to ICS higher adherence levels have been maintained throughout the monitoring period (Burgess et al., 2010; Morton et al., 2017). Indeed authors attribute the sustained increase in adherence to regular feedback and discussion with the patients (Chan, Stewart, et al., 2015; Morton et al., 2017) as reminders alone have not had a significant effect on clinical outcomes and have shown a significant decline every two months over a six month monitoring period (Chan, Stewart, et al., 2015).

Routine, which has been linked to forgetfulness, has been cited as a key reason for non-adherence in children with asthma (Penza-Clyve, Mansell, & McQuaid, 2004). Patients in our study were found to have significantly worse adherence on Friday and Saturdays as compared to Thursday to Sundays. This may be because teenagers are more likely to socialise on Friday and Saturday evenings as they do not have school the next day. However, it should be noted that adherence was lowest on Fridays and that the Friday morning dose would be part of a regular school day and the Sunday morning dose would be considered part of a

weekend and therefore this does not fully account for the differences. This is explored further in the qualitative chapter as this was not explored quantitatively within this chapter. Based on the interviews with CYP from this population reported their ICS routines are often disrupted by weekends, summer holidays or a change of environment (Pearce et al., 2018). It is difficult to reflect this granularity in the quantitative data however, it is discussed further as part of the qualitative interviews. Routine and child-raising issues have been previously stated as nonintentional barriers to ICS treatment in children with asthma (Klok, Kaptein, & Brand, 2015) as well as specifically the weekend in patients age 12-16 years old (Koster, Philbert, de Vries, van Dijk, & Bouvy, 2015). This thesis however is the first to show this pattern with quantitative data using objective electronic monitors in children with asthma.

Interestingly participants frequently took their inhaler once a day rather than twice a day as prescribed. To establish the reasons behind this pattern of behaviour further qualitative work is necessary. It could be that this pattern is due to unintentional non-adherence whereby the patient has a poor routine and therefore forgets the second dose or due to intentional non-adherence related to their beliefs about the medicine either that the higher dosage is not necessary or that they have concerns over taking so much ICS (Chapter Results 6.3). No patients took their inhaler every day during monitoring as prescribed as compared to a significantly greater proportion of patients who took their inhaler at least once a day every throughout the monitoring period. Previous patient preference research has shown that a large proportion of patients (73.5%) would prefer an effective once daily treatment (Chapman et al., 2017). Although this study alone cannot be used to advocate the use of one dose daily medication as the consequences of missing the dose would be more serious (e.g. no medication for 48 hours as opposed to 24 hours with a twice daily dose.)

There were no significant differences in adherence across the months of the year or the seasons (not including severity as a variable). This is unexpected as previous research has found adherence to be lower in the summer when potentially symptoms were less frequent and routine was poor (Julious, Horspool, et al., 2016). The Julious et al. study (2016) was conducted as adherence was suspected to be low in children in the summer holidays leading to peak in unscheduled hospital attendance in September. The simple intervention encouraged parents and children, aged 5-16 years old, to collect their medication over summer via a letter from the GP. The intervention successfully increased adherence (measured by prescriptions pick-up in August), although unscheduled visits were not decreased in September. Our findings contrast that of Julious et al. (Julious, Horspool, et al.,

2016) as no significant difference was found in adherence across the months of the year. This could be due to the setting from which these data are drawn (Primary care versus Tertiary care) with patients in this sample potentially having more severe symptoms in the summer and therefore being more adherent than in other groups, due to the different measurements of adherence (prescription pick-up compared to objective electronic monitoring data) or due to the high atopy level within this group (e.g. grass allergy).

In the current study atopy was common (89% of patients atopic) and the non-atopic group was small therefore this analysis was underpowered. In other studies participants have been found to be more likely to take their ICS alongside their hay fever treatment and in relation to an increase in symptoms (Durham, 1998; Halm et al., 2006). Unfortunately, specific allergen data were not available in this secondary analysis which would allow for further understanding of the atopy data. To be able to understand seasonal patterns of adherence in relation to allergen exposure, specific sensitization data would be needed i.e. if during the pollen season adherence increases. Ideally, this study would have also included a measure of asthma control to enable exploration of how asthma control influences the episodic treatment of asthma. The idea of no symptoms no asthma (Halm et al., 2006) was explored by analysing adherence rates, severity and atopy in children with asthma. Patients with early onset asthma who are atopic were investigated within this study. Seasonal variations in adherence were hypothesised to also be related to an episodic understanding of asthma by patients influencing their daily adherence to ICS, whereby patients when feeling well in certain seasons stop taking their ICS or reduce the dosage (Halm et al., 2006). However, we did not find an interaction between asthma severity and adherence or atopy and adherence. This analysis was underpowered and was likely to be nonsignificant due to so few of the participants being categorised as non-atopic (11%).

Severity alone was not found to significantly affect adherence however when severity was included in a generalised linear model with season and adherence different patterns of adherence emerged. There was an interaction effect between severity and the season as adherence was significantly different and lowest in the STRA group in summer compared to the other groups and the other groups' adherence was significantly lower in spring compared to STRA. This is the first study to show differing adherence behaviours within the aforementioned asthma severity groups. However, these analyses were exploratory and will need confirmation.

The cluster analysis revealed three groups related to their adherence over the monitoring period (11-56 days of monitoring; higher adherers; those whose adherence began high then dipped in the middle of monitoring before increasing again towards the end of monitoring and those that began high and lowered gradually). The third group, poor adherers that began high and reduced over time, are perhaps influenced by the Hawthorne effect (Adair, 1984) and the effect of approaching outpatient appointments on their behaviour or they could simply be patients that treat their asthma episodically in relation to worsening symptoms (Halm et al., 2006) perhaps due to allergen or virus exposure. However, these data were not available and therefore these interactions could not be tested.

#### **5.4.3 Strengths and limitations of the study**

This study is the first to explore patterns of adherence in children with asthma using a robust prospective follow-up of patient adherence measured using a well validated objective electronic measure (Smartinhaler™). However, Smartinhaler™ do have some limitations such as only measure actuation of the inhalers and therefore they can be manipulated by patients. The Smartinhaler™ does not measure inhalation and therefore it cannot measure if the inhaler was taken or if technique is correct. Newer devices are in development that also monitor inhalation and suggest that adherence is on average over 20% lower when monitored in this way (Sulaiman, Mac Hale, et al., 2016; Sulaiman, Seheult, et al., 2016). This could impact on the patterns of non-adherence found within this analysis which is why it is always important to use the most objective and accurate measurement tool for adherence that are currently clinically available. Indeed, the included participants had also received a diagnosis of asthma from a specialist respiratory physician using objective diagnosis tests.

The main limitation is that it was a retrospective analysis and some of the data which could have been used to explore interactions further (such as allergen load, specific allergen sensitisation, viral infections) were not available. However, by basing a qualitative study on objective and granular Smartinhaler™ data these influences could be explored further with the individual.

A further limitation to this work is the lack of exploration of clinical factors such as FeNO or FEV<sub>1</sub> in relation to patterns of adherence. However, adherence to ICS and clinical outcomes of asthma are reported to be highly correlated within previous literature and therefore this

study, in the first instance, focused solely on behaviour outcomes (Murphy, Proeschal, et al., 2012).

#### 5.4.4 Conclusions

The patterns of nonadherence in this study are likely to represent common adherence patterns in all patients with asthma, however, the reasons for these patterns (intentional or unintentional) need to be explored further using qualitative methodologies. Nevertheless, this work does highlight key areas that clinicians can discuss with patients within their consultations in relation to nonadherence. The findings can be used as a factual basis to normalise discussions of nonadherence and to help to focus discussions about non-adherence.

These findings suggest that using a Smartinhaler™ alone to monitor patients will not sustainably improve adherence in all patients without additional intervention. Instead Smartinhaler™ should be used to determine targets for personalized, tailored interventions. Clinicians and intervention development teams should also consider the dose and treatment burden when discussing medication use with patients and aiming for optimal adherence. This research also highlights the need for tailoring future adherence interventions as different individuals have their own patterns of nonadherence with specific reasoning behind them. For example, some patients may respond well to adherence monitoring alone e.g. cluster 2 (consistently higher adherence) and some patient may need additional interventions to increase their adherence e.g. cluster 1 and 3, potentially both targeting perceptual and practical barriers to adherence.

The next chapter will explore these patterns of non-adherence with a sample of patients who had been identified as non-adherent over a period of EMD (<80%). Without the patient perspective behind why they are using their ICS in the ways described above any intervention developed would be based on the researchers' hypotheses' regarding their reasoning for certain patterns of ICS use rather than being supported by the patients' perspective. Again, the research described in Chapter 6 will use EMD measuring adherence to ICS as the basis for the interviews and broaden the understanding of patients' illness beliefs, treatment beliefs and practicality barrier which underlie their patterns of ICS adherence.



## Chapter 6: The Patients' perspective of non-adherence

### 6.1 Introduction

To enable a deeper exploration of the results of the quantitative patterns of non-adherence highlighted within the previous chapter (Chapter 5:), qualitative research within the same population was necessary. Qualitative analysis is crucial to explore and understand the reasons why such non-adherence behaviours occur so that appropriate adherence support packages can be developed. Both pre-defined and newly emerging adherence determinants must be explored from the patients' perspective to create an effective intervention, suitable for this population, young people with problematic asthma. The barriers and facilitators for adherence to ICS must be explored within the specific patient group as they are likely to differ from other patient groups such as young people with mild or well controlled asthma or adults. Previous meta-analysis results suggest that adult patients with more severe diseases may be more likely to be non-adherent to their medication (DiMatteo, Haskard, & Williams, 2007).

A previous study in adults demonstrated that a concordance discussion could help to identify non-adherence and that adherence improved following the discussion (Gamble, Stevenson, & Heaney, 2011). The discussion consisted of the respiratory nurse communicating to the patient that they were found to be non-adherent to their preventer ICS inhaler and agreeing a treatment plan with the patient to increase their adherence. The concordance interview was assessed for the effect of three things: the fact that the healthcare team were aware of the non-adherence, the communication of the non-adherence to the patient and the concordance discussion content. Within the same study, after the initial concordance discussion patients who were still non-adherent were randomised to a psycho-educational intervention which led to a significant increase in percentage adherence to preventer ICS inhalers (37.3% versus 82.3%,  $p < 0.001$ ). Similarly, an intervention including a non-judgemental tailored discussion around EMD monitored adherence with paediatric patients with poorly controlled asthma, has been shown to both increase adherence (49% versus 70%,  $p < 0.001$ ) and significantly decrease hospitalisations ( $p \leq 0.001$ ) and courses of oral steroids ( $p = 0.008$ ) (Morton et al., 2017). Burgess et al. (2010) also showed a significant difference in adherence between the intervention and control group (79% versus 58%,  $p < 0.01$ ) in a study with a similar methodology involving non-judgmental non-adherence feedback however, differences in lung function post intervention did not reach significance

(13.8% versus 9.8%,  $p=0.9$ ), likely due a small sample size (Intervention group= 14 and Control group= 12) and lack of power. These finding provide support for a negotiated approach to adherence in which the views of the patient/parent are elicited (Horne, 2006). Negotiating treatment and tailoring support to the individual need was recommended in a comprehensive review of medication adherence in long term conditions (Elliott, Barber, & Horne, 2005). The review also advocated the PAPA. Central to this approach is the need to tailor adherence support to the individual by identifying and addressing both the perceptual barriers (e.g. beliefs about asthma and medication) and practical barriers (e.g. limitations in capacity and resources) that influence an individual's motivation and ability to start and continue with treatment.

Although previous work has investigated patient perceptions about adherence in asthma the research was conducted in younger children (age 2-12 years old) via focus groups with their parents and only in patients with mild/moderate asthma severity (Klok, Brand, Bomhof-Roordink, Duiverman, & Kaptein, 2011). This work found that objective electronically measured adherence rates were high in children aged 2-6 years who were prescribed ICS and that this was linked to parental perceptions regarding the child's need for the medication and their concerns about medication use. Although parental perspectives clearly influence younger children's perspectives about asthma treatment, older children's perspectives, in particular, are likely to be more closely related to patient behaviour. Indeed, as stated previously (Chapter 3.2.6) parental and child treatment beliefs are only moderately correlated (Yilmaz et al., 2012). Adherence has also been shown to be lower in older children than in younger children (McQuaid et al., 2012; McQuaid, Kopel, Klein, & Fritz, 2003). Increased non-adherence in older children compared to younger children is likely to be related to shift in medication responsibility. Indeed, children as young as 12 years old have been highlighted as having limited supervision, largely being responsible for their own medicine taking and therefore any related non-adherence (Orrell-Valente et al., 2008). It is thought that this age group would be useful to focus on as the children are beginning to become more independent of their parents/guardians in terms of control of their own medication use, and therefore may have different drivers behind their behaviour compared to younger children, whose medication is primarily still the responsibility of their parents. It was also postulated that targeting older children would be crucial for better adult adherence behaviours to be developed, and that the late stages of paediatric care where patients are transitioned to adult care would be an ideal opportunity for intervention. It was however

not within the scope of this PhD to study both young children and parental beliefs and older children's beliefs in two qualitative studies and therefore only older children's beliefs will be explored.

Qualitative work has previously been conducted to assess the acceptability of EMDs for measurement of adherence in both secondary (Howard, Lang, Sharples, & Shaw, 2017) and tertiary care (Stewart et al., 2018) in patients from the Royal Brompton Hospital. However, EMD data has not previously been used to guide a qualitative interview discussion around adherence behaviour. The present chapter reports on a study in young adults with problematic severe asthma (PSA) aged 12-17 years old.

### **6.1.1 Aim**

The aim of the study was to explore the reasons, both perceptual and practical, as to why young people with problematic severe asthma do not adhere to their asthma preventer medications. This information can then inform tailored adherence interventions within this population in the future.

### **6.1.2 Objectives**

The primary objective of this study was to identify the barriers and facilitators to non-adherence in this population using qualitative interview with young people with PSA. Specifically the objectives were to:

- Explore illness beliefs
- Explore treatment beliefs both for reliever and preventer medication
- Trial new interview methodology based on objective EMD data and the use of creative methods to aid interviewing in this population
- Explore the role of parents as perceptual or practical barriers and enablers to adherence

## **6.2 Methods**

### **6.2.1 Design**

This study was designed as an in-depth qualitative interview study. Interviews were favoured over questionnaires as there are limited validated questionnaires available in children (Murray & Chamberlain, 1999) and treatment perceptions related to adherence currently

available. Semi-structured interviews were conducted to allow both pre-conceived and newly emerging topics to be discussed. Young people with PSA (Bush & Saglani, 2010) who were identified as non-adherent ( $\leq 80\%$ ) to their preventer asthma medication (as recorded by their Smartinhaler™ data (Jochmann et al., 2015) after a period of monitoring (Median= 66 days, IQR= 56-90 days) were recruited from the Royal Brompton Hospital to take part.

Participants were selected for interview as a purposive sample, whereby known participant characteristics were used to select patients to decrease the bias of the sample and to increase study rigour and generalisability (Ritchie, Lewis, McNaughton Nicholls, & Ormston, 2013). Purposive sampling was conducted based on the participants' pre-collected (Median: 465 IQR= 202- 889 days before the interview) Smartinhaler™ adherence data, age, gender, and ethnicity.

In addition to previously collected data from the Jochmann et al. (2017) study, more recently collected data was accessed as The Royal Brompton Hospital had begun to monitoring adherence to ICS (for clinical use) using Smartinhaler™ prior to the commencement of this qualitative research. Therefore, some data were collected in the period of time immediately prior to the interview where previously collected data could be up to two years old. Unfortunately, as clinically monitoring adherence was only a recent feature to clinical practice there was insufficient data to rely only on the most recent dataset and therefore both recent and older EMD data (collected for research purposes prior to EMD use in routine care) had to be used.

Smartinhaler™ data was not only used to select appropriate participants for the study but was used as a basis to aid discussion of the patients' patterns of non-adherence during the in-depth qualitative interview. Prior to the interview but after the consent process each participants' adherence monitoring data were downloaded or retrieved from their medical records, printed in a tabulated format (Table 13) and visually examined for patterns of non-adherence. The parameters used to examine differences in adherence were: morning and evening adherence, days of the week, months of the year or periods of time (e.g. school holidays), and the number of doses per day. Days, or times, where dosages were higher than prescribed were also noted for discussion although periods of 'overuse' were not considered in the overall percentage adherence (as adherence percentages were truncated at 100%). This type of behaviour was considered important as an indicator of poor illness and treatment coherence (understanding) in patients. Patients may believe that the time of the

dose does not have an impact which could cause side-effects from over-use and a lack of effect at different points within a 24-hour period. This type of interview where Smartinhaler™ data is used to guide interview discussion – or the Adherence Monitoring Interview (AMI) approach – is a novel approach to qualitative explorations of adherence and has not previously been trialled in patients with asthma or in other long-term-conditions. The rationale was that by using an objective measurement of adherence behaviour, patients would be more willing to be honest about their adherence barriers and facilitators in the context of their own individual patterns of adherence. This type of interview also aided the interviewer in their ability to be non-judgemental and base the discussions around the facts (i.e. the objective Smartinhaler™ data). As qualitative interviews which do not adopt the AMI approach may be hindered by social desirability bias in terms of self-reported adherence, the AMI approach using objective EMD data allows an open discussion around the adherence behaviour.

Table 13: An illustrative excerpt of Smartinhaler™ data output used for the AMI interview

Date	Day	Doses Taken a.m.	Doses Taken p.m.	Doses Taken Daily	Adherence in %	Adherence a.m.	Adherence p.m.
25 Sep 2014	Thursday	2	2	4	100	100	100
26 Sep 2014	Friday	2	2	4	100	100	100
27 Sep 2014	Saturday	2	2	4	100	100	100
28 Sep 2014	Sunday	2	1	3	75	100	50
29 Sep 2014	Monday	2	0	2	50	100	0
30 Sep 2014	Tuesday	0	4	4	100	0	100
01 Oct 2014	Wednesday	1	0	1	25	50	0

02 Oct 2014	Thursday	1	0	1	25	50	0
03 Oct 2014	Friday	2	0	2	50	100	0

The interview introduction was developed to firstly highlight that the interviewer's perspective is non-judgemental and also that the interviewer is a researcher who was herself diagnosed with asthma at a young age. This introduction was created to try to build immediate rapport with the patient and to normalise non-adherent behaviour, not to condone such behaviour but to allow the patient to open-up fully within the interview. The topic guide began with a discussion of the objective EMD data before moving onto more structured questions developed to explore beliefs about asthma and its treatments and practical barriers/facilitators to adhering to ICS treatment. The interview topic guide was informed by the Common Sense Model (Leventhal et al., 1992), the Necessity and Concerns Framework (Horne & Weinman, 1999) and the PAPA (Horne, 2001) (see Appendix 7). Pilot testing of the topic guide was conducted with a patient aged 13 years old with difficult asthma known to the interviewer personally. The pilot was conducted to check the estimated time to complete the interview to ensure the time commitment outlined in the information sheet was accurate and also to highlight any missing topic areas. It was estimated that the interview would take between 30-45 minutes, which the pilot confirmed. The pilot testing also revealed one additional key area to include. Questions around parental help with prescription ordering and collection were added to the topic guide based on the pilot test (Appendix 7).

The topic guide and study materials were also reviewed to ensure these were written at a reading level that was deemed to be acceptable at age 10-11 on the Flesch reading grade tool available through Microsoft word. All of the study materials were also reviewed by the patient and public involvement group of young people (SPEAK asthma funded by Asthma UK Centre for Applied Research, <https://www.aukcar.ac.uk/public-involvement/speak-asthma>). Amendments were made to address the reviewers' comments before ethical approval was sought particularly around the language that was used (Appendix 8).

Another novel aspect of this qualitative study of non-adherence was the use of creative methods to enable patients to answer the interview questions in a medium in which they felt comfortable. Drawing materials (paper and coloured pencils) were provided and offered to the patients to use if they wished to help them to answer the questions. The use of drawing in research to explore health and illness has been advocated as being particularly helpful in young children or in those who English is not their first language (Pridmore & Bendelow, 1995), which is the case for some children in the target population. Historically, drawing has also been used to explore beliefs about illness such as cancer, in older children (15 years) and therefore the patients', Drawing materials were offered within this study as a useful tool to aid expression of beliefs and experiences (James, 1993), and may be particularly useful for exploring their understanding of asthma and the biology of asthma and its treatments in relation to illness and treatment beliefs as outlined by the e-CSM (Broadbent, Schoones, Tiemensma, & Kaptein, 2018). The interviewer attended training in using this creative methodology with children in research prior to data collection. The drawings were used as basis for further discussion and explored with the child verbally as opposed to being used as stand-alone data. This therefore mitigates any researcher bias in interpreting the drawings without confirmation of meaning from the child.

### **6.2.2 Quantitative Supporting Data**

In addition to the qualitative data collected, demographic information was also gathered, with permission, from the patient's medical record and any missing data were queried and clarified with the participant. This comprised relevant information:

- Participant demographics: date of birth; ethnicity and gender
- Smartinhaler™ adherence data

### **6.2.3 Participants**

Children aged 12-17 years old were eligible to participate in the qualitative study. This age group was targeted for several reasons: adherence rates are lower in older children (Bender, Wamboldt, O'Connor, et al., 2000; McQuaid et al., 2003); older children become more responsible for taking their asthma medication alone (Orrell-Valente et al., 2008) by themselves compared to younger children; and similar work had already been previously conducted in younger children with asthma (2-6 years old) in a Dutch population but where

adherence to ICS was high across the participants (Median= 92%, IQR=76–97%) and parental beliefs were examined (Klok, Kaptein, Duiverman, & Brand, 2012).

#### 6.2.3.1 Eligibility Criteria

##### 6.2.3.1.1 Inclusion Criteria

- Young person and parent/carer fluent in the English language (does not need to be their first language) and able to give informed consent
- Patients have been diagnosed as having problematic asthma at the Royal Brompton Specialist Centre
- Patients that have previously completed a period of electronic monitoring using a Smartinhalers™ (Median= 66 days, IQR= 56-90 days) and have been found to have adherence of  $\leq 80\%$  during the period of monitoring.

##### 6.2.3.1.2 Exclusion Criteria

- Patients with another disease deemed likely to significantly impact their adherence to ICS (if relevant this was highlighted at the time of recruitment by a member of the patients' medical care team, for example one patient who had Primary Ciliary Dyskinesia and asthma).

#### 6.2.4 Recruitment

The custodian of the data for the Jochmann et al. (2017) Dr Louise Fleming allowed access to the electronic monitoring data that was previously collected. Dr Louise Fleming and a specialist nurse Angela Jamalzadeh identified eligible patients, from both the Jochmann et al. (2017) data and new data which had been collected more recently using Smartinhaler™ within routine care. A list of anonymised data was shared with the researcher for the purposes of recruitment in the current study. Potential participants and their families attending routine clinical appointments were introduced to me by a member of the medical care team. The study was then discussed with the patients and their family before they were provided with both the young person information sheet and the parental information sheet (Appendix 2 and Appendix 3). Patients were given time to thoroughly read the information sheet while waiting for their appointments with the multidisciplinary team. I was available within the clinic for any queries and participants were approached again, if they were not



already in a consultation, to check their understanding of the study and study procedures. Patients and their parents were then asked if they would like to participate in the study and if so, whether they would like to participate on that day, either immediately after their appointment or during the appointment wait time if there were due to be delays in their consultation. Participation on the day without further time to consider their decision was deemed acceptable both by the study team and the ethical committee as patients' travel time was often high, appointments were scheduled on average only every three months, the study was non-invasive in terms of medical procedures and agreement to participation on the day was thought to reduce the burden of participation. If patients agreed to take part, the participant information sheet was then read aloud or summarised to patients and their families before consent was completed. This procedure was usually conducted in the paediatric outpatients' waiting room whilst patients waited for their appointments.

As I held an honorary non-clinical contract, once consent was given, the patients' medical notes in particular their Smartinhaler™ data were able to be accessed from the hospital computer system. The young person and their parent/guardian were informed that their participation, refusal to participate or withdrawal from the study would not affect their normal medical care or legal rights.

Participants were accompanied to Respiratory Clinical Research Facility, where a quiet, private room was available to complete the study. The interview with the young person took place in a separate room to the parent/guardian, who were asked to either remain in the adjoining waiting room or to come back in 30-45 minutes to meet their child. The interviews were conducted in this way firstly to separate the interview location from the location of their routine clinical care and secondly, to reduce the influence of the parent/guardian on the young person's responses within the interview. This method was devised to create a non-judgemental environment that was more conducive to honest and uninhibited discussions around non-adherence and experiences of asthma.

Where patients were unable or unwilling to take part immediately their consent was sought to access their contact details from the hospital files in order to contact them to arrange a mutually convenient appointment, quite often before or after their next appointment. Patients who did not wish to take part were asked if there were any reasons for not participating, although they were assured that they did not have to give a reason. These reasons were recorded on a recruitment log which was kept securely on a personal

encrypted UCL computer. Where patients were willing to take-part, the original completed participant and parental consent forms were stored in the hospital case notes after completion. A copy was also given to each young person and parent / guardian.

#### *6.2.4.1 Recruitment barriers*

This study was a single-time point cross-sectional qualitative study. As such, participants were not followed up, although, with their consent, their contact details were kept for future related studies (see Chapter 7). Recruitment ceased once no new data were emerging with the addition of new participants (thematic saturation).

This study originally had an eight-month recruitment and data collection phase however a number of unforeseen issues arose meaning that an extension was necessary. Firstly, a new approach had been implemented to see all asthma patients within a once monthly dedicated asthma clinic, where possible. This meant that that clinics that could be used for recruitment were held less often than originally anticipated. Secondly, patients' appointments were less frequent than anticipated, with the majority of patients being seen once every three months as opposed to once a month (if attending for biologic treatment) as initially expected. Finally, many patients and their parents did not attend their booked appointments. This seems to be a particular issue for the patients eligible for this study, i.e. adolescent asthma patients with high levels of medication non-adherence.

During the first eight months, only 15 participants were recruited and interviewed. An extension was then applied for and granted by the NREC until December 2018 in order to complete the interviews and ensure thematic saturation.

#### **6.2.5 Ethical Approval**

Full ethical approval was sought and granted via proportionate review by the NHS North of Scotland Research Ethics Committee (Ref: 16/NS/0082) in August 2016 (Appendix 4). The study then received Health Research (HRA) approval in August (Appendix 5) and Research and Development approval from the NHS site (The Royal Brompton Hospital) at the end of September 2016 (Appendix 6). Due to competing PhD priorities, recruitment began on December 21<sup>st</sup>, 2016. This study was accepted onto the NIHR Clinical Research Network portfolio in March 2017 and updates were given to the portfolio throughout the recruitment period. As mentioned above a minor amendment was then made in August 2017 to extend

the recruitment phase to December 2017. The amendment was approved by UCL as sponsor; NREC; HRA and The Royal Brompton as the research site in August 2017.

## **6.2.6 Data Analysis**

### *6.2.6.1 Data collection*

Interviews were conducted between March and December 2017 and were audio recorded to allow transcription of the interviews and uploaded to NVivo 11 QSR International's version 11 software, 2015 (computer-assisted qualitative analysis software) (*NVivo qualitative data analysis software*, 2015; Richards, 2005). Intelligent verbatim transcription (excluding sounds such as ums and ahs) of the interviews was conducted by a university approved company after the signing of a confidentiality agreement (1st Class Transcriptions) as soon as possible after the interview had taken place. Once received the transcripts were read and checked against the audio recordings, any corrections were made particularly around anonymization and depersonalisation of the data, before the audio files were deleted in accordance with the ethical approval.

### *6.2.6.2 Data analysis*

Framework analysis (Ritchie et al., 2013) which was developed for use in applied healthcare settings was used to analyse the data. Framework analysis benefits from a structured approach to organising thematic codes under a pre-defined framework whereby new emergent themes that do not fit within the framework can be highlighted. In line with the topic guide the framework was based on the PAPA model including the extended-common sense model. Iterative analysis was conducted by two researchers with guidance on interview style and questioning from the project supervisor, Professor Rob Horne. Thirty percent of the interviews were initially independently double-coded by Christina Pearce and Amy Chan and then discussed. The emerging themes were mapped to the pre-defined framework. Interviews and changes to the coding were conducted in parallel. I then independently coded a further 45% of the transcripts and Amy Chan independently coded the final 25% of the transcripts in line with the developed codes, noting any emerging themes. Transcripts were then re-visited to ensure the most recent version of codes had been applied. NVivo 11 was used to organise and store the analysed data (*NVivo qualitative data analysis software*, 2015; Richards, 2005).

## 6.3 Results

### 6.3.1 Summary of the dataset

Twenty patients participated in the AMI study. Although ethical approval was sought for up to 30 patients to complete the study, no new themes or codes were emerging from the interviews, meaning thematic saturation was reached by patient 20. Of the patients approached only one patient declined to participate. One potential family was not approached due to a complex medical care relationship and social service involvement giving an overall participation rate of 91%.

A Purposive sampling technique achieved a varied sample in terms of both demographic factors and level of adherence to their ICS during the EM period (Table 14). Of the 20 participants, 11 were male (55%). The mean age was 14.4 years (SD=1.6). Median adherence was 52% (Range= 14%-76%). Interviews lasted approximately 41 minutes (SD=9.4) and ranged from 26 and 60 minutes. Participants reported a range of ethnicities: White British (n=7/20, 35%); Black British (n=6/20, 30%); Asian British (n=5/20, 25%) and other (n=2/20, 10%). Patients reported being prescribed a range of ICS and ICS combination inhalers including Symbicort, Seretide, and Clenil within the interviews however type of ICS was not systematically recorded within this study.

Table 14: Results of the purposive sampling

Number of Participants	Sex	Age	Self-reported Ethnicity	Percentage Adherence
20	Male= 55% (11/20) Female=4 5% (9/20)	12-17 years old Mean age 14.4 (SD=1.6)	White British= 35% (7/20) Black British= 30% (6/20) Asian British= (25% (5/20) Other=10% (2/20)	14-79% Mean percent adherence=56.5 % (SD=18.2)

### 6.3.2 Framework Analysis

The framework analysis is presented in the below table below. Each theme will be presented and discussed within this chapter (see Table 14 for a summary of the findings). Patient identification numbers will be given in parenthesis but in the interest of anonymisation, given the small sample size and small population group (5-10% of all paediatric patients with asthma (Nagakumar & Thomas, 2017), patients' age and gender will not be presented alongside the quotes to protect patient anonymity. The results of the framework analysis are also depicted in Figure 25 in relation to the e-CSM. As would be expected in interviews targeting participants who are non-adherent to treatment more barriers to adherence were found. Where facilitators for adherence were identified they are highlighted below.

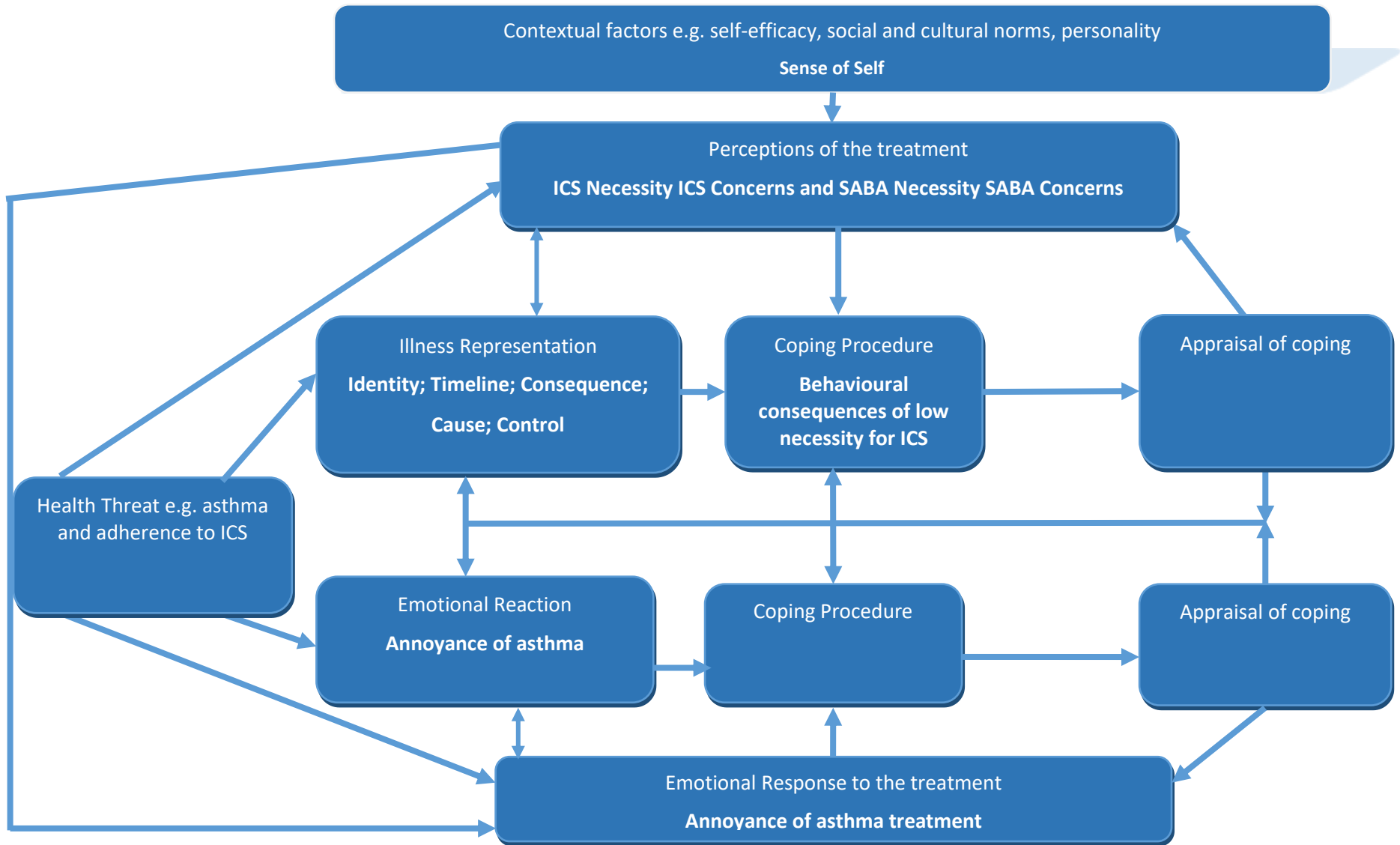


Figure 25: e-CSM Results of the Framework Analysis: Diagram adapted from (Horne, 2003)

Table 15: Framework, Themes, subthemes and exemplar quotes

Domains	e-CSM Domains	Subthemes	Barrier or Facilitator to adherence	Quotes
1. Sense of Self	Emotional Reaction to Asthma: the annoyance of asthma		Barrier	<i>Normally, like, annoyed, because, you know, I can't, like, go out, can't see my friends, can't really do much apart from stay at home, so it, kind of, makes me just annoyed, mainly (Patient 1)</i>
				<i>It's really annoying because it limits the activities you can do. Well, you can still do the activities but you have to be careful and stuff like that, yeah." (Patient 10)</i>
	Societal Impact (overarching contextual factor)	Societal acceptance versus stigma	Facilitator	<i>No, they're [their friends] pretty supportive and there's no negative about it. (Patient 18)</i>
			Barrier	<i>Everyone just comes up and asks me, why do you take it [reliever inhaler] and stuff and it's just embarrassing... I have to tell them why and it's just embarrassing. (Patient 20)</i>
	Feeling different	Barrier	<i>...I can do exercises but obviously not as a healthy person could. Like I will have like more breaks and I'll be more</i>	

				<i>breathless and all that, whereas another person would be fine. So that's what frustrates me because it's like, if that person can exercise for 30 minutes why can't I? But obviously it's because of my asthma, so I can't really do anything with it because it's just there. (Patient 12)</i>
		Trivialisation of asthma	Barrier	<i>Quite upset, because it's really not taken that seriously, to be honest, like, there's one charity in the whole of the UK for it and it just, like, really annoys me that there's only, like, it isn't taken as seriously as same as, like, people don't understand there's different stages, so there's, like, oh, you're fine, you only need it once in a while and then there's a stage when you're really sick and you're, like, missing so much school and it just, like, really annoys me and upsets me that no one just takes it seriously enough. Like, if I was to say, oh, I have lung cancer, then people would take it seriously, but if I say, oh, I have asthma, people just think, oh, and it's just annoys me how there's, like, one charity and no one takes it as seriously as it is. (Patient 2)</i>
<b>2. Perceptions</b>	Illness Perceptions			
	Identity	The norm to be ill	Barrier	<i>I'm fine, why am I taking this I'm fine? (Patient 8)</i>



		Seriousness of asthma	Facilitator	<i>I've learned that I've got bad asthma rather than just asthma. (Patient 8)</i>
		Understanding of asthma pathology	Barrier	<i>Well I've been told that it's when the tube...your breathing tube tightens up because of an irritation, so you get less airflow so it's harder to breathe. (Patient 13)</i>  <i>...I think is just a ball of gas just sitting there in your lungs and constricts your breathing... I don't know what it is...I'd say it's like your lungs and your heart connected. Because I know they're connected in one way." (Patient 18)</i>
	Timeline	Episodic /symptom based treatment	Barrier	<i>Because sometimes I'm feeling really great and I'm probably, and I'm thinking to myself, I don't need this, I'm pretty much okay. (Patient 9)</i>
	Consequences	Being held back or activity limitation	Barrier	<i>...but I always feel that my asthma is sometimes holding me back from being able to run better or being physically active. (Patient 6)</i>
	Cause	Triggers	Barrier	<i>I don't need it, I'm well, but then I forget that I've got hay fever as well which triggers my asthma, so I</i>

				<i>equally need it in summer than I do in winter. (Patient 12)</i>
Control	Understanding of ICS as a treatment for asthma	Facilitator		<i>Well, when I got prescribed it, like, they said it was like, they described asthma again and then they described it [ICS] would open my, like, airways and allow me to breathe. So I understood that it was like a good thing from day one. (Patient 7)</i>
		Barrier		<i>I still don't get what does it do, like, I still don't get what it does. I use it but I don't know...It helps you to breathe better, I guess. (Patient 10)</i>
Treatment Perceptions				
ICS Necessity	High ICS necessity	Facilitator		<i>... my inhalers help me... I have noticed a big difference between taking my inhalers and not taking my inhalers...So now that I know that I've realised that if I want to be well I take them and I will be well, if I don't I'll be in hospital and stuff... Once you see it you realise that they are actually really good. (Patient 7)</i>
	Low ICS necessity	Barrier		<i>I don't think there's a difference. I feel like the blue just...it satisfies my body more than the red does. Like I feel the red is unnecessary to me. (Patient 12)</i>

		Behavioural consequences of low ICS necessity		
		Lying	NA	<i>Sometimes, I'll be like, yes, and I'm like, no I haven't [taken it]. (Patient 14)</i>
		Dosing adjustments	NA	<i>Then when I do forget it sometimes I just take four in the evening just to make it equal, or I just take four like I suppose six o'clock and then like just before I sleep. So overall in the day I do have four (Patient 12)</i>
	ICS Concerns	Dislike taking inhalers long-term	Barrier	<i>It's all fine now [now adherence] but back then [when non-adherent] it's just like, oh, I've got to do this for the rest of my life. It's stuck with me. I can't do anything about it. That sort of mindset. (Patient 8)</i>
		Long-term effects	Barrier	<i>I'm also concerned about the long-term effects of the inhaler...so I might take it a little less regularly. (Patient 6)</i>
		Experienced Side effects	Barrier	<i>I don't like taking it because it makes me eat...makes me like hungry...I just put on weight and I don't like it...I'm just worried about myself putting on weight. (Patient 20)</i>

	SABA Necessity	Reliance on or preference for reliever	Barrier	<i>It was like, because I had the mentality of the blue one was like my saviour (Patient 7)</i>
		Onset of effect and duration	Barrier	<i>... I just stick to the blue because I feel like the Symbicort is just not necessary because the blue is just a reliever and the Symbicort doesn't do the same effect. The Symbicort does take a while to actually like make my breathing better whereas the blue is instant. (Patient 12)</i>
	SABA Concerns	Dislike dependence on inhalers	Barrier	<i>That it's obvious that like, you have asthma, or it's like an extra thing to carry, it's really annoying to have. (Patient 5)</i>
<b>3. Practicalities</b>	N/A	The Importance of Routine		
		No routine	Barrier	<i>Yeah, just in the house, because I don't really have a specific place for it... I just say that it's because it's just out of my routine, 'cause I don't really have a specific routine. (Patient 4)</i>
		Disruption of routine ➤ Split family difficulties	Barriers	<i>I live...five days a week I'm at my mum's house. Two days a week I'm at my dad's flat. Monday, Tuesday and then the rest of the week...It's much more difficult to take it at my dad's. (Patient 8)</i>

		<ul style="list-style-type: none"> <li>➤ Competing priorities</li> <li>➤ Unintentional forgetting</li> <li>➤ Holidays and Weekends</li> </ul>		<p><i>Yeah and I feel like, oh it's just an inhaler, I don't need it, I'll be fine... I've got so many other things to do, why should I pay attention to an inhaler, that's like the last thing that I need to look at. But in fact it's the first thing I need to look at because that is what keeps me going.</i> (Patient 12)</p> <p><i>It's just that remembering part I forget.</i> (Patient 18)</p> <p><i>...I just get tired so I don't take it, but I mean it's more just me being so tired that I forget to take it."</i> (Patient 13)</p> <p><i>I think it'll be less because when it's summer time or summer holidays you always have places to go and stuff so then you forget to take it.</i> (Patient 19)</p> <p><i>'Cause when I wake up, I just do things, I get up, brush my teeth, have a breakfast, get ready for school. If it's the weekend, I just sleep in.</i> (Patient 11)</p>
		Environmental cues	Facilitator	<p><i>Yeah, because I always...I have a habit of just looking on my left-hand side every morning when I wake up, and then obviously my inhaler is there so I can't forget it even if I wanted because I'm looking at it.</i> (Patient 12)</p>
The importance of parents				

		No parental reminders	Barrier	<i>...I think usually my mum would tell me to take it when it's bad and that also helps me to remember to take it, and when she feels that I'm doing fine she won't tell me, and so I wouldn't do it unless I remember myself. So, I think that also takes part. (Patient 13)</i>
		The importance of parental reminders	Facilitator	<i>...have you taken your purple pump, and sometimes I would say, yes, but I hadn't actually, so then I'd quickly run upstairs and take my pump... (Patient 5)</i>
		Parental importance in providing prescriptions	Facilitator	<i>...I don't ever go to get my medication, my parents always do that. I've never even seen my prescription in my life because that's just their little duty, they just do it, because they know I don't want to get my medications. So they go and get all my medications. They see...like they've made a little draw in their room, they've made a draw of my medications and they just always see whether everything's updated, like all the medications are...none of them are expired and all of them have something in it, rather than just empty boxes. When it's not there they refill it and go to the doctor's and get it all for me. (Patient 12)</i>

### 6.3.2.1 *Sense of Self*

Several themes emerged in relation to how the illness and the treatments made the patients feel about themselves. As theorised by the e-CSM these wider issues related to the patients' sense of self impacted their illness and treatment beliefs and therefore their adherence. The influence on the adolescents' sense of self was related to internal emotional reactions to asthma (e.g. annoyance of asthma) and external influences from society.

#### 6.3.2.1.1 Emotional Reaction to Asthma: the annoyance of asthma

Even though patients find having a certain level of asthma symptoms normal, patients still often describe having asthma and taking asthma medication as annoying.

*I get angry or annoyed or upset, and sometimes I worry that I have asthma, and that I'm different to everyone else (Patient 5)*

*...because sometimes I'm so well and then other times I'm just so sick and it's just annoying that it keeps going up and down. (Patient 2)*

This was often related to feeling different and being left out of activities. This also coincided with emotional distress and in three cases a referral was made to psychology by the interviewer.

*I hated it, yes, this [asthma] has made me absolutely hate my condition...Which is really bad because it's making me hate myself as a person...whenever I can't do something, if I have to sit out an event or something it will really put me down because I am now alone sitting out watching everyone else do it while I have to think about my condition on the side lines. (Patient 8)*

#### 6.3.2.1.2 Societal impact

##### 6.3.2.1.2.1 Societal acceptance versus stigma

Patients talked about how generally asthma is understood as a common condition which many people have experience of. This could facilitate adherence as they discussed feeling comfortable taking their inhalers in front of their friends and family in the majority of situations such as at sleep-overs and at home in front of family members.

*...I think now, generally, society has accepted asthma as a thing, so...because lots of people do have it. (Patient 6)*

However, patients often also discussed standing out by taking their inhalers in public and not wanting to look weird or different. This was most often around reliever rather than preventer

inhaler use as preventers can be kept more private as they are taking in the morning or night rather than in public as required.

*...they make fun of me carrying around all these weird medicines, so I just wouldn't take it. So I wouldn't look weird. (Patient 5)*

#### 6.3.2.1.2.2 Feeling different

Patients often compared themselves to other people who do not have to take inhalers to get by.

*No, my friends know about it, it's fine. It's just...because I'm not the only one but, like, because you're kind of the only one, it's just, yeah, it makes you different kind of. (Patient 10)*

Patients also compared their asthma severity to others who have milder or more controlled asthma.

*But asthma to most people is almost non-existent and so for example, at my school, they had to develop a whole set of asthma protocol for me as opposed to my friends... mine is probably worse than most. Not as bad as it could be. It's worse than most and it's different and a lot of people don't have experience. (Patient 15)*

#### 6.3.2.1.2.3 Trivialisation of asthma

Although they discussed asthma as a common condition, they often discussed feeling asthma was trivialised. This was in relation to the severity of their asthma compared to others with asthma and also as a whole, that asthma does not get the focus it deserves as a serious condition.

Patients discussed that family members often challenges the amount of medication they were taking in relation to the seriousness of their asthma or symptoms and how that influenced their medication use.

*I basically did that [reduced the dose] ... because someone [an auntie] was saying I was taking too much"...but because of my allergies I take Cetirizine a lot and she realised I was taking it a lot and she said, come on, you're taking way too much medicine but she doesn't understand that I need to take the medicine because she doesn't know...Because...so I feel that everyone that doesn't need to take the medicine feels like you're taking too much...because they haven't experienced it themselves. It could be for whatever reason. (Patient 8)*



*And then my brother sometimes says that, you know, asthma isn't a thing, it's just me being unfit, which I don't really agree with, and it's, kind of, annoying when people say things like that... (Patient 6)*

One patient discussed, very emotionally, a lack of understanding in her family of the influence of their actions related to her asthma triggers and worsening her asthma. The patient clearly finds it upsetting that her father does not consider her asthma day-to-day.

*"He smokes, which is quite bad, but he won't stop... so that, like, impacts my breathing, not physically, like, or mentally, he doesn't impact on it, but it's just, like, smoking...I don't care, to be honest, what he does, to be honest, I don't really care about him, so, he's not my problem what he does, to be honest... It's his choice, but if he cared, I really hate my dad, if he cared, he would stop, but if he can't and then he won't even go for, like, what's it...counselling on how to stop and he won't even try to stop. So, to be honest, I just...so I just try to stay away from him, to be honest." (Patient 2)*

#### 6.3.2.2 Illness Beliefs

##### 6.3.2.2.1 Identity

The identity of asthma was explored in line with the CSM in terms of patients understanding of the label of asthma and its symptoms. Patients described it being normal to be ill and that only when they cause asthma attacks this can influence their perception of their asthma as serious and influence their subsequent adherence behaviour.

##### 6.3.2.2.2 The norm to be ill

An alternative explanation for patients mainly describing asthma attacks rather than general symptoms is that the patients are used to a certain level of symptoms on a daily basis. As children with severe asthma are often diagnosed at a young age and if they have not had full control of their asthma in the past it is not surprising that they would consider having daily symptoms to be normal.

*...I've had it since I was really small, like, so I don't know any different, but I feel like if it was to come, like, later in life or if you discover it later, if I was to discover I had it, like, now, then I would find the change a lot harder, but because I've had it all my life and I don't know any different, it's fine, like, I find it easier to deal with. (Patient 2)*

*Yeah, some months I normally have coughs and a mini asthma attack but nothing too major...I do get symptoms on and off says but I don't know I'm getting them to be honest. (Patient 9)*

Often patients did not realise how bad their symptoms were until their asthma was well controlled through appropriate use of their preventer medication.

*So now that I know that I've realised that if I want to be well I take them and I will be well, if I don't I'll be in hospital and stuff...Once you see it you realise that they are actually really good [preventer inhalers]. (Patient 7)*

#### 6.3.2.2.3 Seriousness of asthma

Some patients' asthma identity shifted after an asthma attack or period of worsening symptoms. These patients believed the condition to be more serious as the health threat was increased and this facilitated their adherence as a coping strategy. However, there were individual differences as to whether not the increase in severity altered the patient illness perceptions and therefore their adherence.

*Like I've had some serious asthma attacks but even that hasn't encouraged me to take it more. So, I don't really think much has made me...or has influenced me in taking it. (Patient 13)*

*Where I've had episodes of really bad asthma, I've realised that I've needed, my purple pump has like a big impact on my actual asthma, it's not just the blue pump that does it. (Patient 5)*

#### 6.3.2.2.4 Understanding of asthma physiology

The participants generally had a poor illness coherence including a lack of understanding of what asthma is, how the ICS work to prevent asthma symptoms, the difference between the reliever and preventer inhaler and the effectiveness of preventer inhalers (for those without STRA). The majority of patients only understood that asthma involved the lungs. Much of the rest of their explanations were incorrect and confused.

*Your lungs and your...well, you breathe from your lungs, don't you?...And your...not ventricles, what? Yeah, I just think your lungs and stuff. (Patient 19)*

*Your airways get tighter, so you can't take in as much oxygen, so you need to take the medicine, so it can open up and the circulation can go quicker" (Patient 15)*

Many patients also mentioned the heart and lungs being connected and related to asthma but their explanations had very little detail and they were very unsure if they were correct or not.

*“The heart and the lungs?... Well, they like blocks the air from coming, something like that (Patient 3)*

Some patients did have a basic knowledge of what asthma is, but this knowledge was not always gained from health care professionals and was often gained opportunistically through other sources. For example, a patient while having asthma symptoms visited the nurse and only while waiting in the medical room did she by chance see a poster and read about asthma.

*“The lungs, and I read this thing in my medical room, something about bronchial tubes, I think that’s what it’s called. And it has a picture where, if it’s inflames, it’s like very small, and I think it’s called phlegm, that’s coming out of it, but when it’s normal, it’s very large and air can easily pass through, but when it has phlegm and tight, air can’t really pass through, which gives you hard, like, you can’t breathe properly.” (Patient 14)*

Although this knowledge of asthma was quite extensive, she reported to have only gained this after several years of having asthma and seemed to recite the explanation as if having little understanding of what that meant for herself.

*I know the airways get smaller – the hole in the airways – but I’m not quite sure how it happens, but I think part of it is because the walls thicken or something, or the muscles tighten. Yeah. Do you have muscles in your airways? I don’t know. (Patient 15)*

*Inflammation of the airways and lungs and then the immediate inhaler releases the inflammation and widens them. (Patient 8)*

Patient’s descriptions of asthma are not always accurate but indicate that they have some level of knowledge about why they are experiencing asthma symptoms. Participants chose to use drawing to express themselves only when discussing asthma (Figure 26) and asthma treatments. Only two patients drew pictures during the interviews, and both were about the airways.

*My main idea of it is – so can I like...it’s, kind of, hard to explain...[drawing] So if this was like, an airway, I guess, this would be like a normal airway, so kind of like, a doughnut or a ring shape. And I imagine if you’ve got asthma you’ve got something like this, and it’s, kind of, clogged, so it would be a smaller hole...That’s, kind of, my idea of it; it’s like, kind of, got stuff in it, and stuff. That’s like my main idea... [when asked what clogs the hole] Well, I think it might be mucus and phlegm, or something? (Patient 1)*

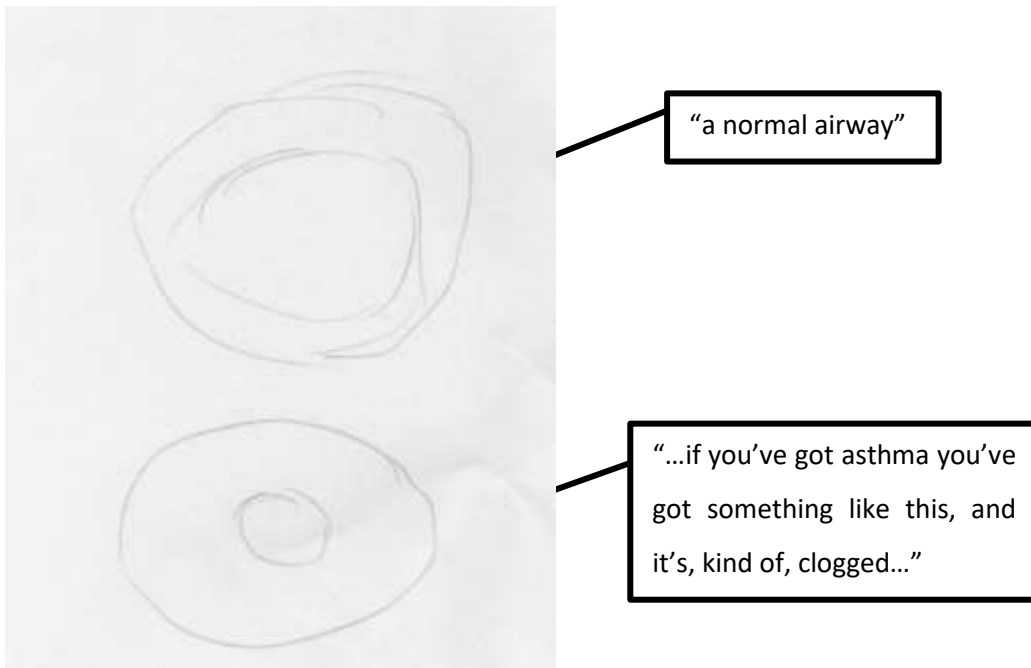


Figure 26: Patient 1's drawing of asthma with mucus in the airways

#### 6.3.2.2.5 Timeline

##### 6.3.2.2.5.1 Episodic/symptom based treatment

The majority of patients described treated their asthma episodically in relation to an increase in symptoms rather than as a long-term condition which is always present. This also included taking their ICS inhaler prior to an asthma attack or exposure to their triggers e.g. the cold, pollen season. Patients often did not take their ICS throughout the year despite using their reliever frequently.

*I wasn't getting any symptoms so I didn't take it...And I'm not sure I knew it was a preventer inhaler at the time... I thought it was just an inhaler. I thought...I had no idea what it did...basically (Patient 8)*

*... when it's worse I take it more often because of the wheeze but I think the wheeze actually helps me remember to take it. So, when I do feel wheezy I'd go take it because I remember to (Patient 13)*

Patients described how taking their preventers enables them to do physical activity as it prevents symptoms from occurring and that they may take their preventers for this reason for a short period of time.

*...when I know I have like a day where I have sports I try and take it. I take it more often on those days than I would when I'm not. I think the sports is*

*just...helps me...it's just a reminder of me to take it for that day, yeah.  
(Patient 13)*

Patients did not always understand the long-term nature asthma and even when adherent and controlled discussed reducing their preventer inhaler usage.

*“Well, in the past I was taking it often, like every day, but now because I'm thinking that asthma attack is probably like a one off thing, I'm starting to not take it often but I still take it. (Patient 9)*

#### 6.3.2.2.6 Consequences

##### 6.3.2.2.6.1 Being held back or activity limitation

Patients often mentioned asthma as causing activity limitation and generally holding them back in their lives.

*but I always feel that my asthma is sometimes holding me back from being able to run better, or being physically active. But it's not that big an issue.  
(Patient 6)*

This was often accompanied by feelings of sadness and being different to “everyone else”.

*...whenever I can't do something, if I have to sit out an event or something it will really put me down because I am now alone sitting out watching everyone else do it while I have to think about my condition on the side lines. (Patient 8)*

Activity limitation was frequently mentioned. Interestingly patients that claimed to have become adherent (since the SI monitoring period) mentioned that being adherent to ICS enables activity and for them to feel normal.

*But, ever since I've got the Symbicort, I've kind of felt differently, because now I can do what other people can do, and what I couldn't do before, so yeah. (Patient 14)*

##### 6.3.2.2.7 Cause (Triggers)

When patients were asked about what caused their asthma patients focused on their symptoms and asthma attacks rather than underlying long-term condition. Asthma triggers were mentioned by the participants in relation to increased severity of their asthma/ asthma flare ups and how this related to their ICS use. Often encountering triggers coincided with increased ICS use rather than using their ICS regularly as prescribed.

#### 6.3.2.2.7.1 The Weather

Cold weather whether it be seasons such as winter or autumn or a spell of cold whether were often reported in relation to differing levels of adherence to their ICS.

*"I see it as take more in the winter then take less in the summer." (Patient 8)*

Patients reported increasing their adherence during cold weather. This is related to both the cold weather and also getting viral colds.

*I mean like in the winter it's probably much worse, so I would have to take it because it's getting bad, and then in the summer it usually tends to calm down because it doesn't get triggered as much, so I feel like I take it less in summer. (Patient 13)*

*Well, my asthma gets really...like, I feel really irritated when I have a cold or something, so usually in the cold and 'flu season, that's mainly when my asthma is the worst... when I have a cold or something, I always take it. (Patient 6)*

However other patients mentioned hot weather being a trigger.

*So late summer, so mid to late August through to end of October would be probably the lowest [adherence to ICS], because there's no hay fever, there's hardly any pollen or any pollen that I'm allergic to, so birches and grass is all over. The temperature's as nice as it ever gets in this country, and it's not too hot like it is in the summer and if it's too hot because I sometimes struggle, get constrained, can't breathe properly. (Patient 15)*

Often summer weather as a trigger was either links to excessive heat, or hay fever.

*Because that helps me know that I still need it in the summer because I still need it in the summer because I've got hay-fever and allergies." (Patient 8)*

#### 6.3.2.2.7.2 Other triggers

Other triggers that were reported within the interviews were cats, stress, exercise or a combination of triggers.

*But had I forgotten it for three days, plus maybe a contact with a cat, and it was cold, that could have easily caused an attack. (Patient 1)*

*So like, if it was cold and I was doing, like, P.E. that was really physically demanding, that would probably set off my asthma... and it was quite cold*

*on that day, so that set off my asthma, and just like, other combinations like cats and cold; having a cold and cats; a lot of cats and cold. (Patient 1)*

*Normally my exercise is at school or a bit after school and stuff, and the main cause of my asthma was really just sprinting for the bus in the morning... (Patient 6)*

Interestingly patients sometimes confused triggers with cause of asthma insinuating that they believe themselves to only have asthma when they have asthma symptoms or an attack.

*Mainly that day I was like having asthma (Patient 13)*

Patients often referred to periods of time when they have asthma or when they are asthmatic rather than recognising themselves as always having asthma and being asthmatic. This highlights the lack of understanding of asthma and therefore the lack of understanding of the need for regular treatment of asthma through a daily preventer medication. Patients also when asked to describe symptoms of asthma often described asthma attacks rather than the daily symptoms that they may experience.

*Well, when, with asthma I normally get a bit of itchy chin...and, my throat, then my chest starts to feel like it's being compact between a sandwich, sandwich crusher! You know them things that compress cars into squares? (Patient 9)*

*I will breathe with my stomach...instead of my chest. My nails might go blue... [interviewer clarifies] this will be an asthma attack, yes. (Patient 8)*

#### 6.3.2.2.8 Control/Cure

##### 6.3.2.2.8.1 Understanding of ICS as a treatment for asthma

Some patients also had a basic knowledge that ICS is used to control asthma by reducing inflammation and therefore opening the airways (Figure 27). This could facilitate adherence as some patients recognised that the ICS controls their ability to breathe more easily.

*Then I take my purple pump it opens up my airways, where like my airways...can I draw?...[drawing] If I have an asthma attack my lungs would be like that, but when I take my pump they'd kind of open up, if you get what I mean? So they'd like expand and help me breathe better. I think when it like opens up my airways, it helps me breathe better, that's like I thought, yeah. (Patient 5)*



Figure 27: Patient 5's drawing of the airways before and after ICS (Seretide/ "the purple pump")

However, more commonly patients stated that they didn't know what ICS does or that it works in the same way as the reliever. Patients were confused about why they would take their inhaler when they were fine (low necessity beliefs).

*... I didn't know what was in it, what it was actually doing. It was for my asthma but what part of it is it doing. I'm fine, why am I taking this I'm fine? (Patient 8)*

*...it's a gas so I think it...like the gas goes inside of your...what are these things called? Not your vein because...well, it goes through your mouth and your nose but most times it goes through your mouth, so it goes down the tubes to your lung and it...it just helps it. (Patient 19)*

*Whenever I missed it I wouldn't feel bad about it, I wouldn't feel guilty that oh I've missed it. I would feel, like, oh I don't really know what it does, so I'm not really missing out here. (Patient 7)*

Patients do not know what the medication does, only that it is meant to help them when they take it. Patients described their beliefs about why healthcare professionals had not, in their recollection, provided them with an explanation of asthma and ICS or discussed it with them. They describe the gap in knowledge transfer between two time points. Initially, their parents were given an explanation of asthma when they were young and first diagnosed/referred to specialist care and then, an adolescent, certain assumptions about their understanding of their condition and treatments are made.

*And then I would say, more recently [as an adolescent rather than child], they either assume you know, or that you don't know, but if they explain it to you, you wouldn't understand maybe. (Patient 4)*

*So I think, like, if kids and teenagers knew, like, if they got, like, when they got prescribed it and if they got sat down and it was like okay this does this, take it like, you know how to take it but, like, if you are feeling like this take it then and it will help you, it would be much better... A really in depth, say*



*there was a new medication and like it would be a really in depth explanation would be really good. (Patient 7)*

*I do wonder why I'm, why I need it that sometimes that's why I don't take it as well. (Patient 9)*

*Interviewer: ... to start taking it again more often, what do you think you would need from anybody?*

*Patient: More reminding and more what it means to take it as well. (Patient 9)*

Indeed, patients' lack of understanding of asthma and poor illness coherence indicates the need for a "common-sense" rationale for the use of a daily ICS without the presence of daily asthma symptoms. Patients said being given an explanation of asthma and why daily adherence to ICS is important from the outset makes a difference to their adherence behaviours.

*Well, when I got prescribed it, like, they said it was like, they described asthma again and then they described it would open my, like, airways and allow me to breathe. So I understood that it was like a good thing from day one. (Patient 7)*

### **6.3.3 Treatment Beliefs**

#### *6.3.3.1 ICS Necessity*

##### *6.3.3.1.1 High ICS necessity*

Patients who were non-adherent to their ICS frequently reported a limited or unknown need for the preventer. However, patients currently claiming to be adherent to their ICS (unknown due to the up to 1 year retrospective nature of the Smartinhaler™ data) frequently discussed the necessity of their preventer medication. This high necessity was described as facilitating their current high adherence behaviour.

*...I feel like, oh it's just an inhaler, I don't need it, I'll be fine... But in fact it's the first thing I need to look at because that is what keeps me going. (Patient 12)*

*I rarely use it now, because the Symbicort, it's helped so much that the reliever is not really needed as much, but I still keep it, just in case. (Patient 14)*

The patient below used to lie to their parents and say they had already taken their ICS when the reminded by them to take it but now they are adherent they know the benefit of it.

*Now it's not so much a case of lying, because I know the benefit of it.  
(Patient 5)*

Patients who reported now being adherent discussed the change from episodic use of their preventer to using it regularly and how freeing it is to be able to be in control and use of the preventer inhaler enabling them to do activities like other children.

*"...if I had symptoms I would want to take my medication more...Now that I've realised that if I take it when I'm good I won't ever be like that so I won't need to do that.... I've always, like, based my thoughts off, like, if I do this I could go out with my friends and then we could, like, have a good time and we will not have to worry, you know, and if I didn't I could have to say ah I can't make it and stuff." (Patient 7)*

Some patients had conflicted views over the necessity of their preventer. Some patients seemed to struggle between what they have been told in terms of adherence and what they actually do. It was difficult for them to describe their need for ICS as they recapped what previous doctors had said to them but highlighted their low necessity for ICS and their poor understanding of what the medication does.

*Yeah, I need to...the doctor even said I need to take the purple one more...I should because maybe I'm not getting better or something because I don't take it enough, I don't know...what does it do? I don't know what it does.  
(Patient 10)*

#### 6.3.3.1.2 Low ICS necessity

In addition to not knowing why they were taking the treatment or how daily use of ICS is meant to help their asthma patients also did not perceive ICS to be effective.

*...to know what I'm putting into my body and what outcome it's doing for me...Instead of just putting a random thing in my body and does nothing for me. (Patient 9)*

Patients also reported that their forgetting of their ICS was related to the lack of necessity they felt for taking it.

*I think it would just be where I'd forget, 'cause even now I forget and sometimes I just wouldn't take it because I didn't think it had an impact.  
(Patient 5)*

*My attitude towards it. I didn't stand it and I didn't like it, I hated it. It wasn't in my routine. I didn't care. But now...now it's all different (P8)*

Finding asthma and asthma medication (mainly ICS) annoying is not conducive to regular usage of a medication and acceptance of their condition as long-term and therefore likely highly related to non-adherence behaviours.

#### 6.3.3.1.2.1 Behavioural consequences of low ICS necessity

Patients talked about manipulation of both other people e.g. parents and health care professionals and also of their Smartinhaler™ devices. This was in a relation to low necessity beliefs for the use of ICS and for fear of what people might say or think of them for not taking their prescribed ICS.

##### 6.3.3.1.2.1.1 Lying

Although parental reminders in this group were often reported to be helpful, in preventing forgetfulness, patients in this study reported sometimes lying to parents in response to some reminders. In addition to low perceived necessity this was often also related to competing priorities for their time.

*And how much it was actually helping [the ICS] because at one point...before this [period of EMD monitoring] I just...I didn't take it. I was telling my mum I was taking it. I think I told the GP I was taking it. (Patient 8)*

In contrast one patient described being non-adherent intentionally and due to high necessity for ICS in order to have a day off school with worsening asthma symptoms. This was not a common sub-theme.

*Not really, the only thing I can ever think of is if I was just really, really not in the mood for school, I might intentionally, this obviously doesn't happen now, but maybe when I was like in Year 7, I might have occasionally intentionally not taken it, so that I could be like, oh I've got quite bad asthma today, and I might need a day off of school. (Patient 4)*

##### 6.3.3.1.2.1.2 Dosing adjustments

Patients discussed intentionally reducing their dosage or taking more at a different time of the day when they had forgotten. This was related to a poor understanding of ICS and of asthma.

*I felt like my inhaler wasn't as important, but I was still taking it regularly, because I ended up halving the dose, so it was better (Patient 6)*

In one case a patient admitted to manipulating the Smartinhaler™ by activating the inhaler without taking the medication. This was due to a fear of being told off for their non-adherence by doctors at the Hospital.

*I think I thought that if I take like if I ,twist it [the Symbicort Smartinhaler™], that will count up to my times I used it, so I kept twisting it to see and then I never knew you'd show the dates...I thought it would all add up to one number...When I come here, I didn't want it to be zero, zero, zero... [when asked why] They'll tell you off. (Patient 11)*

#### 6.3.3.2 ICS Concerns

##### 6.3.3.2.1.1 Dislike taking inhalers long-term

Patients were sometimes concerned about having to take inhalers for the rest of their lives. They dislike the idea of having to rely on medication forever.

*I'm at the stage where I know that I should be taking it, and I do take it sometimes, but then I feel like sometimes, I don't really want to take it, but I have to, but I don't want to. So, I have to take it, and that's what I feel sometimes. (Patient 14)*

##### 6.3.3.2.1.2 Long-term effects

Patient mainly had concerns around the future and long-term effects of ICS which influences their adherence, rather than about immediate side-effects or general concerns.

*I'm also concerned about the long-term effects of the inhaler...so I might take it a little less regularly. (Patient 6)*

Despite their age the patients were concerned about the long-term unknown effects of their medication and described the need for information and understanding of the medication they are being asked to take. This belief was held by few patients but is a general treatment belief related to a lack of trust in pharmaceuticals and suspicions about the consequences of taking the medication.

*... I need to understand it is, as I said, I don't want a foreign substance coming into my body and it screwing with it to be honest and that if I knew what it was doing to my body then I would be more comfortable taking it. (Patient 9)*

##### 6.3.3.2.1.3 Experienced Side Effects

Side effects were mentioned less often than long term effects but when they were discussed they were generally related to steroids. The few instances where current side-effects were

discussed were in relation to severe side effects including damage to teeth, weight gain and mood.

*...we went to the GP and she said it (small weak teeth) was because of steroids....That hit my confidence about my inhalers... (Patient 8)*

*"Yeah, sometimes I feel angry for no reason. Sometimes I'm depressed for no reason, like I'm sad. Sometimes I'm just so deep in thought. Sometimes I'm just really reactive for no reason. It's just all over. Like when I take my medication...it doesn't do like a literal effect or impact, but like I feel like it kind of makes me have mood swings and makes me a little moody or something." (Patient 12)*

Were one patient discussed weight in particular it was clear that there was confusion between the side-effects related to oral steroids and ICS which was deep-rooted. This perceived side-effect was a very important determinant of poor adherence in this individual.

### 6.3.3.3 SABA Necessity

#### 6.3.3.3.1 Reliance on or preference for reliever

Due to patients low ICS necessity (Theme 6.3.3.1.2) and low perceived efficacy of preventer inhalers, their experience of the onset of effect and duration and their poor understanding of asthma and ICS they often preferred to use or rely on their reliever inhaler to treat symptoms rather than ICS for the underlying asthma.

*"But then when I don't need it [Symbicort] I just stick to the blue because I feel like the Symbicort is just not necessary because the blue is just a reliever and the Symbicort doesn't do the same effect..." (Patient 12)*

Patients discuss the relationship between the use of their preventer and reliever inhalers and that they more often rely upon the ability to use the reliever inhaler when they don't take the preventer inhaler. Again, the patient refers to asthma as an increase in symptoms or an attack rather than as a long-term condition linked to their identity of asthma.

*"... I take Ventolin much more. No, I think that the Ventolin's just there so...in case I do get the asthma, which is very...like it's not very often, so I take it much less, and the Symbicort, I try and take it but I do forget very often. So, I think I'm trying to take it more than I try to take the Ventolin but I don't...I think I forget to take it, so I sort of take it the same amount." (Patient 13)*

Patients also discussed the importance of “the blue inhaler” and that when non-adherent this was often perceived to be the most important medication, which of course during an acute asthma attack as a rescue medication it is.

*“I can’t take my purple pump as often as my blue, so I guess I thought the purple was kind of different, which they are, but I thought my blue pump was more important than my purple pump, but now I realise that it’s not really different, I think the purple pump affects me more than the blue....I thought the purple pump didn’t really matter, that’s why I didn’t take it.”  
(Patient 5)*

*“I was normally thinking my Ventolin saves me from asthma attacks, hurrah!” (Patient 9)*

Patients also highlighted that as well as having an immediate effect the reliever (blue) inhaler is easily accessible as it is always carried around with them unlike a preventer inhaler.

*“because it works well, I guess, because it's always with me... I just have the blue one with me all the time. So, yeah, I think I just take it more because I have it all the time.” (P19)*

#### 6.3.3.3.2 Onset of effect and duration

Often patients described the onset of the effect of the medication as opposed to the different effect it has when comparing ICS to reliever inhalers.

*Because the blue one, like, if I can't breathe, I take it, because it'll make me better, like, in two minutes or something. (Patient 10)*

*The Symbicort does take a while to actually like make my breathing better whereas the blue is instant. (Patient 12)*

Patients reported feel a difference when taking the “blue inhaler” (reliever) and as they do not report experiencing instant relief with Symbicort it would take more to convince them to take it and that it is worth taking it regularly instead of the quick relief of the reliever only.

#### 6.3.3.4 SABA Concerns

##### 6.3.3.4.1 Dislike dependence on relievers

Patients dislike having to rely on reliever inhalers to complete normal tasks such as swimming, dancing and physical education at school.

*Because, like, in PE, because there's pollen and stuff, also because I'm allergic to it, like, my asthma gets bad or something like that, so I have*

*to...like, sometimes I forget to carry it into the field with me, so I have to go back to get it, and then...yeah. Or I forget to take it before, and the teacher will be, like, oh, can you go back to the medical or go back to the changing room to get it. (Patient 10)*

#### **6.3.4 Practicalities**

##### *6.3.4.1 The importance of routine*

In addition to having their prescriptions available patients often discussed the practicalities around their routine or lack of routine and how that influences their ability to take their inhaler.

Several patients mentioned putting alarms on their phones while being monitored with the Smartinhaler™ but that this, although effective, was annoying when not tailored in relation to their specific routine, and that this was not a long-term reminder system.

*Because it was annoying me. Because basically, like, on Mondays I do dance, so in the evening I finish late. So the alarm would go off when I'm out. So yeah, I don't want that to happen. (Patient 10)*

##### *6.3.4.1.1 No routine*

Patients often had no specific time to take their inhaler. They had not tried to fit taking their medication into their preparing for school routine and they often did not have a specific location where the inhaler is kept within their house.

*"Sometimes I'm like really early, sometimes I'm late and it's like sometimes I'm just on time... I don't really have like a set routine of when they sleep, when I wake up, so it's really hard to piece something in to, like, a not working puzzle or so." (Patient 7)*

*Maybe also because I can't find it, because I need to...I don't put it in a good place so I need to, like, always find it, yeah. (Patient 10)*

Patients also described the reason that it was not in their "plan" or routine was because it was not important to them (links to Low ICS necessity).

*Maybe it was rarely part of my plan because my brain just rarely needed it to be there, it's just a preventer. (Patient 18)*

*"To be honest taking my inhaler is half luck." (Patient 8)*

#### 6.3.4.1.2 Disruption of routine

Patients that felt they did have good routine found that it was often disrupted for example by the weekends, holidays, staying at another parent's house or by other competing priorities.

*...I have other things on my mind: the weekend, and things like that. And it's more out of my routine. (Patient 6)*

*It's just on days where maybe I'm really tired, so I'll lie in bed for a bit longer, or something like that, where the routine just changes slightly, that I'm not as good with it. (Patient 4)*

#### 6.3.4.1.3 Split family difficulties

It was not uncommon for patients to have two family homes which increases the need for a good routine and also complicates the routine for the patient. One patient described how their routine was good at one parent's house but at the other house it was completely disrupted due to the inhaler being kept in a different place to at their mother's house, on the father's bedside table rather than the child's bedside table.

*My dad's got asthma as well...He also takes the Symbicort... Usually it's by the side of his bed and that makes it a bit more difficult for me to remember. (Patient 8)*

Through further probing it became obviously that as the father was also asthmatic he was using the child's inhalers likely due to children's medication being free on the NHS whereas adult asthma medication is not. Although this is a rare case it highlights the complex social context of asthma and regular use of ICS.

#### 6.3.4.1.4 Competing priorities

Young people often found that they had competing priorities in their lives interfered with taking their medication including not taking their ICS when they are running late for school, prioritising homework late at night, preferring social activities with friends and not wanting to break off from TV, films or computer games to take their ICS.

*...I'd be thinking of everything non-important...My priorities are like really bad, but I know, I'm aware of that, but it's like I can't help it. I always think of the stuff, non-important things what I need to know, but end up forgetting the necessities and stuff. (Patient 7)*



#### 6.3.4.1.5 Unintentional forgetting

Forgetfulness was frequently mentioned particularly at the beginning of the interview, as patients' initial reaction to questions about their inhaler use. Often once probed many other reasons were divulged by the patients that explained the forgetfulness. The reasons stated were often related to the other themes presented such as Low ICS necessity, poor understanding of asthma and a lack of routine.

Less commonly patients described true forgetting, unintentional non-adherence.

*...it's never like a conscious decision not to take it (Patient 4)*

Unintentional forgetting was also related to fatigue in the adolescents. Patients often described feeling too tired in both the morning and the evening and that this interfered with them taking their ICS.

*...the sight of seeing my bed makes me want to jump in it and fall asleep straightaway...So, when I'm really tired I normally do exactly that. (Patient 9)*

*... well I'm meant to take it before I go to bed, I just get too tired and forget (Patient 2)*

#### 6.3.4.1.6 Environmental cues (facilitator of adherence to ICS)

Those that claimed to be adherent regularly had a specific location for the inhaler and often kept the inhalers in a highly visible and accessible location such as on their bedside table, by their toothbrush or by their mobile phone. Patients described that seeing the inhaler triggered their memory and reminded them to take it more often than when the inhaler was in the same location but not visible such as a drawer or kitchen cupboard.

*...that's the first thing I look at [the preventer inhaler] 'cause I'm facing my bedside and then I see that and then I think about it and I look and I get it and use it. If it's in the cupboard I won't think about it. The chances that I'd think about it are low and if I do I won't use it in the afternoon 'cause it's in the drawer, 'cause I'm downstairs and I won't be arsed to get it. (Patient 11)*

One patient also highlighted the importance of a personalised approach for developing adherence solutions in that a one size rule does not fit all. Not all teenagers will brush their teeth twice a day and therefore being told to keep their inhaler by their toothbrush as a standard instruction will not necessarily increase adherence. Likewise, not all teenagers have their phone

visible by the side of their bed which is why an individual patient led approach for developing adherence solutions are necessary.

*... now I keep it near my bedside, literally next to my phone and the first thing in the morning what I do is I check my phone, so obviously when I look there, my inhaler's just next to it. So I pick up my phone and inhaler together, until I'm on...trying to unlock my phone, I quickly take my inhaler. So it is more convenient having it in my room rather than my brush, because they did say keep it near your toothbrush but I felt like that didn't really...like I never used to remember then. It was better than not having it anywhere, but I feel like next to my bed is way more convenient for me.  
(Patient 12)*

#### 6.3.4.2 The importance of parents

##### 6.3.4.2.1 The importance of parental reminders (facilitator of adherence to ICS)

Parents were mentioned as extremely influential in reminding patients to take their ICS.

*So like when they even see me cough or anything...like every day they ask me have I taken my inhaler, that's like a must for them, like one of them always asks, have I taken my medication. That reminds me what I've taken and what I haven't and then whatever I haven't I just go and take it then. If not, then they just actually bring the medication to me. (Patient 12)*

##### 6.3.4.2.2 No parental reminders (barrier of adherence to ICS)

When parents do not remind their children the patients often reported forgetting or not wanting to take their inhalers.

*No, it's my responsibility, I think, maybe they used to, I don't think they've ever really tried to remind me, I think they take the approach that I've had it for so long, that it's my responsibility and they think I'm responsible enough to take it myself. (Patient 4)*

##### 6.3.4.2.3 Parental importance in providing prescriptions (facilitator of adherence to ICS)

In nearly every case parents organised, ordered and collected medication on behalf of the child. This was both mothers and fathers and children reported having little to do with the process.

*...my dad keeps my prescriptions... he does it, and then if I ever feel like I need more inhalers, I'll just let him know (Patient 4)*

*...my mum would call the pharmacy and they would come and deliver it.  
(Patient 19)*

## 6.4 Discussion

This study furthered the literature of non-adherence in children with severe asthma using novel methods to explore specific determinants of non-adherence in adolescents in a tertiary care NHS setting. The study highlighted the need for tailored discussion around non-adherence with the adolescents themselves, as although forgetfulness was stated initially as the key reason for non-adherence, a non-judgemental discussion revealed much more complex illness and treatment beliefs as the root to forgetfulness. Determinants related to perceptions and practicalities were explored utilising an adherence monitoring interview technique with patients, which revealed non-adherent patients to have poor or disrupted routines for their ICS use, low necessity beliefs for ICS as a treatment for asthma based on poor illness coherence, and important parental influence with practical elements of their ICS use only (e.g. verbal reminders to take their ICS and support with prescription ordering and collection).

### 6.4.1 Summary of the themes and comparison with prior literature

#### 6.4.1.1 *Sense of self*

Patients reported that generally asthma was a condition which people knew about, and that their friends and families did not make them feel stigmatised about having asthma. However, when asked about taking asthma treatment in front of people many participants described feeling social stigma around taking their reliever inhaler in public. This was often outside of the home and in front of strangers or their class and could be related to exercise such as physical education at school. As mentioned previously, the stigma that is felt during this time could be used in an intervention to encourage preventer rather than reliever reliance. Patients often felt that taking the reliever inhaler and having asthma makes them feel different to other people and they often compared themselves to others with a “why me?” attitude. This comparison with others was also in relation to other people with milder or less well-controlled asthma. Patients reported that they were different and that asthma in general was not seen as serious because of so many people having less severe asthma. This finding highlights the patient with severe asthma perspective consistent with research outlining the potential over-diagnosis of asthma in current medicine as reported by Bush and Fleming (2016) and the importance of developing an objective test for asthma (NICE 2017a) as discussed in Chapter 1.3.

Similarly, patients reported that asthma is often trivialised in different ways and viewed as a non-life-threatening condition. This included that family would underestimate the condition in terms of their triggers and the amount of medication needed, and also that the wider world

does not think asthma is important, highlighted by the lack of charities and awareness of severe asthma. This finding is novel to this study and could be related to the asthma severity of the population studied. It is of importance because if patients feel that their condition is not considered serious, including by others, and that it is socially stigmatising, this may cause significant non-adherence issues and a reluctance to use emergency reliever treatment in public.

#### 6.4.1.2 *Illness beliefs*

Patients described their asthma as episodic in nature in relation to specific triggers and that thus influenced how often they took their ICS. They also described how they were used to, and put up with, a certain level of poor asthma control: as many patients were diagnosed with asthma at an early age they had a different perception to what is normal for them and they described being accustomed to having mild daily symptoms. Patients frequently described their asthma and both inhaler treatments as annoying, particularly in relation to their inability to participate in activities and having to take the preventer inhaler as a regular part of their routine. Some patients reported that a serious asthma attack changed their beliefs about asthma as a condition and that the newly perceived seriousness of asthma then changed their adherence behaviour. However, as reported in other conditions, such as Myocardial Infarction, a serious life-threatening event is not always a catalyst for a change in behaviour (Petrie & Weinmann, 2013). The behavioural outcome depends on the patients' illness and treatment beliefs about the event and subsequent coping strategies (Leventhal et al., 1992). Perhaps severe health events could be seen as "teachable moment" at which point intervention to access and modify illness coherence may be most effective (McBride, Emmons, & Lipkus, 2003). These beliefs related to patient's CSM identity of asthma should be considered in any intervention targeting non-adherence.

Recent guidelines for asthma indicate that poor control is defined by risk factors such as loss of lung function and increased symptoms such as day time symptoms and night-time waking, and that medical professionals aim to reduce these factors for every patient (GINA, 2019). However, patients may be unaware that there is the possibility that when prescribed the right medication, and when taking it appropriately, that no symptoms may be an option. Patients often normalise symptoms and become unaware of them compared to those around them. Indeed, one survey study found that 40% of respondents classified their child as having good asthma control despite experiencing symptoms, using a reliever inhaler and missing days from school (Dozier, Aligne, & Schlabach, 2006; GINA, 2019). Discussing complete asthma control as a goal with patients and their parents, may alter their identity of asthma if patients realise their level symptoms can be

reduced further (not the norm to be this ill) and increase their perceived need for treatment and reduce non-adherence. Indeed, the importance of exploring patient understanding of asthma control is recognised and recommended in the 2019 GINA guidelines. Future research may utilise audio technology to provide patients with biofeedback of their symptoms to provide some objectivity to discussions around their audible symptoms.

Even within this group of patients with severe asthma who were seen regularly in a specialist care hospital, understanding of asthma and its treatments were generally poor. Patients often described having no knowledge of previous discussion with their clinicians around what asthma is, how the two main inhalers differ or how ICS works to prevent asthma attacks. Asthma illness coherence is raised as part of a transition protocol from paediatric to adult care with the Royal Brompton Hospital. However, given the young age that many paediatric asthma patients are diagnosed with asthma, an early refresher of these topics may be warranted on admission to the hospital. This patient-led discussion should start from the patient's current understanding in order to access and correct any inaccuracies, rather than clash with these as a clinician-led lecture may do.

Consistent with Halm et al.'s (2006) description of "no symptoms, no asthma" the patients interviewed considered asthma an episodic condition rather than a long-term condition and therefore the use of a daily preventer inhaler does not fit with their illness beliefs (Horne & Weinman, 2002). Revealingly, when asked the question of what asthma means to them patients most often describe activity limitation or the experience of having an asthma attack, rather than the daily experience or their understanding of asthma as a condition. This is consistent with an episodic experience of asthma and helps us to pinpoint what is important to them, e.g. the ability to participate in activities like other children do. This information could be useful when designing an intervention, again to frame adherence as enabling participation in activity.

#### *6.4.1.3 Treatment Beliefs*

Patients consistently report a perceived low necessity for ICS and high necessity for their reliever inhaler. The comparison between the onset of effect of the two types of inhaler were reported as related to the level of reliance placed on each treatment and therefore the frequency of use of each device. Patients reported disliking the reliance on their reliever inhaler but feeling anxious when they do not have it with them. This too could be targeted in an intervention to encourage use of the preventer inhaler to reduce feelings of anxiety over the proximity of the reliever inhaler, although carrying the reliever should still be encouraged at all times in case an

emergency situation arises unexpectedly. Due to this poor understanding of asthma and ICS and their reliance on reliever inhalers, patients described lying to their parents and doctors about their adherence and adjusting both their doses and their Smartinhaler™ devices accordingly. This theme has been previously described in the literature by Stewart et al. (2018) who reported that although patients felt there were benefits to being monitored using EMD they also felt that they were under surveillance and that this affected the health care professional-patient relationship.

Although ICS concerns were reported by the participants in this study, the concerns were generally future focused, such as depending on relievers and preventer medication forever and the long-term effects of medication. Current side-effects were less frequently reported by patients in this study of adolescents with severe asthma, and rather than side-effects, again activity limitation and being held back from activities were often discussed in relation to the condition itself. The findings in this study were richer and more heavily discussed by patients regarding a lack of perceived effect of ICS and therefore low necessity compared to concerns. This contrasts with the treatment beliefs of parents of children with asthma in which concerns are heavily described specifically around the use of steroids (Conn et al., 2005; Orrell-Valente et al., 2007). This study supports Yilmaz et al (2012) as it shows low reporting of concern beliefs in children (Yilmaz et al., 2012).

Importantly, despite forgetfulness previously being the most commonly reported reason for non-adherence in children with asthma (Koster et al., 2015; Penza-Clyve et al., 2004), this study exposed that the majority of initially reported forgetfulness could be attributed to low perceived need for ICS in this population and other modifiable factors. It appears that within this population it is lack of necessity for ICS, increased necessity for reliever inhalers, poor understanding of asthma treatments, practicality issues e.g. routine, rather than concerns.

#### *6.4.1.4 Practicalities*

In support of Phillips et al. (2013), research related to adherence and routine was frequently reported as a problem in patients who were non-adherent to their ICS. A lack of routine, or an easily disrupted routine was reported by patients with low ICS beliefs and low adherence. Forgetfulness was infrequently truly unintentional. In these instances, patients discussed forgetfulness in terms of tiredness and that particularly when tired late at night or early in the morning patients found it difficult to remember or to want to take their medication. Fatigue is well documented to commonly occur in adolescents and can be related to daily routine with

consequential lack of sleep and internal factors such as puberty (Moore & Meltzer, 2008). Although intrinsic factors are not modifiable, a good sleep routine and good medication routine leading to habitual medication use and increasing ICS necessity beliefs could be targeted within an intervention.

In contrast, patients who claimed to now be adherent reported facilitators to adherence including established medication taking routines including placing their medication in a visibly prominent position as an environmental cue for medication taking. This is a recognised behaviour change technique (Michie et al., 2013) that is related to practical/ability barriers to adherence. However, the most common reasons given for established routines being disrupted were intentional reasons related to a lack of perceived necessity for ICS daily for example competing priorities.

The importance of guardians (in particular parents) were described by patients in relation to medication management, such as reminding the adolescents to take their medication and in ordering collection of the patients' prescriptions for their asthma treatments. Patients reported that these were the areas in which their parents supported their adherence and that without them they would forget or run out of their medication. Where patients' parents were not helping to remind them (in a limited number of participants), patients reported frequently forgetting to take their ICS. This theme related to previous literature around the benefit of reminders in increasing adherence (Chan, Stewart, et al., 2015), however, this population are reliant upon their parents rather than an electronic reminder. This finding mirrors that of Koster et al. (2015) in a Dutch study in focus groups within primary and secondary care in adolescent patients with asthma.

The majority of the facilitating factors that were mentioned by patients were within the practicality domain and were related to cuing memory of medication taking and the supply of medication. These practical facilitators were often mentioned by patients who claimed to be currently adherent to their ICS treatment. These practicality based facilitators would not outweigh perceptual barriers to medication taking in patients currently non-adherent to their ICS. Therefore, although exploring adherent patient's facilitators and barriers to ICS is important we cannot assume barriers and facilitators will be polar opposites for patients at each end of the adherence spectrum. However, comparing barriers and facilitators for high and low adheres could yield interesting results for the development of a targeted intervention for non-adherent patients by comparing and contracting facilitators and barriers for the different groups. This was

the method used for the exploration of adherence to nebulisers in patients with Cystic Fibrosis in a study with similar EMD methodology to the current study (Drabble et al., 2019).

#### 6.4.2 Limitations of the research

Although this qualitative work used an EMD to record adherence as an objective tool, there were limitations with this methodology. The EMD device used to measure adherence for inclusion in this study and for the AMI was the Smartinhaler™ (now known as the Hallie™ platform, by Adherium), as this was the only clinically available device to measure actuation including a time stamp for each dose. As discussed in Chapter 2: there are advantages and disadvantages to each device. The predominant disadvantage for this study was that Smartinhaler™ do not measure inhalation or inhaler technique. In brief, this means that some patients may have been included in the study who were manipulating their Smartinhaler™ (which we know to be true for at least one participant) and therefore the device gave an overestimation of their adherence, or conversely a non-adherent participant may not have been approached as they appeared adherent from their Smartinhaler™ data. Similarly, in terms of inhaler technique, the Smartinhaler™ is likely to overestimate the medication dosage entering the airways as it does not record data inhalation correct or otherwise (Sulaiman, Seheult, et al., 2016). This limitation will be discussed in greater detail in the general discussion as this tool was used to measure adherence throughout the PhD as it was already in use at the recruitment site, The Royal Brompton Hospital.

A second limitation with the Smartinhaler™ adherence data is that some of the data was collected up to two years prior to the interviews for the Jochmann et al. (2017) study. The data therefore was not always accurate in terms of the patients' current adherence, and their beliefs about adherence may have changed within that period of time. Indeed, some patients claimed to now be adherent and therefore when asking them to think back to the period of time in which they were monitored, recall bias was a limitation. Although it was not possible to tell if patients were currently adherent or non-adherent to their ICS without recent monitoring, the comparison of barriers to adherence previously and currently added interesting detail to the interviews in terms of what patients reported had changed. Unfortunately, when this study began not all patients attending the clinic had had a period of electronic monitoring for adherence, and of those only a proportion were classified as non-adherent and therefore were eligible to take part in the study. Ideally, patients would be recruited for their AMI interview as



soon as a period of electronic monitoring had finished to reduce recall bias, which was the case in some of the patients recruited.

Although creative methods were offered as a medium for patients to respond to the interview questions only two participants chose to draw pictures and the pictures only related to questions around asthma and medication understanding. This could be due to a myriad of reasons, but two likely explanations are that 1. The interviewer did not adequately inform and engage the participants with the option to draw pictures or write to help them express themselves due to limited expertise in this novel type of interviewing, or 2. That patients' age and level of English language ability was such that alternative, creative methods of communication were not needed between the participants and interviewer. Nevertheless, the two pictures that were used indicate that these methods were useful for some patients, particularly in helping them to express their explanations of the lungs and how their medications work. These methods may perhaps be more useful in interviewing younger children regarding their illness and treatment coherence and in children with limited English verbal language skills, and also in initial explanations of these complex mechanisms with children and their families.

#### **6.4.3 Strengths of the research**

Qualitative research in children with asthma is often conducted with parents of children rather than with the child themselves. However, this study targeted the adolescents themselves and as it was focused on exploring the determinants of adherence for participants, their parents were not present. This strengthened the research as adolescents are less heavily supervised than younger children and therefore it is logical that their beliefs will be a better indicator of adherence than their parents' beliefs or their beliefs reported while their parents are present. This small but important difference in research methodology in exploring adherence in children with asthma was designed to increase the likelihood of honesty and an open discussion with the interviewer.

Similarly, the novel use of objective adherence EMD as a basis for the interview and for discussion of patterns of adherence aimed to create a non-judgemental factual based starting point for the interview. The use of patients' own data meant that patients did not deny non-adherence but sought to explain it within the interview, which was a valuable position from which to examine the determinants of non-adherence. Equally, the interview introductions highlighted the non-blaming culture of the forthcoming interview as I explained my own history

of asthma and non-adherence as an adolescent. This was with an aim of normalising the behaviour without supporting the concept of non-adherence. This was commented upon by participants as therefore coming from a perspective of understanding, and empathy with their reasons for non-adherence. This highlights the need for empathy for their condition to be verbally shared in a normalising manner by their clinicians despite not necessarily having the condition themselves.

Despite recruitment difficulties thematic saturation was reached and a purposive and diverse sample of patients participated in the study. This was a strength of the study as tertiary care, adolescent patients with problematic asthma who are known to be non-adherent are a niche and difficult to reach group of people. Many challenges were overcome to enable their participation such as ill health, ability to attend appointments and being granted parental consent in order to participate in the study.

#### **6.4.4 Future research**

This research exploring the determinants of non-adherence in a specific group of patients with problematic asthma is a fundamental stage for the development of a tailored intervention. Future research should utilise these findings to create tailored elements to address these determinants and therefore non-adherence to ICS as a whole. Vivaly, future work should target patients' perceptions: understanding of asthma as a long-term condition rather than as episodic, and the difference between preventers and relievers with a focus on reframing ICS in a positive light. In addition, any intervention should elicit and address medication concerns and practicality barriers: by involving families in the intervention particularly around parental reminders and prescription pick-up and the transfer of responsibility for these, and finally anchoring inhaler use with an already habitual task, all of which should be tailored to the patient.

Future research investigating patients with a different severity of asthma and different age groups should be conducted, as adults and even those with other long-term conditions could benefit from the AMI approach as EMD objective measurement of adherence has not previously been used to explore determinants in this way. I would recommend that future research aims to complete the AMI shortly after the adherence electronic monitoring data has been collected to avoid recall bias, where practical to do so.

## 6.5 Conclusions

This chapter outlined, from a patient perspective, determinants of non-adherence in relation to illness and treatment perceptions. The methodology utilised was novel and found discussions around adherence behaviour based on objective EMD data to be useful in enabling an honest patient perspective of their non-adherence. The study enabled a more thorough exploration of the patterns of non-adherence such as those identified in Chapter 5: within a targeted group of patients, adolescents aged 12-17 who were non-adherent to ICS. Low perceived necessity for ICS, as opposed to a large amount of concern beliefs, appear to drive non-adherence in contrast to previous research in adults with asthma and in parents of children with asthma. The qualitative study also, in contrast to previous literature reliant on patient honesty, found that forgetfulness is not one of the primary reasons for non-adherence in this group but more often a consequence of other perceptual and practical reasons. The chapter highlights and explores how the identified determinants may be addressed within a tailored intervention to address both motivation and ability barriers to adherence.

The next chapter describes the process by which the above findings were consolidated into an adaptation of the Beliefs about Medicines Questionnaire (BMQ), to enable quick and thorough exploration of these beliefs within a research or clinical setting. A tailored questionnaire adaptation to enable a quick understanding of this rich data was the logical next step prior to development of any intervention. The questionnaire will allow clinicians and researchers to assign patients to different tailored adherence packages for a more personalised approach to intervention.

## Chapter 7: **Adapting the Beliefs about Medicine Questionnaire for Young People With Asthma (BMQ-YPWA) to Identify Determinants of Adherence**

### **7.1 Introduction**

As discussed previously (Chapter 2.2.1.4.6) EMDs such as the Smartinhaler™, which measure when and how often patients activate their inhaler, are currently the gold standard for measuring adherence in asthma (Chan, Harrison, et al., 2015). However, EMDs do not provide insight into the reasons why patients are non-adherent, and the devices are expensive and are not widely available. Therefore, there is a need for a more feasible, practical and reliable way to evaluate adherence including adherence-related beliefs.

Although less accurate for the measurement of adherence than EMDs, self-report measures could be a cost-effective tool for the exploration of modifiable beliefs and practical barriers which are a risk factor for non-adherence. One self-report questionnaire that has been previously validated for identifying the beliefs driving non-adherence in adults is the Beliefs about Medicine Questionnaire (BMQ; Appendix 9) (Horne, Weinman, & Hankins, 1999). This questionnaire was developed to assess patients' treatment beliefs (see Chapter 3.2.6) regarding a wide variety of preventative medications. The original questionnaire comprises two sections: one assessing general belief about pharmaceutical medicines as a class of treatment (BMQ General), and the other assessing beliefs about medicine(s) prescribed for a particular condition (BMQ Specific). The BMQ Specific, which is the focus of this chapter, includes five items assessing beliefs about personal necessity of the medication (Specific Necessity) of the specific medication and five items assessing concerns about medication. A sixth item that has been added to the concern scale more recently assesses side-effects: "This medicine causes unpleasant side-effects". The first BMQ validation study was conducted with 524 adult participants recruited from a secondary care outpatients' clinic in the UK. The patients all had a long-term condition and 78 were patients who had a diagnosis of asthma. The questionnaire was validated and has since been used to assess treatment beliefs in a wide range of conditions across the world (Brandstetter et al., 2017; Foot et al., 2016; Horne et al., 2013).

The BMQ has, however, rarely been used in a paediatric population with children completing the questionnaire for themselves (Alsous et al., 2018; Trachtenberg et al., 2012), and it has not been adapted or validated for such use. Therefore, this study aimed to adapt the BMQ for use in young people with asthma (BMQ-YPWA) in addition to pilot-testing the questionnaire to test its validity and reliability compared to relevant current gold standard measurement tools.

### 7.1.1 Objectives:

- To adapt the BMQ for use in young people with asthma;
- To explore how patients responded to the newly adapted BMQ-YPWA;
- To preliminarily evaluate the internal validity of the BMQ-YPWA using Cronbach's alpha analysis;
- To preliminarily evaluate the convergent, criterion and discriminant validity of the BMQ-YPWA via correlation analysis.

## 7.2 Methods

The study design was a questionnaire adaptation followed by a cross sectional survey study.

### 7.2.1 Adaptation of the BMQ and additional item development

In line with the authors' suggestions for maintaining the integrity of the original BMQ, the 10 specific sub-scale items developed to assess necessity beliefs (n=5) and concern beliefs (n=5) were used as the basis for the adapted questionnaire (BMQ-YPWA). In line with the original BMQ, all statements were scored on a 5-point Likert scale from 1-5 (strongly agree to strongly disagree), however as the new items were created from a non-adherent population perspective the answer direction was reversed for the new necessity items (BMQ original (Strongly disagree to Strongly agree). Practicality items were also reversed with higher scores meaning fewer practicality issues. Higher scores on the BMQ-YPWA therefore indicate higher adherence in line with both the BMQ and Smartinhaler™ adherence percentage.

The new statements were written from the perspective of patients who were identified as non-adherent to normalise the beliefs as an attempt to produce more honest responses in the self-report questionnaire. The items therefore would potentially feel more authentic for other young people with asthma, as opposed to items written from an ICS adherence position. The statements were also written in accessible language for the young people aged 12-17 with mapped phrasing from the qualitative interview themes where possible. In addition to the original items targeting specific necessity and concern beliefs about preventer medication, this adaptation included three additional domains: practical factors; beliefs about SABA (both necessity and concern) and asthma identity beliefs. These themes arose from the prior qualitative work as important determinants of non-adherence in this group of young people with problematic asthma.

The research team who developed the adapted BMQ were Christina Pearce and the multidisciplinary team with expertise in pharmacy, questionnaire development and

psychometric testing, behavioural medicine, health psychology and respiratory. The BMQ adaptation was conducted over several meetings and six versions primarily by Christina Pearce and Amy Chan. Senior supervisors were consulted regarding the adaptation and alignment to the original BMQ (with Professor Robert Horne, creator of the BMQ) and clinical context expertise (Professor Andrew Bush and Dr Louise Fleming). As the items were developed directly from the qualitative work proceeding it, and the study procedures and documents only included minor amendments to the previous version, patient review of the study documents was not repeated.

The final adapted BMQ for young people with asthma comprised 30 items which included:

- 10 original BMQ specific preventer items (necessity = 5, Concern = 5)
- 7 additional preventer items (necessity = 5, Concern = 2) \*
- 2 asthma items (necessity = 1, Concern = 1)
- 5 SABA (reliever) items (necessity = 3, Concern = 2)
- 6 Practicality items (not beliefs but ability items)

\*note there are more necessity items, as necessity beliefs were more common compared to concern beliefs within the qualitative findings (Chapter 6). One of the additional concern items for the BMQ-YPWA was the sixth BMQ item used in recent publications (regarding side-effects).

Readability of the adapted BMQ-YPWA was checked using Microsoft Word grammar tools. The final BMQ-YPWA had a Flesch reading ease of 67.6 which equates to plain English and a Flesch-Kincaid Grade level of 6.6 which is easily readable by 11-13 year olds. The scores were thought to be acceptable given the target age group of 12-17 year olds and that the questionnaire included words that may increase the score such as preventer and reliever.

## **7.2.2 Exploring the reliability and validity of the BMQ-YPWA**

### *7.2.2.1 Participants*

The same group of patients were approached (12-17 year olds with problematic asthma) for the pilot testing of the BMQ-YPWA as in the previous qualitative study (Chapter 6.2.3) with the following additional criteria:

- Patients identified as both adherent and non-adherent were eligible to take part in the study

- Patients' period of EMD for adherence (Smartinhaler™ data) must have been within the last 12 months prior to the BMQ-YPWA data collection to reduce recall bias (a limitation of the previous AMI study)

Thirty patients were sought to test the newly developed BMQ-YPWA in line with recommendations for pilot testing questionnaire reliability (Radhakrishna, 2007). Due to the small sample size and age of the Smartinhaler™ data the reliability and validity testing outlined below is not definitive and was conducted to explore the necessary methodology for a larger future study.

#### 7.2.2.2 Measures

The patients completed a questionnaire pack (Appendix 10), during the waiting time for their appointments in paediatric outpatients, which consisted of:

- The newly adapted **BMQ-YPWA**
- **The Brief Illness Perception Questionnaire (B-IPQ)** (Broadbent et al., 2006)
- **The Asthma Control Test (ACT)** (Nathan et al., 2004)
- A single item visual analogue scale (VAS)

Qualtrics, a free cloud-based survey tool, was used to integrate the questionnaire measure into one survey (<https://www.qualtrics.com/uk/>) which was then presented to patients on either a tablet or a paper-based version for completion. Paper questionnaires were only used when the tablet was in use by another participant during busy clinic times. Qualtrics is a secure UCL-approved platform for conducting research studies and is favoured by universities as it has sophisticated survey functions, such as embedded editable scoring for each question, the application of logic, and forced entry options to avoid participants skipping questions and therefore missing data ([https://www.ucl.ac.uk/teaching-learning/sites/teaching-learning/files/running\\_a\\_student\\_survey\\_for\\_the\\_tl.docx](https://www.ucl.ac.uk/teaching-learning/sites/teaching-learning/files/running_a_student_survey_for_the_tl.docx)). These features were utilised to save time for data scoring once the data collection was complete.

#### 7.2.2.3 Procedure

Participants were identified by Dr Louise Fleming, consultant paediatric respiriologist and Angela Jamalzadeh, a specialist respiratory nurse using Smartinhaler™ data that had already been collected. Patients were recruited by CP at a regular outpatient's clinic appointment. Patients who had taken part in the prior qualitative study and who had consented to be contacted for

further related studies by the study team were telephoned where appropriate (i.e. when they met the updated inclusion criteria and were not currently hospitalised).

Love2shop vouchers were purchased to be used to repay families for their time. The vouchers were given to families through a prize draw for three winners: 1<sup>st</sup> prize was £50, 2<sup>nd</sup> prize was £30 and 3<sup>rd</sup> prize was £15. As patients and families were only informed of this benefit after giving consent to take part it was not intended to incentivise participation in the study and the method was approved by the NHS ethical committee (Ref: 16/NS/0082). Three winners were selected at random at the end of recruitment via an online randomisation website (participant IDs were used to ensure confidentiality).

#### 7.2.2.3.1 Ethical Approval

Ethical approval was sought as a major amendment to the previous qualitative study (Chapter 6). The application was prepared and submitted on the 20<sup>th</sup> of February 2018 and the substantial amendment was approved on the 23<sup>rd</sup> of March 2018 (Appendix 11). A further minor amendment was submitted on the 18<sup>th</sup> of May 2018 to increase the recruitment time until the end of December 2018 (Appendix 12). The application was approved on the 22<sup>nd</sup> of May. Recruitment therefore begun at the end of March 2018 and due to both the pilot nature of this study and the PhD timeline recruitment ceased in August 2018.

### 7.2.3 Hypotheses:

#### 7.2.3.1 *Internal reliability*

1. The BMQ-YPWA domains (necessity, concerns and practicalities) will show good internal reliability comparable to that of the original BMQ domains (only necessity and concerns).

#### 7.2.3.2 *Validity*

##### 7.2.3.2.1 Criterion Validity

2. The BMQ-YPWA necessity domain will be positively correlated with objective Smartinhaler™ measurement of adherence and with a single-item visual analogue scale of adherence.
3. The BMQ-YPWA concerns domain will be negatively correlated with objective Smartinhaler™ measurement of adherence and with a single-item visual analogue scale of adherence.



4. The BMQ-YPWA practicalities domain will be negatively correlated with objective Smartinhaler™ measurement of adherence and with a single-item visual analogue scale of adherence.

#### 7.2.3.2.2 Discriminant Validity

5. The BMQ-YPWA mean necessity scores will be higher in participants with good asthma control and lower in participants with poor asthma control (measured by a dichotomised ACT).
6. The BMQ-YPWA mean concern and practicalities scores (fewer practical issues) will be lower in participants with good asthma control and higher in participants with poor asthma control (measured by a dichotomised ACT).
7. The BMQ-YPWA mean necessity scores will be higher in participants who are adherent and lower in participants who are nonadherent (measured by dichotomised Smartinhaler™ adherence data).
8. The BMQ-YPWA mean concern and practicalities scores (fewer practical issues) will be lower in participants who are adherent and higher in participants who are nonadherent (measured by dichotomised Smartinhaler™ adherence data).

#### 7.2.3.2.3 Convergent Validity

9. The BMQ-YPWA necessity domain will be positively correlated with the B-IPQ domains identity, and timeline as was predicted within the original BMQ validation paper (Horne et al., 1999) and consequences as was predicted in an asthma specific study (Horne & Weinman, 2002). These B-IPQ items related to the seriousness of asthma were hypothesised to be positively correlated with preventer necessity.
10. The BMQ-YPWA concerns domain will not be correlated with the B-IPQ domains consequences, identity, and timeline.

#### 7.2.4 Data Analysis (Psychometrics)

The data were analysed in IBM SPSS Statistics 22. Univariate analyses were conducted to explore the responses to the items. Patients' responses to the items (necessity, concerns and practicality domains) were explored descriptively to highlight how patients in this adolescent group responded to the BMQ-YPWA items. Items were split at the mid-point (3) of the Likert scale response (1-5) to identify patients that agreed or disagreed with each statement. Items were explored separately for the core BMQ items and the newly-developed additional items from the BMQ-YPWA.

Attitudinal groups were explored in relation to BMQ-YPWA necessity and concern beliefs. This was done in line with previous literature to create groups of patients which could easily be understood (Aikens, Nease, Nan, Klinkman, & Schwenk, 2005; Chater, Parham, Riley, Hutchison, & Horne, 2014). Necessity and concern belief domain totals were split at the median as a cut-off for high and low beliefs and frequencies were calculated for each group. Due to the small sample size in this study the attitudinal groups were not explored further in relation to dichotomised objective adherence.

#### 7.2.4.1 *Internal Reliability*

Internal reliability, which checks that all items measure the same construct, was calculated for the whole BMQ-YPWA using Cronbach's Alpha. A score of 0 is indicative of no internal reliability where a maximum score of 1 is indicative of total reliability, meaning the items are measuring the identical construct. The Cronbach's Alpha for the BMQ-YPWA were then compared to the original BMQ Cronbach's alpha scores for the asthmatic sample (n=78). As the original BMQ only contained questions around preventer/maintenance medication the newly added domains from the BMQ-YPWA were assessed separately with necessity and concern items internal reliability assessed for each of the new domains. Standard cut-offs for Cronbach's alpha internal reliability are: 0.9 excellent, 0.8 good, 0.7 acceptable, 0.6 questionable, 0.5 poor, and less than 0.5 unacceptable (George, Mallery, & George, 2012). Test-retest reliability was not conducted for this pilot study due to time constraints but would be recommended for future validation of the BMQ-YPWA.

Item deletion was investigated for both constructs (necessity and concerns) to explore potential problematic items influencing the Cronbach's alpha values. It has been recommended that item investigation and possible deletions should be conducted where the corrected item total correlation is less than 0.3 and the Cronbach's alpha is increased based on the deletion of the item (Ferketich, 1991). This methodology was used to explore the potential item deletions necessary to increase the total BMQ-YPWA based on this small pilot data. Of course, this will need to be replicated with a larger number of participants to be a valid analysis. Where items corrected total correlations greater than 0.7, the items within the scale should be investigated as this would mean the item accounts for much of the variance in the scale and therefore other items may be redundant (Ferketich, 1991).

#### 7.2.4.2 Validity

Validity was explored using variables from the questionnaire pack to test different types of validity for the BMQ-YPWA. Correlations were assessed between the BMQ-YPWA and each additional variable for specific purposes. Analysis will be compared throughout to the core BMQ items for the specific preventer necessity and preventer concern subscales.

**Convergent validity:** Correlations between the BMQ-YPWA and domains of The Brief Illness Perception Questionnaire (B-IPQ) (Broadbent et al., 2006) were used to assess convergent validity. That is: does the newly adapted measure correlate well with variables from a similar theoretical context? The practicality domain will not be tested for convergent validity as it does not measure perceptual factors and therefore relate to the B-IPQ.

**Criterion validity:** Correlations between the BMQ-YPWA and a single item visual analogue scale (VAS), and also between the BMQ-YPWA domains and Smartinhaler™ data, were used to assess criterion validity as all are measures of adherence.

**Discriminant validity:** Independent t-tests comparing mean scores between the BMQ-YPWA sub-scales (necessity, concerns and practicalities) and ACT (dichotomised into good control and poor control with poor control having a score of  $\leq 19$  (Nathan et al., 2004)), and also BMQ-YPWA sub-scales (necessity, concerns and practicalities) and Smartinhaler™ adherence (dichotomised into adherence versus non-adherent with a cut off of 80%, Chapter 2:) will be conducted to explore the questionnaire's ability to distinguish different groups of patients.

## 7.3 Results

### 7.3.1 Participant Demographics

Thirty-three patients completed the Qualtrics survey (2/30 completed the study on a paper version of the questionnaire). However, three participants had faulty devices (adherence of between 0-13%) and therefore on advice from their medical care team these patients were excluded as the Smartinhaler™ data was not representative of their behaviour. Thirty participants were therefore included in the analysis and in the following descriptive summary of the participants. Patients were aged 12-17 years old (Mean=14.3, SD: 1.4) and included an equal number of males and females. Median adherence score was 74% (IQR=47.8%-84.1%). Sixty percent of patients were prescribed Symbicort and 40% of patients were prescribed Seretide.

Ethnicity of the participants also varied with 43% of participants self-identifying as being White British, 20% as Mixed Race and 37% as other including Asian and White European.

### 7.3.2 Univariate descriptive statistics

#### 7.3.2.1 Distribution of the BMQ-YPWA

The BMQ-YPWA (the dependant variable) was found to be normally distributed when assessed by Shapiro-Wilk ( $p=0.89$ ). Each domain that was explored within this study (preventer necessity and concern beliefs and practicality issues), were also normally distributed based on their Shapiro-Wilk result ( $p=0.26$ ,  $p=0.37$  and  $p=0.31$  respectively) and examination of histograms. There were also no extreme outliers in any of the domains although the response ranges were large. Based on the normal distribution of the BMQ-YPWA domains, parametric tests were used. However, the small sample size in this study may affect the results of the normality testing and reliability and validity testing. Any results reported are therefore preliminary.

#### 7.3.2.2 Exploration of the BMQ-YPWA item responses

Close to half (47%) of participants responded that their health in the future will depend on their ICS, and that without their preventer inhaler they would be very ill (43%; Figure 28). Seventy three percent of participants also responded that their life would be impossible without their preventer inhaler (73%). Fewer participants agreed with the statement “my health, at present, depends on my preventer inhaler” (37%) and very few agreed with the statement “my preventer inhaler protects me from becoming worse” (13%).

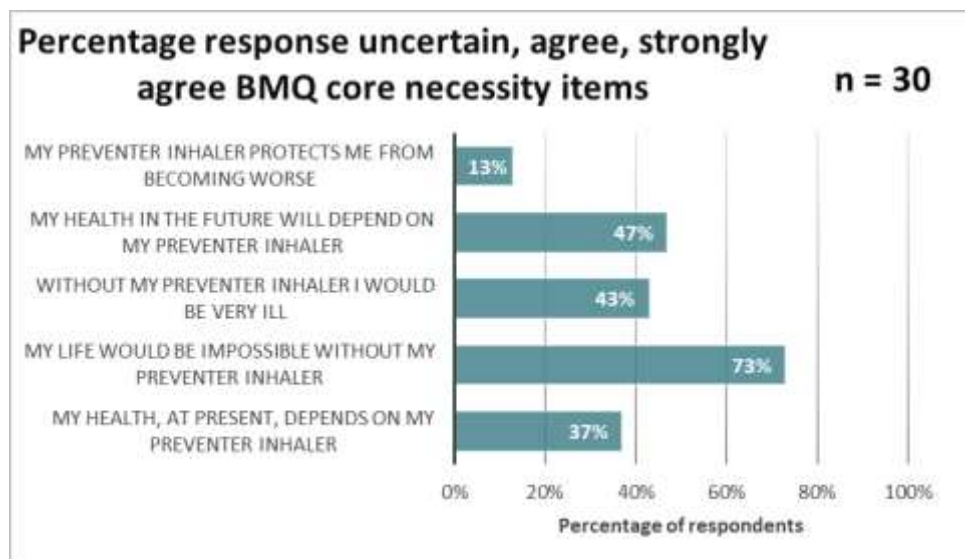


Figure 28: Percentage of patients who responded (uncertain/ agree/ strongly agree) to each of the BMQ core necessity items.

The majority of participants disagreed with the additional necessity statements which were written from a non-adherent patient perspective (Figure 29). One hundred percent of patients did not agree with the statement “nobody cares about my asthma so why should I take my preventer inhaler”; the vast majority (93%) also did not agree that “my asthma is still controlled without following all my doctor’s instructions” and finally the vast majority (88%) also did not agree with the statement “I don’t notice a difference whether I take my preventer inhaler or not”.

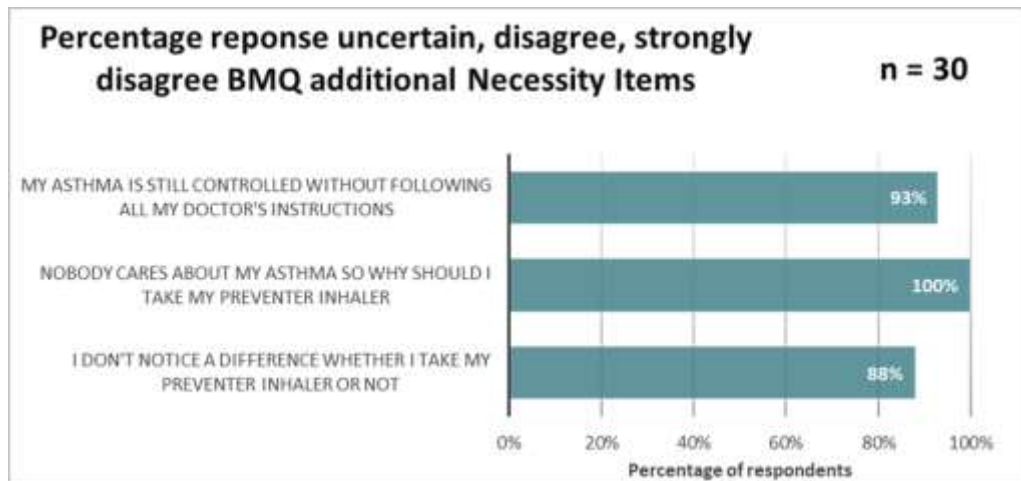


Figure 29: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the BMQ additional necessity items

The vast majority of participants disagreed with the BMQ core concern statements: “my preventer inhaler disrupts my life” (90%); “my preventer inhaler is a mystery to me” (93%) and “having to use my preventer inhaler worries me” (93%; Figure 30). Fewer participants disagreed with the statements “I sometimes worry about becoming too dependent on my preventer inhaler” (70%) and “I sometimes worry about the long-term effects of my preventer inhaler” (73%).

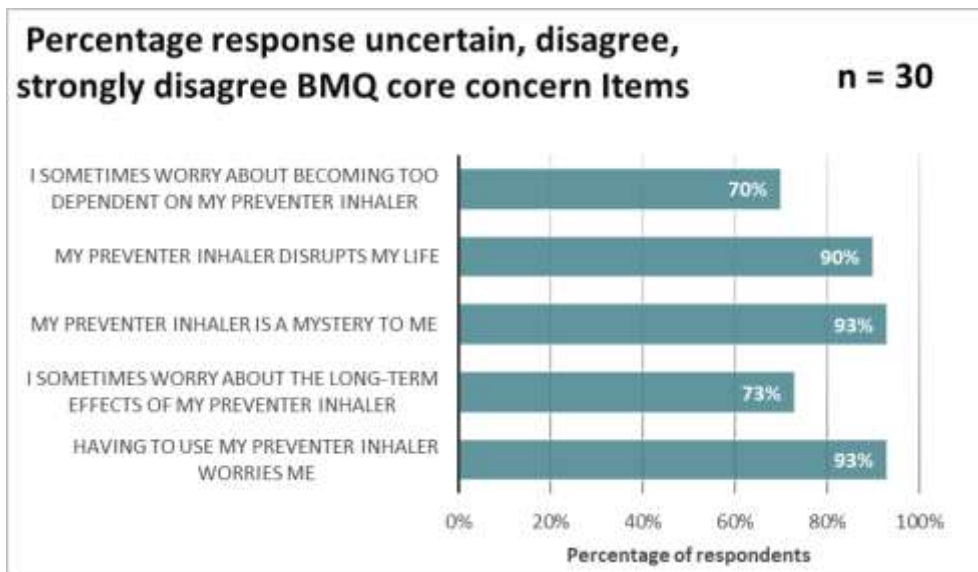


Figure 30: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the BMQ core concern item

All the participants disagreed with the statement “I do not trust my preventer inhaler” (100%) and the majority of participants disagreed with the statement “my preventer inhaler gives me unpleasant side-effects” (88%; Figure 31).

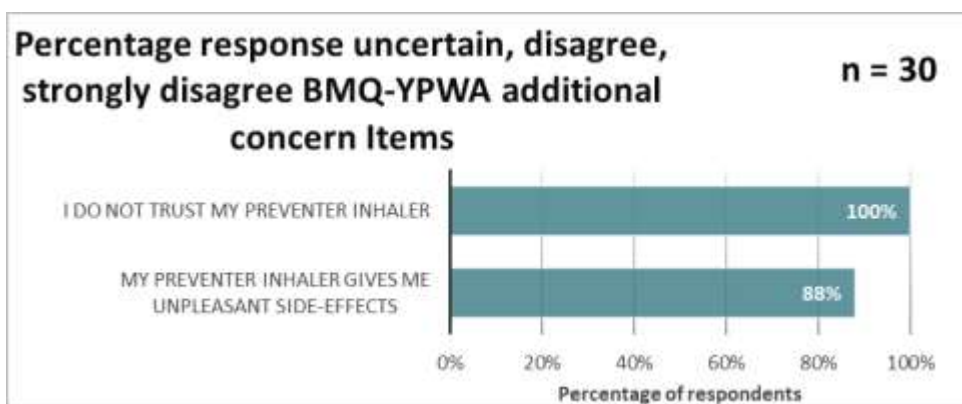


Figure 31: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the BMQ additional concern item

Sixty percent of participants disagreed with the statements “I find my routine for taking my preventer inhaler is easily disrupted e.g. at the weekend or during school holidays” and with the statement “When I am very tired, I sometimes don't take my preventer inhaler” (Figure 32). Over eighty percent of participants disagreed with the statement “I don't have a routine for taking my preventer inhaler” (87%).

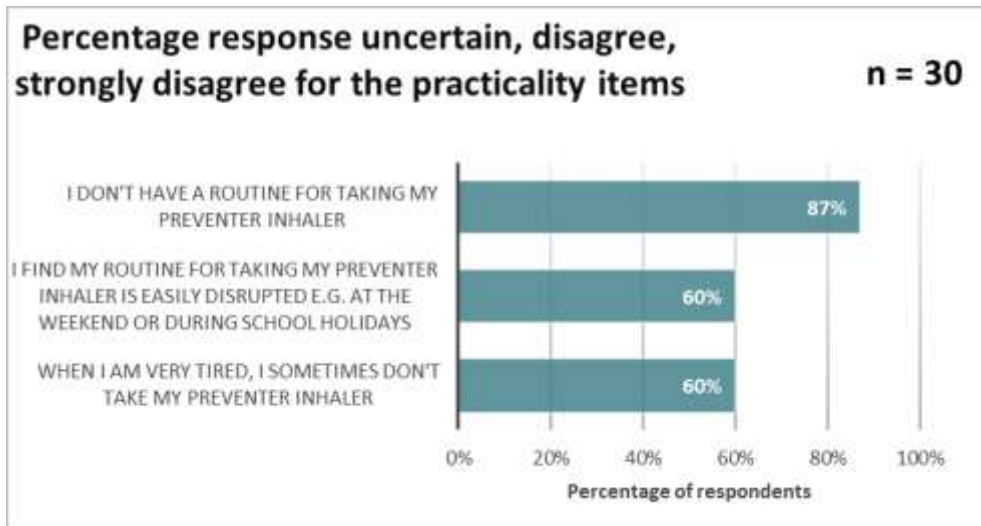


Figure 32: Percentage of patients who responded (uncertain/ disagree/ strongly disagree) to each of the practicality items

### 7.3.2.3 Attitudinal profiling

As shown in Figure 33, attitudinal groups were explored based on levels of necessity and concern beliefs (Aikens et al., 2005). A fifth of the sample (20%) were classified as having sceptical beliefs about ICS. Patients in this group had low necessity for ICS and high concerns about ICS. A fifth of the sample (20%) were also classified as indifferent whereby patients had both low necessity for ICS, and low concerns about ICS. Patients were categorised as accepting of ICS in a third of the patients (33%), who had high necessity for ICS and lower concerns about using ICS. A slightly smaller group of patients (27%) had ambivalent attitudes towards ICS, holding both high necessity beliefs for ICS but also high concerns about ICS.

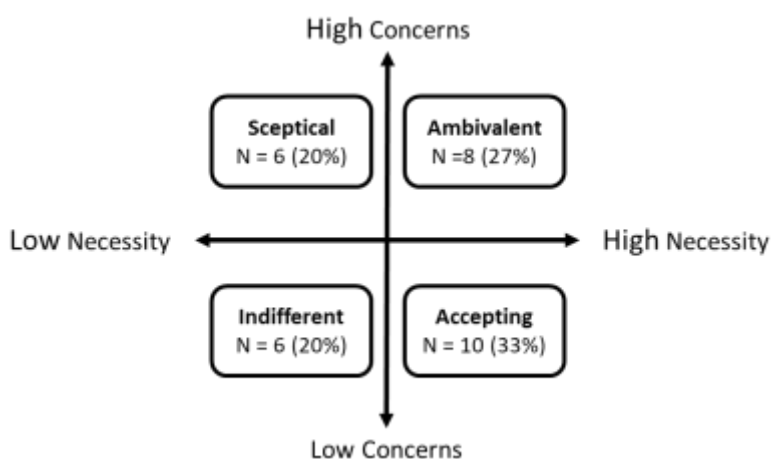


Figure 33: Proportion of the sample allocated to each attitudinal group defined by beliefs about ICS adapted from Chater et al. (2014)

### 7.3.3 Internal reliability

The BMQ-YPWA questionnaire was found to have good internal reliability ( $\alpha = 0.83$ ) as a total measure of beliefs about medicines including all 30 items.

Preventer necessity had questionable internal reliability ( $\alpha = 0.64$ ) based on 10 items from the BMQ-YPWA, compared to the 5-item BMQ specific subscale which had good internal reliability ( $\alpha = 0.80$ ). Preventer concerns had good internal reliability ( $\alpha = 0.83$ ) based on 7 items from the BMQ-YPWA, compared to the 5-item BMQ specific subscale which had acceptable internal reliability ( $\alpha = 0.75$ ). The new BMQ-YPWA domain Practicalities (6-items) internal reliability was initially unacceptable ( $\alpha = 0.24$ ).

#### 7.3.3.1 Item Deletion

Item deletion was conducted for both the necessity and concern subscales and the practicalities subscale to explore potential problematic items influencing the Cronbach's alpha values (Table 16, see Appendix 13 for all item deletion data). Within the necessity domain, items 2, 6, 8 and 9 had corrected item total correlations less than 0.3, however only items 6 and 9 if deleted would increase the domain's internal reliability (both to  $\alpha = 0.66$ ). Item 6 was deleted first as it had both a low corrected item total correlation and increased the internal reliability of the scale more than the other items. Then item 9 was deleted, which increased the internal reliability to an acceptable level ( $\alpha = 0.73$  with 8 items). Item deletion was deemed unnecessary for the concerns domain as the internal reliability for the scale was good ( $\alpha = 0.83$  with 7-items, higher than the 5-item original BMQ) and none of the items were under the 0.3 total correlation threshold. Although, concerns item 1 did have a high total correlation above the 0.7 threshold (0.74) this was not considered significant and should not be deleted as it is a core item from the original BMQ.



Table 16: Internal reliability: items deleted

Domain	Item Number	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Necessity Domain: Round 1	6. Having to use my preventer everyday annoys me	0.18	0.66
Necessity Domain: Round 2	9. When I feel well I don't think I need my preventer inhaler as much	-0.01	0.73
Concerns Domain: Round 1	1. Having to use my preventer inhaler worries me	0.74	0.79
Practicality Domain: Round 1	2. I keep my preventer inhaler in the same place, so I can remember to take it	-0.29	0.43
Practicality Domain: Round 2	3. My parent(s)/ guardian(s) help me to remember to take my preventer inhaler	-0.50	0.67
Practicality Domain: Round 3	6. I find it difficult to use my preventer inhaler with my spacer	0.22	0.74

Within the practicalities sub-scale items 1,2 and 6 had corrected item total correlations less than 0.3, however only the removal of item 2 would increase the internal reliability of the scale ( $\alpha = 0.43$ ), which is still deemed unacceptable. Item 2 was removed from the domain first. Item 3, despite having a corrected item total correlation of ( $\alpha = -0.50$ , a reverse scored item) was removed as the alpha if item 3 was deleted would be increased ( $\alpha = 0.67$ ). Finally, item 6 was removed, which had a corrected item total correlation less than 0.3, and which would increase the Cronbach's alpha value to 0.74. The practicalities subscale was therefore cut from 6 items to 3 items and had acceptable internal reliability as a sub-scale of the BMQ-YPWA ( $\alpha = 0.74$ ).

In summary, the BMQ-YPWA 8-item necessity scale, 7-item concerns scale and 3-item practicality scale after item deletion have acceptable, good and acceptable internal reliability respectively ( $\alpha = 0.73$ ,  $\alpha = 0.83$  and  $\alpha = 0.74$ ).

### 7.3.4 Validity

#### 7.3.4.1 Criterion validity: VAS and Smartinhaler™ analysis

The VAS and BMQ-YPWA preventer necessity were not correlated but the relationship was in the hypothesised direction, with adherence on the VAS increasing with higher preventer necessity beliefs ( $r=0.18$ ,  $p=0.35$ ). The VAS and BMQ-YPWA preventer concern were not correlated and were not in the anticipated direction ( $r=0.26$ ,  $p=0.17$ ).

Smartinhaler™ and BMQ-YPWA preventer necessity were not correlated but the weak relationship was in the hypothesised direction with adherence increasing with higher preventer necessity beliefs ( $r=0.16$ ,  $p=0.41$ ). Smartinhaler™ and BMQ-YPWA preventer concern were not significantly correlated but unlike the VAS the relationship was in the hypothesised direction ( $r=-0.12$ ,  $p=0.57$ ) with adherence decreasing with increasing preventer concern beliefs.

The BMQ-YPWA new 3-item practicality domain was significantly positively correlated with the adherence VAS ( $r=0.42$ ,  $p=0.02$ ) in support of hypothesis 4, however the relationship was weaker and non-significant with objective Smartinhaler™ data ( $r=0.17$ ,  $p=0.38$ ).

#### 7.3.4.2 Discriminant Validity

##### 7.3.4.2.1 Preparatory work: Exploring the relationship between ACT and Smartinhaler™ data

As there are no absolutely accurate measures of adherence, initial preparatory work was necessary, prior to commencement of the validity analysis of the BMQ-YPWA, to ensure that the measures identified for validation of the BMQ-YPWA were appropriate. Firstly, for discriminant validity the dichotomised ACT (cut-off 19) was compared to dichotomised objective Smartinhaler™ data (cut-off 80%) to test the hypothesis that those with high ACT scores (good control) would have higher necessity scores, lower concerns and fewer practicality issues as would conventionally be expected.

However, the dichotomised ACT was not correlated with objective Smartinhaler™ measurement of adherence ( $r=-0.10$ ,  $p=0.61$ ). Therefore, ACT was not deemed to be a good measure of the discriminant validity of the BMQ-YPWA since the self-reported ACT scores did not appear to reflect objective adherence data. As the ACT scores cannot distinguish between high and low objective adherence data, it would not be valuable to continue to explore the ACT as a tool for discriminant validity with the BMQ-YPWA data.

7.3.4.2.2 Discriminant validity for adherent versus nonadherent patients Smartinhaler™ data  
 The BMQ-YPWA domains' (necessity, concerns and practicalities) relationship with dichotomised Smartinhaler™ objective adherence scores were explored using independent t-tests to test if the BMQ-YPWA domains can determine adherence or nonadherence measured by the Smartinhaler™.

There was no significant differences between scores for adherent and nonadherent patients on either the necessity ( $t(28)= 0.12, p=0.90$ ) or concern ( $t(28)= -0.57, p=0.58$ ) scales of the BMQ-YPWA (Table 17).

However, the practicality scores (now only 3 items) did differ significantly ( $t(28) = 2.49, p=0.02^*$ ) between adherent and nonadherent Smartinhaler™ scores. Patients who had higher scores for the practicality domain (fewer practicality issues) were significantly more likely to be adherent to their ICS measured by the Smartinhaler™. Although, with only 30 participants in total the analysis was not appropriately powered.

Table 17: Discriminant validity of the BMQ-YPWA domains based on dichotomised Smartinhaler™ percentage adherence

<b>BMQ-YPWA Domain</b>	<b>Number of Participants (n=30)</b>	<b>Mean</b>	<b>Standard Deviation</b>
Necessity (higher scores indicate higher necessity beliefs)	Adherent= 11	24.36	6.68
	Nonadherent= 19	24.58	2.91
Concerns (higher scores indicate fewer concern)	Adherent= 11	28.00	6.68
	Nonadherent= 19	26.90	4.10
Practicality (higher scores indicate fewer practical issues)	Adherent= 11	19.46	3.39
	Nonadherent= 19	16.74	2.51

### 7.3.4.3 Convergent validity and the B-IPQ

Convergent validity was tested by exploring the relationship between the BMQ-YPWA (preventer necessity and concerns domains) and domains of the B-IPQ. Firstly, the correlation between the preventer necessity domain and B-IPQ items one, two, and five (consequences, timeline, and identity respectively) were tested.

This hypothesis was not supported as only one of the three items was correlated with preventer necessity, which was moderately negatively correlated with timeline beliefs ( $r=-0.59$ ,  $p=0.001$ ; Figure 34). Patients who stated that they felt their illness would last forever were more likely to have lower preventer necessity beliefs. Both the identity and timeline B-IPQ items were not correlated with the necessity domain of the BMQ-YPWA ( $r= -0.07$ ,  $p=0.70$  and  $r= -0.13$ ,  $p=0.50$  respectively).

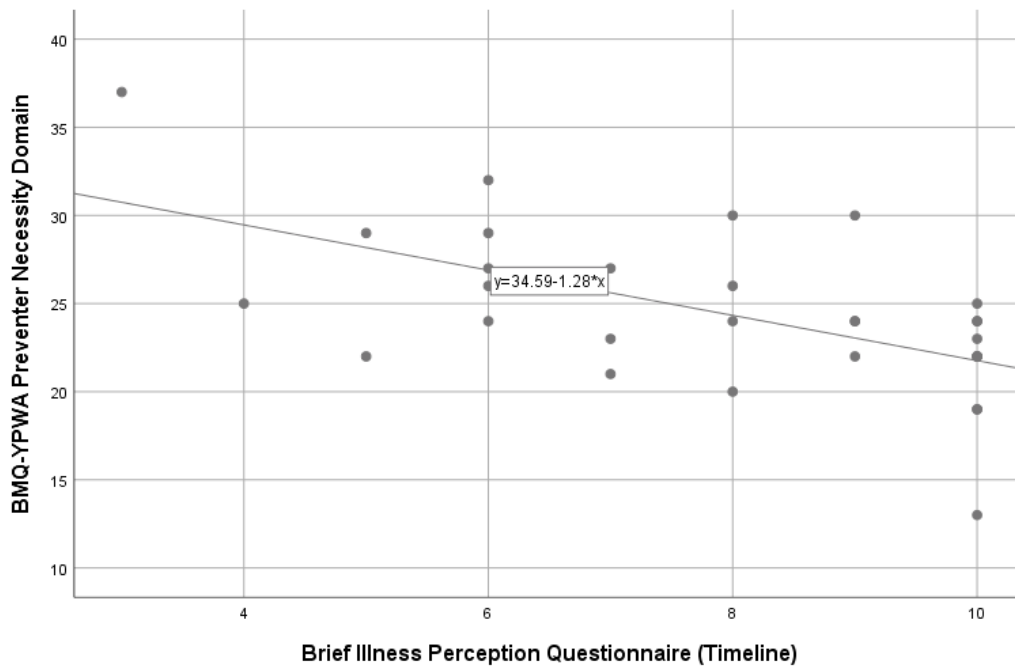


Figure 34: Correlation between scores from the BMQ-YPWA domain and the B-IPQ timeline domain

Similarly, when assessing the correlation between the original items from the BMQ necessity domain (5-items) in this adolescent sample, a similar relationship was shown with item two (Timeline) of the B-IPQ ( $r=-0.67$ ,  $p<0.01$ ).

Concerns about preventer medication (both BMQ-YPWA and BMQ original versions) were not significantly correlated with items one, two, or five (consequences, timeline, and identity respectively).

## 7.4 Discussion

### 7.4.1 Summary of the main findings

This chapter describes the development and pilot testing of a previously validated questionnaire, the BMQ, for use in young people with asthma. The 30-item questionnaire was developed to enable a quick assessment of beliefs relevant to non-adherence for clinical and research use. The BMQ-YPWA was developed to measure both beliefs about preventer inhaler and new theoretically driven domains thought to relate to adherence behaviour (e-CSM and PAPA). The inclusion of these constructs (the identity of asthma; reliever inhaler beliefs and practicality issues) in the questionnaire is novel and driven by patient data (Chapter 6.4.1). Due to the sample size for this pilot study, definitive conclusions on the internal reliability and validity cannot be drawn. However, initial testing of the BMQ-YPWA highlights overall good internal reliability and some support for hypothesised relationship between the BMQ-YPWA and variables measures for validity, albeit with weak and non-significant correlations.

#### 7.4.1.1 *Exploration of the BMQ-YPWA item responses*

The majority of patients disagreed with BMQ core necessity statements related to the efficacy of ICS (“my preventer inhaler protects me from becoming worse”, “my health at present depends on my preventer inhaler”). As hypothesised in this study, these beliefs contrasts with parental necessity beliefs for ICS for children with asthma (Klok et al., 2012; Klok, Kaptein, Duiverman, et al., 2015). Parents’ views typically were in line with the medical team’s view of the necessity of ICS and parents generally agreed with the statement “My child’s health at present, depends on the medicines” and “my child’s medicines protect him/her from becoming worse”(Klok, Kaptein, Duiverman, et al., 2015). Within the BMQ-YPWA study, fewer participants disagreed with a statement related to their reliance on an inhaler (“my life would be impossible without my preventer inhaler”). Some of the patients with problematic asthma realise that they rely on having a preventer inhaler (even if they do not always take it every day) to use when they feel they need it (when symptomatic (Halm et al., 2006).

The additional BMQ-YPWA necessity items again showed perceived efficacy to be an issue as 12% of participants agreed or strongly agreed with the statement “I don’t notice a difference whether I take my preventer inhaler or not”. The statements based on topics of trivialisation of asthma and not following doctor’s instructions were disagreed with (“my asthma is still controlled without following all my doctor’s instructions” (93%) and “Nobody cares about my asthma so why should I take my preventer inhaler” (100%). These statements will need further

refinement and exploration to explore why participants disagreed with them so often. Potentially the outpatient's clinic setting where patients answered the questionnaire influenced their responses in terms of social desirability of their answers (i.e. concerns about the nurses or doctors seeing their answers).

The results of the BMQ core concern items support the qualitative findings reported in chapter 6 as patients disagreed with many of the concern statements, and those that they did agree to more often were regarding long-term effects of ICS and being dependant on the preventer inhaler for the rest of their lives ("I sometimes worry about the long-term effects of my preventer inhaler" and "I sometimes worry about becoming too dependent on my preventer inhaler"). This may highlight differences in the concerns held by children and young people (CYP) with asthma compared to adults with asthma, one participant group that was used to validate the original BMQ (Horne et al., 1999). Similarly, the additional items were in support of concerns being less frequent in CYP with asthma as a large percentage disagreed with the two additional statements. A small number of participants did agree with the statement regarding side-effects ("my preventer inhaler gives me unpleasant side-effects") which is also in line with participants in the qualitative study (Chapter 6) and in previous research in adolescents with asthma (De Simoni et al., 2017).

Participants often disagreed with the statement "I don't have a routine for taking my preventer inhaler" but more often agreed that their routine was easily disrupted and that their tiredness affects whether or not they take their ICS (40%). Again, these findings are as expected and highlight the role that habit has to play in nonadherence (Phillips et al., 2013).

#### *7.4.1.2 Attitudinal profiling*

Within this sample there are a smaller number of sceptical patients as opposed to those who are classified as ambivalent and indifferent compared to figures found in previous literature in adults with chronic illness (Aikens et al., 2005; Chater et al., 2014). This could be due to the necessity of ICS being more important to adolescents than concern beliefs, as indicated in Chapter 6. The attitudinal groups are as expected considering the split of adherent (n=11) versus non-adherent (n=19) patients recruited to the study, although this could not be tested statistically due to the small sample size. Only 33% of patients were categorised as accepting of ICS and only 37% of the sample were classified as adherent based on their Smartinhaler™ data. This is in line with previous research (Chater et al., 2014), which found that 90% of patients with accepting beliefs were high adherers measured by the MARS (Horne & Weinman, 1999).

#### *7.4.1.3 Exploration of the reliability and validity of the BMQ-YPWA*

This PhD study sought to demonstrate the adaptation of the BMQ for use in young people with asthma and the methodology for testing the validity and reliability of the BMQ-YPWA. Given the small sample size and age of some of the Smartinhaler™ data these methods must be replicated in a future study to conclusively assess validity and reliability. In comparison to the original BMQ, the BMQ-YPWA had good overall internal reliability. However, analysis of the individual domains revealed that only the preventer concern domain had equivalent internal reliability to that of the original BMQ. The preventer necessity domain had questionable internal reliability perhaps due to a large number of items being added to this domain (5 additional questions compared to 2 additional preventer concerns). Therefore, item deletion was conducted for both for the necessity and the practicalities domains. Although ideally a larger number of responders would have increased the validity of the item deletion process, it was considered useful in this instance to initially explore redundant items. Once item deletion was completed, hypothesis 1 was supported and the internal reliability of the BMQ-YPWA was comparable to that of the original BMQ (Horne & Weinman, 1999).

Two types of sensitivity analysis were considered as additional analyses for exploring internal reliability of the BMQ-YPWA. These were firstly, in line with findings from Chapter 4:, to consider excluding the first 10 days' worth of adherence monitoring data whereby patients' EMD data showed little variance. Secondly, to explore the relationship between the participants' type of inhaler regimen (Seretide = traditional use as a preventer inhaler, versus possible maintenance and reliever therapy (MART), using the preventer as both a preventer and reliever inhaler in some patients prescribed Symbicort) Chapter 1.6.1.3) and BMQ-YPWA. It is hypothesised that patients using MART may respond differently to the reliever questions than those on a traditional ICS regimen. These differences should be considered when exploring individual items in a larger validation study where both reliever and preventer domains are examined in greater detail. Due to limited patient numbers neither of these sensitivity analyses were deemed appropriate for the initial testing of the BMQ-YPWA.

Both the objective Smartinhaler™ data and the adherence VAS had a weak non-significant relationship with the BMQ-YPWA necessity domain, however both relationships were in the direction put forward in hypothesis 2. Although the BMQ-YPWA concern domain had a weak non-significant negative relationship with the adherence VAS, the relationship between the BMQ-YPWA concern domain and the Smartinhaler™ data, although again weak and non-significant, supports hypothesis 3. This finding, although tentative, highlights the quality of the

adherence measurements. The single item VAS was a non-validated self-report whereas the Smartinhaler™ data is more objective and therefore more reliable as a measure of criterion validity (Chapter 2). However, the same cannot be said for the BMQ-YPWA practicality domain which also supported the hypothesis set out (hypothesis 4), but the VAS had a stronger and more significant relationship to this domain than the Smartinhaler™. Tentative conclusions are all that can be drawn from such a small sample, however these findings are promising for the criterion validity of the BMQ-YPWA. A meta-analysis that investigated the relationship between adherence and the necessity domain from the original BMQ (preventer inhaler only) reported stronger correlations with adherence measurement in adults with asthma ( $r= 0.33$ ,  $CI= 0.26–0.41$ ) (Foot et al., 2016) than found within the current validation study. The meta-analysis also reported similar correlations between the concern domain from the original BMQ and adherence in asthma ( $r=0.19$ ,  $CI=0.28–0.08$ ) to this study's findings in terms of Smartinhaler™ data (Axelsson, Cliffordson, Lundback, & Lotvall, 2013; Byer & Myers, 2000; Emilsson et al., 2011; Menckeberg et al., 2008; Moss-Morris et al., 2002; Sofianou et al., 2013; Van Steenis et al., 2014).

In this study ACT was completed by patients to measure the discriminant validity of the BMQ-YPWA. However, preliminary analysis revealed a lack of relationship between an objective measure of adherence (Smartinhaler™ data) and ACT, and therefore the questionnaire was excluded for this validity test and hypotheses 5 and 6 could not be explored. Additionally, outlined in a previous section (Chapter 2), asthma control measured by the ACT is unlikely to discriminate between patients' adherent and non-adherent to ICS as there are different problematic asthma phenotypes which have differing levels of asthma control. For example, patients that have STRA may have poor asthma control despite high adherence as described by Jochmann et al. (2017). Low adherence and high asthma control may also occur if patients are over-treated with ICS as they may become non-adherent as a rational response to a lack of need for the treatment (no symptoms or asthma attacks). Given that the respondents in this pilot validation study were recruited from the same setting as participants from the Jochmann et al. (2017) study, it is probable that these groups are present and influencing the relationship between ACT and adherence in this study. Indeed, a recent large, longitudinal cohort study has explored the predictive validity (not measured within this study) of the ACT for severe asthma attacks in patients 12 years and older and found it to be only modestly sensitive and specific (42.7% and 73.1%, respectively) as a tool to predict asthma attacks for up to 6 months (Cajigal et al., 2017). The ACT may be more predictive and be able to discriminate between adherent and non-adherent patients with mild to moderate asthma.



The BMQ-YPWA necessity and concerns domains were not able to distinguish between patients who were non-adherent, or adherent based on dichotomised Smartinhaler™ data (contrary to hypothesis 8). However, the BMQ-YPWA practicalities domain was able to distinguish between non-adherent and adherent patients based on the Smartinhaler™ data. The discriminant validity of the BMQ-YPWA was therefore partially supported in relation to hypothesis 7.

The hypotheses for convergent validity of the BMQ-YPWA were partially supported. Hypothesis 9 was not supported as the BMQ-YPWA necessity domain was negatively correlated with the B-IPQ timeline domain. Patients who responded that their illness will continue forever were more likely to have low treatment necessity beliefs. Participants scored B-IPQ item-2 (Timeline) within the upper end of the 10-item scale (Mean=7.87, SD=2.08), meaning all patients believed their asthma to last a longer rather than a shorter period of time. Conversely, participants scored within the mid-range of the necessity scale (Mean=24.5, SD=4.52), meaning patients were less sure of the necessity of their preventer medication. These findings could be at odds with previous findings (Horne et al., 1999) because despite the fact that many patients are told that asthma is chronic condition, this conflicts with their personal experience of asthma as an episodic, symptomatic condition. This leads to the perception of ‘no symptoms, no asthma’ (Halm et al., 2006). This perception is often associated with episodic use of ICS as the patient perceives that they only need treatment during times when their asthma appears to them to be problematic or ‘active’ (Horne & Weinman, 2002) (Chapter 6:). As predicted in hypothesis 10, the BMQ-YPWA was not correlated with any of the three B-IPQ items tested (identity, timeline or consequences).

#### **7.4.2 Strengths of the study**

In addition to the traditional necessity and concern beliefs associated with beliefs about medicine, Chapter 6: of this thesis highlighted practical barriers as important determinates of non-adherence in this population. This study has extended the beliefs about medicine work of Horne et al. (1999) to young people with asthma exploring the use of additional domains relevant to adherence, and in line with theories of illness and adherence (e-CSM and PAPA).

The use of Qualtrics to collect this survey data was highly advantageous for a number of reasons. The ability to stop participants from skipping answers meant that there were no missing data and given the small sample size for this study this was beneficial. Similarly, given the short duration for completion of the study during the timeframe of the PhD, the scoring tool

incorporated into the website allowed me to apply scores to the questionnaire before patients completed it, and the digital nature of the tool saved valuable time in data entry. This survey can be made available for future studies at any time and could be used as a mailing survey, to specific patient groups, to increase the sample size.

Further adaptation and testing of the BMQ-YPWA is necessary in order to fulfil the aim of developing an easy-to-use tool to highlight adherence-related beliefs. The ability for clinicians to quickly and accurately identify adherence related beliefs in an individual to help focus their interventions, in addition to having a percentage adherence value from EMDs, is paramount (Pavord et al., 2018; Royal College of Physicians, 2014). An accurate tool to measure adherence related beliefs in CYP with asthma could help to optimise the use of prescribed treatment – thus reducing morbidity, mortality and the costs associated with asthma in this population (Heaney & Horne, 2012).

#### **7.4.3 Limitations**

This pilot study is underpowered for the majority of planned analyses. Limited time for completion of the study as well as a limited pool of eligible patients meant the study could only explore reliability and validity of the BMQ-YPWA in a small number of young people. This study was a late addition to the PhD plan and as such was conducted with a limited recruitment time frame (initially three months). Delays in approval from the sponsor meant the initial recruitment period was limited to two months. It became evident that the recruitment pool of patients was smaller than expected as patients often attend only every three months (some did not attend or were not brought to clinic) and not all patients had yet had a period of electronic monitoring of their adherence. The total recruitment period due to ethical amendments was five months. Predictive validity was not able to be explored within this study as health outcome measures including the ACT could not be collected at a separate timepoint to the BMQ-YPWA, which is required for this type of validation. This study was only designed as a one time-point study and given the limitations outlined this methodology would not be feasible for the recruitment of patients for the completion of the questionnaire at two time points. Further testing and adaptations will be necessary before the BMQ-YPWA will be able to be widely used.

In light of the limitations of the previous study (Chapter 6.4.2), participants were only eligible for this study if they had a period of Smartinhaler™ adherence monitoring within the last 12 months. However, adherence rates may change over time and perceptions of treatment might

be informed by adherence experiences. Despite clear efforts to reduce the recall bias and to use the most recently collected objective adherence data within the pilot study, we were unable to be even more stringent with the inclusion criteria within this timeframe. Due to limited funding for this type of study validation of the questionnaire may be best placed embedded within a larger trial as others in the field have done (Bland et al., 2015) or alternatively using a multi-centred approach with patients recruited from different hospitals. This study was registered on the NIHR clinical research network which could, in the future, aid in the recruitment of appropriate sites in England. For the larger validation study, a study-specific lead-in time with patients being given Smartinhaler™ for both their SABA and their ICS would be recommended.

A key limitation of the work presented in Chapter 2: is that it was initially developed directly from the results of a qualitative study which was believed, at the time, to be enough to constitute acceptability of the questionnaire items that were developed. However, a think-aloud task where participants are shown the questionnaire and asked to read the statements and questions aloud, and then talk through their thought process while answering the questionnaire, is needed for further validation of the BMQ-YPWA (Van Someren, Barnard, & Sandberg, 1994). Based on the finding of the think-aloud task the BMQ-YPWA item wording and/or questionnaire design could be refined and truly reflect patient acceptance and understanding of the BMQ-YPWA. This approach has been advocated by colleagues for questionnaire design in an asthma context to reduce participant error and participant burden (Mes et al., 2019). Indeed, issues arose during data collection where young people with asthma did not understand the question “My preventer inhaler is a mystery to me”. However, this item was a core item from the original BMQ so any adaptation of the item would need permission from the developer (Professor Rob Horne). Potentially some items do not translate from adults to young people and therefore more patient and public involvement prior to testing of the BMQ-YPWA would be recommended.

Difference in responses between patients prescribed Seretide or MART Symbicort were expected particularly in the and practically domains. As patients with Symbicort have no spacer for their MART inhaler this question within the practicality domain may be answered in relation to their reliever instead of their preventer. This is particularly relevant in this population as understanding of the differences between preventer and reliever inhalers is poor (Chapter: 6.3.2). However, within this study the participant numbers were too small to investigate this level of granularity with the data, however, this is a critical step for any future validation of the BMQ-YPWA.

Although reliever inhaler beliefs were included in the adaptation of the BMQ, there were too few items (3 necessity and 2 concerns) and participants (n=30) to warrant analysis. Future studies building on this work should explore reliever beliefs in relation to preventer beliefs and adherence and include objective EMD for reliever use to assess the utility of this domain.

#### *7.4.3.1 Further necessary validation*

This pilot study could not explore all aspects of psychometric testing for the BMQ-YPWA due to a limited sample size, lack of repeated testing over a second time-point and the age of some of the Smartinhaler monitoring data. The study should be replicated in a larger sample of participants, with an objective tool to assess asthma control and predictive validity. To enable recruitment of a larger sample a multi-centre study may be warranted. It would increase the generalisability and use of the questionnaire if patients from other care settings were included in the validation process such as those within secondary care. If the usage of the questionnaire were to be broadened, particularly if the questionnaire was also to be used in primary care, care would need to be taken in developing the items accordingly including, engaging these patient groups to participate in the think aloud task. This study formed the basis of three post-doctoral fellowships to the British Medical Association (BMA), The Maplethorpe Fellowship and a postdoctoral fellowship for the Asthma UK Centre for Applied Research (AUKCAR). Of these applications one was unsuccessful (BMA), one application was shortlisted and proceeded to an interview stage (The Maplethorpe Fellowship 2018) and one was successful (AUKCAR postdoctoral fellowship).

#### **7.4.4 Conclusions**

This study is the first to explore the extension of the BMQ for use in young people with problematic asthma, including the measurement of preventer necessity and concern beliefs and practicality issues in relation to adherence. This study outlined the initial adaptation work for developing the BMQ for young people with asthma (BMQ-YPWA) and found the questionnaire overall to have good internal reliability. Due to the small sample size, definitive conclusions on the validity of the questionnaire cannot be drawn, however this pilot work has uncovered some key areas for improvement in a larger validation study. In particular, the use of the ACT as a measure of asthma control and for assessing discriminant validity of the BMQ-YPWA may not be appropriate in this problematic asthma group. Further validation work should also conduct sensitivity analysis, particularly in relation to inhaler type and the EMD monitoring period used, as these are likely to alter patients' responses and the results of the analysis (respectively).

Developing a tool such as the BMQ-YPWA is necessary, in addition to measuring percentage adherence, to identify modifiable beliefs and targetable practicality issues that can be addressed in an intervention.

## Chapter 8: General Discussion

The following chapter will outline the extent to which the PhD aims were met. The chapter will briefly summarise the PhD and highlight how the key findings add to the paediatric asthma literature and the wider psychology literature. The chapter will then list the limitations of the current research, and research questions for the future. Finally, the chapter will conclude with the implications for practice, research and policy.

### 8.1 Summary of the Principle Research Findings

This PhD thesis aimed to identify and describe modifiable factors related to non-adherence, which could be considered when developing an intervention, to increase adherence to ICS in children with severe asthma. This PhD also utilised a health psychology lens to explore and understand different patterns and reasons for non-adherence to ICS, and to explore how the BMQ might be adapted specifically for this population.

The **first three chapters** explored the clinical and psychological setting of this PhD including recent advances in adherence measurement tools. This work reported the strengths and limitations of the diagnosis and understanding of paediatric asthma and of the available tools to measure non-adherence in this population. This work was further explored within **chapter four** where a systematic review was conducted to investigate published interventions for increasing adherence to ICS in children with asthma. This review furthered the literature by critiquing the objectivity and therefore quality of both the diagnostic methods used in participating patients and by the objectivity of the adherence measurement tool in the included studies, expanding upon the main points of the introductory chapters of the PhD. The review also used psychological theory to understand the content of the effective studies and revealed the value in addressing both perceptions and practicalities within a tailored adherence intervention (PAPA (Horne, 2001; Horne et al., 2019; Nunes et al., 2009).

**Chapter five** used objective EMD adherence data to explore patterns of non-adherence and found distinctive patterns relevant to future research as well as clusters of adherence behaviour over the monitoring period. This work highlights the need to explore EMD data for patterns of behaviour and to recognise and adjust for the Hawthorne effect in patients being monitored. These patterns of adherence were explored further from a patient perspective in **chapter six** using novel methodology (the AMI and for two young people, drawing) to qualitatively explore the determinants of non-adherence in a group of patients with problematic asthma. This work

extended our knowledge of adherence in this tertiary care group and found that forgetfulness was a consequence of other factors led by low perceived need for ICS and over-reliance on SABA inhalers. Concerns about the potential adverse effects of ICS seemed to be less important drivers of nonadherence than doubts about personal need for ICS. This finding contrasts with studies of parental adherence to ICS prescribed for their children where concerns about ICS were a significant barrier to adherence (Conn, Halterman, Lynch, & Cabana, 2007; Klok et al., 2012; Yilmaz et al., 2012). Finally, **chapter seven** outlined the adaptation and pilot study of the validated BMQ for use in young people with asthma (BMQ-YPWA) which incorporated the findings from chapters five and six. This work specifically developed from a tertiary care non-adherent patient group built on the previously developed BMQ using a theoretical basis (e-CSM) and a framework for intervention development (PAPA) to create domains investigating practical barriers to adherence, illness identity, preventer and reliever treatment beliefs.

## **8.2 Strengths of the research and contribution to the literature**

### **8.2.1 Literature review (Chapters 1-3)**

These chapters highlighted key gaps in the literature regarding children with problematic asthma and their adherence to ICS. Chapter 1 outlined the importance of research to improve asthma adherence given the high mortality and morbidity rates in the UK (Shah et al., 2019). This chapter summarised the medication for the treatment of paediatric asthma, in particular the use of ICS to manage asthma and the issue of non-adherence in patients with asthma. Chapter 1 concluded by summarising the problem of adherence in children with problematic asthma. Chapter 2 then summarised the limited data available investigating non-adherence in this population and also the variety of tools used to measure adherence to asthma preventer treatments. This chapter concluded that EMD, despite limitations in their current form are one of the best tools to objectively measure adherence to ICS. Chapter 2 highlights that few studies have used the discussed measurement tools to explore the underlying reasons for non-adherence in children with asthma. The exploration of theoretical approaches to adherence presented in Chapter 3 summarised previous applications of theory to explain nonadherence with particular emphasis on adherence to maintenance treatment for asthma (mainly adults with asthma). It also presented a rationale for the theoretical approaches that underpinned the empirical work (e-CSM, (Horne, 2003)). This chapter highlights the limited data exploring psychological determinants of non-adherence in children and those with problematic asthma.

## 8.2.2 Empirical chapters

### 8.2.2.1 Chapter 4: Systematic Review: What are the Most Effective Aspects of Interventions for Adherence to Preventative Medication in Children with Asthma?

Previous systematic reviews of interventions for adherence to ICS have been conducted with participants of a variety of ages including children (Normansell et al., 2017) but not targeting children specifically. Chapter 4 outlines research that addresses this gap by only including studies focusing on children and adolescents. The systematic review supported Normansell et al.'s (2017) findings that only half of the included randomised control trials were effective at increasing adherence (9/18 RCTs). Chapter 4 also widened this area of research to include important considerations of the reliability of the data not only for risk of bias but for the reliability of both the inclusion criteria for a diagnosis of asthma for participants in each study and the objectivity of the adherence measurement tool. Both of these issues have been raised as current problems in research but not yet explored within a systematic review format (Bush & Fleming, 2016; Pearce & Fleming, 2018). The review found many studies did not use reliable criteria for asthma diagnosis for their included participants nor did they all use objective or high-quality tools to measure adherence. These findings highlight issues with interpreting the findings of such studies as patients who do not actually have asthma would be justified in their non-adherence and therefore reduce the effect of a given intervention. Similarly, less objective measurements are likely to overestimate adherence and therefore be an unreliable outcome for the success of an intervention targeting adherence. Within the effective studies eight were found to be effective at increasing adherence (8/9 high reliability studies).

The research presented in chapter 4 also involved a novel exploration of the content of the interventions in relation to the PAPA which has not been conducted previously in a systematic review of paediatric patients. Due to limitations in the quality of research and reporting (content and design of the interventions) it is not possible to make definitive recommendations for intervention content. However, our analysis showed that interventions were more likely to be effective if they tailored support to individual needs addressing both perceptions and practicalities influencing personal motivation and ability to adhere to ICS treatment. This piece of research supported the applicability of the PAPA in developing interventions targeting ICS adherence in asthma in a paediatric population for the first time (Horne, 2001; Nunes et al., 2009). The findings also replicate recent findings from a meta-analysis of pharmacist-led adherence interventions in adults with asthma that found studies which showed similar findings (Mes et al., 2018).



Also, unlike previous systematic reviews in paediatric asthma BCTs were coded from within the intervention content. The BCTs which were used in effective interventions were summarised and found to be generally used as part of complex interventions involving more than one BCT (association- prompts/cues (e.g. reminders); feedback and monitoring; pharmacological support; shaping knowledge instruction on how to perform a behaviour and information about antecedents). These BCTs could be used as the basis for an intervention developed for the population investigated within this PhD (paediatric patients with problematic asthma) although this would need to be in conjunction with tailored content targeting specific practical and perceptual barriers to adherence. Mes et al. (2019) also highlighted key BCTs (goals and planning; feedback and monitoring, shaping knowledge, comparison of behaviour, repetition and substitution, natural consequences, self-belief, and associations) which differed from the BCTs found within this research however neither study could definitively state that the type or number of BCTs had a direct impact on effectiveness. Similarly, to within this study Mes et al. found that the limited intervention descriptions hindered BCT coding, despite, as done in this study, contacting authors for further details of the intervention content.

The research presented in chapter 4 also supports the use of technology such as EMDs, websites and telephones to deliver these BCTs and intervention content but found that interventions using technology may be more likely to be effective if used in conjunction with a health care professional or researcher. This finding is supported by a previous study that echoed these findings related to the intervention channel (Lycett, 2017). As has been proposed by Horne et al. (2012) the content/ or target of the technology is also important to consider. This research study showed that the majority of previous interventions neglect to target patient beliefs about ICS and asthma known to be key determinants of nonadherence. In response to this findings, subsequent chapters explored determinants of nonadherence in a group of paediatric patients with problematic asthma to enable a targeted intervention to be developed. EMD technology was utilised as indicated in this study as an objective measurement of asthma to conduct an initial quantitative exploration of patients' behaviours by expanding beyond adherence and non-adherence patterns of adherence.

#### *8.2.2.2 Chapter 5: Patterns of Adherence a Secondary Analysis of Smartinhaler™ Data*

Although EMDs such as the Smartinhaler™ have been used to measure adherence in previous studies, adherence is often only explored in terms of a patients' total percentage adherence (adherent or non-adherent) without analysing patterns of adherence behaviour within the data. Although knowing which patients are adherent and non-adherent can be useful, it does not

reveal patterns of non-adherence which may have differing clinical consequences. For example, a total adherence percentage of 50% could mean patients are taking their twice daily inhaler only once a day or that they take it 100% of the time for half of the monitoring period and not at all during the remaining half. Although this type of research has recently begun in adults with mild/moderate asthma (Huvanandana et al., 2018) this study is the first to extensively explore patterns of non-adherence in children and young people with problematic asthma. Patterns of non-adherence can indicate areas for improvement that can be modified once explored with the patient.

Similarly to patterns found in adherence in adults with asthma (Bender & Zhang, 2008; Konstantinou, 2012), chapter 5 outlined findings showing that even while patients' adherence was being monitored using an EMD, adherence reduced throughout the monitoring period (at a population level). This supports previous literature in adults and shows a Hawthorne effect of EMD (Adair, 1984). However, this study explored this pattern in more depth than the previous literature by exploring clusters of patients' adherence over time. This analysis revealed three distinct groups of patients who responded to electronic monitoring of their adherence in different ways. One group of patients had consistently higher adherence throughout the three-month monitoring period, a second group began with higher adherence than lowered during the three-month period (the Hawthorne effect group) and a third group whose adherence was higher at the beginning lower in the middle and higher again towards the end of monitoring. This is the first time these patterns have been seen in EMD adherence data and they highlight that monitoring adherence may work for some patients but will not necessarily be sustainable unless other interventions are introduced. Indeed previous authors conducting studies in adults reported that feedback on adherence was likely to maintain the increase in adherence seen in patients whose adherence was being monitored by EMDs (Chan, Stewart, et al., 2015; Morton et al., 2017). Further investigation is needed to explore the reasons for the change in adherence within the three clusters particularly in those that begin higher, dip down and then rise again. Gathering data on asthma control and specific allergen data could help to explore these patterns in addition to conducting an adherence monitoring interview (AMI) with these participants.

This chapter also outlined patterns of adherence related to a lack of routine in the participants' medication routine. Patients were found to have reduced adherence to their ICS on their non-school nights (Friday and Saturday) compared to school nights (Sunday-Thursday). This difference in adherence is anticipated to be linked to practical factors such as a disruption of routine when they do not have school the next day (e.g. going to bed late and getting up late)

and competing priorities (e.g. activities and socialising) as described in Chapter 6.3.4. Again although poor routine has been cited in previous literature as a reason for non-adherence (Klok, Kaptein, & Brand, 2015; Koster et al., 2015) these patterns have not been explored in paediatric patients with problematic asthma to reveal the extent of the effect on adherence. An additional finding that could be related to poor routine is that patients more often took their inhaler at least once daily compared to fully as prescribed. However, this pattern could also be related to intentional non-adherence due to low necessity or high concerns. This lack of certainty for the reasons behind these patterns indicates the need for the patients' perspective in confirming the individual's reasons for non-adherence.

Finally, this chapter sought to explore patterns of non-adherence using the EMD, highlighted by others in prescription data, for suspected lower adherence over the summer season (Julious, Horspool, et al., 2016). Seasonal differences in adherence were only found when including the severity of asthma in the analysis. The STRA group had worse adherence in summer compared to the other groups of patients who had lower adherence in spring (difficult asthma, mild/moderate asthma and newly referred patients). Although the analysis was underpowered, atopy data was included to explore if an increase in symptoms related to atopy (hay fever in summer and spring) was related to the differing patterns of adherence across the seasons between the severity groups (Durham, 1998). However, this analysis was not significant, likely due to the small numbers and a lack of specific allergen data. Due to the lack of additional data related to atopy and asthma control it is impossible to infer why these patterns may exist. Although no conclusions can be drawn from this analysis it shows differing patterns of non-adherence which could be further explored within a discussion with each individual patient.

These patterns of non-adherence explored within EMD data are novel for the paediatric asthma literature. This PhD furthered this work by exploring the patient perspective of these patterns and their personal determinants for adherence in preparation for the development of a tailored intervention for this population.

### *8.2.2.3 Chapter 6: The Patients' perspective of non-adherence*

This PhD, unlike many other studies in the literature, focused on patients from tertiary care with problematic asthma. Research in paediatric and adult asthma more often targets patients with mild to moderate asthma often via primary or secondary care. Similarly, when exploring adherence, particularly when investigating illness and treatment beliefs research has focused on not only patients with mild/moderate disease but also on parental beliefs rather than the

individual child's beliefs. This chapter focused on child beliefs about ICS and found their non-adherence to be driven by low necessity beliefs rather than high concerns beliefs as reported in previous literature with parents of children with asthma (Conn et al., 2007; Klok et al., 2012; Yilmaz et al., 2012).

The framework analysis, informed by the e-CSM and PAPA, revealed potentially modifiable determinants of non-adherence specific to an adolescent problematic asthma group. One overarching theme influencing non-adherence was the patients' sense of self. Patients reported that despite asthma being a common condition, that taking their reliever inhaler in public can be stigmatising. This stigma could be targeted with a future intervention (section 8.4.3) Similarly, patients' perceptions echoed Bush & Fleming's (Bush & Fleming, 2016) article which stated that asthma may be over diagnosed. This was raised by patients in relation to the severity of their asthma being misunderstood due to misperceptions of asthma related to milder disease. This finding has implications for the wider research area as it shows that non-adherence may be linked to diagnosis issues such as the lack of an objective test for asthma as discussed in Chapter 1. Patients also stated directly that asthma was often trivialised which influenced their perceptions of the seriousness of their asthma and therefore increased their non-adherence.

#### 8.2.2.3.1 Illness beliefs

Patients described their asthma as episodic with triggers causing their asthma. This focus on the cause of asthma attacks and symptoms (their experience of asthma) rather the underlying condition highlights the patients' lack of understanding of asthma as a long-term condition (an abstract concept to them). Despite the concept of asthma as a chronic condition, possibly provided by clinicians (trusted sources), patients concrete experience of asthma is more persuasive to them. Interventions must address this disparity between patients' illness representations and the medical model of asthma (i.e. a chronic condition) in order to influence patients' outcomes such as adherence (Leventhal et al., 1992). Patients also described that worsening asthma symptoms or attacks did not always influence their future adherence. This has been reported previously research in Myocardial infarction (Petrie & Weinmann, 2013) where the event is not always a catalyst for change. However, a significant event could be the trigger for intervention related to their illness coherence during this "teachable moment" (McBride et al., 2003). Patients showed a lack of illness coherence and did not understand the difference between medications. This has been reported previously in asthma where patients consider asthma as an episodic condition and therefore the use of a daily preventer inhaler does not fit with their illness beliefs (Horne & Weinman, 2002). Patients also focused on the

consequences of their asthma in terms of asthma attacks and activity limitation rather than daily symptoms and patients reported that daily symptoms had become normal for them, likely due to poor asthma control from a young age. Again framing adherence to ICS as enabling activity, as some currently adherent patients in the interviews reported, may be useful within an intervention.

#### 8.2.2.3.2 Treatment beliefs

This study was also the first to suggest that non-adherence in young people with problematic asthma may be led by low necessity beliefs for ICS as opposed to high concerns about ICS and high necessity for their reliever inhaler. Data regarding concerns about ICS appeared less influential to patients and were focused on the long-term effects of medication and again consequences of the condition itself in terms of activity limitation. These findings contrast with previous studies which focused on parental beliefs rather than the child's beliefs about their own adherence (Conn et al., 2005; Klok, Kaptein, & Brand, 2015).

Due to low necessity beliefs for the use of ICS patients reported behaviours to manipulate the electronic monitor and people around them. These strategies including lying to their parents and doctors and activating their inhalers to manipulate the number of Smartinhaler™ doses recorded. This highlights both the limitations and the strengths of the use of Smartinhaler™. Firstly, it supports literature suggesting patients feel under surveillance while being monitored with EMDs (Stewart et al., 2018) and that they can be manipulated due to the lack of inhaler technique or inhalation recording device (Chapter 2:). However, dose dumping such as this is trackable and through the non-judgmental AMI conducted with patients these dose dumping episodes and the reasons underlying them can be explored with patients. This highlights the utility of accurate objective EMDs in exploring adherence with patients.

Previous literature has highlighted forgetfulness as a commonly reported reason for non-adherence in children with asthma (Koster et al., 2015; Penza-Clyve et al., 2004) however this study showed that the majority of forgetfulness reported was related to low necessity beliefs and other modifiable factors such as poor routine (discussed below). These findings are akin to recently published qualitative research investigating forgetting as a reason for non-adherence to preventative treatment via nebuliser in another adult patients with Cystic Fibrosis (CF) (Drabble et al., 2019). The authors reported patients with low adherence (measured by EMDs) using forgetting to normalise frequent non-adherence. Similarly, to this PhD chapters conclusion regarding patients reporting forgetfulness as an initial reason for non-adherence Drabble et al.

(2019) recommend a patient-focus, tailored and theory driven approach to intervention with patients with low adherence.

#### 8.2.2.3.3 Practicalities

Indeed, forgetfulness initially reported by participants was vary, rarely truly unintentional. Patients with low necessity for ICS did not prioritise the medication in their routine because for them it was not logical to do so. As reported by others in research exploring non-adherence in long-term conditions (Phillips et al., 2013) factors such as poor routine and lack of habit as well as fatigue were often underlying forgetting. Patients who claimed to be adherent at the time of the AMI reported having established good medication routines including having their medication in a visually prominent location. This technique had been noted within the BCT taxonomy as restructuring the physical environment (Michie et al., 2013) this may help to overcome this lack of ability to take the medication, but only in conjunction with techniques to increase ICS necessity as this was the most common reason given for a lack of routine or a disrupted routine within this study.

Patients' parents were highlighted as crucial to enabling patients to take their medication by both collecting prescriptions and reminding patients to take their medications. These results support the findings regarding the parental role in the Koster et al. (2015) study and the use of reminders (BCT prompts/cues) in addressing practical barriers to adherence (Chapter 4:, (Chan, Stewart, et al., 2015)). Similarly to the conclusions of Koster et al. (2015), this PhD indicated that prior to transition from paediatric to adult care, consultations should be used to discuss this responsibility and use technology such as apps and mobile phones where appropriate to keep the reminders going while transferring the responsibility from the parent to the young adult gradually. However, intervention developers should recognise that a tool to target forgetfulness will be ineffective if the barrier to adherence is perceptual.

#### 8.2.2.4 Chapter 7

The adaptation of the BMQ (Horne & Weinman, 1999) for young people with asthma (BMQ-YPWA) and pilot testing including some psychometric testing is the first time the items of the BMQ have been adapted for use in children above and beyond simple translation. The BMQ-YPWA included new domains which were theoretically derived including specific content from the findings reported in Chapter 6: to measure both perceptions and practicalities. The chapter demonstrated the methodology for testing reliability and validity of the BMQ-YPWA which could form the basis for future testing with a greater number of respondents and more recently

collected EMD adherence data. Initial exploration of the internal validity of the questionnaire (BMQ-YPWA) revealed equivalent internal reliability (once item deletions had been made) to the original BMQ findings (Horne & Weinman, 1999).

The discrepancies between correlations with the self-report VAS for adherence and the objective measure (Smartinhaler™) and the BMQ-YPWA domains highlights importance of the reliability of adherence measurement tools in adherence research as described in Chapter 2: and Chapter 4:. Previously reported correlations between adherence and the original specific BMQ domains (preventer necessity and concern), despite being in the same direction as the BMQ-YPWA equivalent domains, were larger in previous studies (Foot et al., 2016). Given the small sample size within this pilot study the findings for criterion validity are encouraging.

Through the exploration of discriminant validity in this study the ACT was shown to be a poor indicator of levels of adherence based on dichotomised Smartinhaler™ data. This supports Jochmann et al.'s (2017) findings within this group of patients with problematic asthma as they determined different phenotypes of asthma which showed different relationships between asthma control and adherence. Similarly, the BMQ-YPWA necessity and concern domains were not able to distinguish between patients who were non-adherent and adherence (measured by Smartinhaler™) however, the practicality domain was able to discern these groups. This highlights the potential benefits of the addition of a practicality domain to the BMQ in identifying modifiable determinants of non-adherence.

In terms of convergent validity, the BMQ-YPWA concern domain, as predicted, was not correlated with B-IPQ items (identity, timeline or consequences). However, the BMQ-YPWA necessity domain was not related to these items as predicted (identity, timeline or consequences). Indeed, the necessity domain was negatively correlated with the timeline domain of the B-IPQ unlike within the original BMQ validation study where necessity and timeline were significantly positively correlated (Horne et al., 1999). This could be due to the severity of disease in this problematic asthma group in that they may be aware their asthma will last for a long time however only treat it episodically as their illness representation is of an episodic condition (Chapter 6.3). Indeed unlike in studies of adults with asthma and parents of children with asthma (Klok et al., 2012; Klok, Kaptein, Duiverman, et al., 2015) the participants in this study (aged 12-17 years old) often disagreed with necessity statements related to the efficacy of ICS such e.g. "my health at present depends on my preventer inhaler". This study investigating beliefs about ICS in children with problematic asthma may therefore have

highlighted differences in the relationship between illness perceptions and treatment perceptions relevant to CYP compared to their parents which warrant further investigation.

### **8.3 Limitations of the research**

Despite the additions to the literature that this PhD has made there were important limitations in the research which need to be considered and addressed in further research. This PhD was developed from a Health Psychology perspective and focused on adherence behaviour rather than inhaler technique or clinical asthma outcomes. This was for numerous reasons such as data availability (in the case of the systematic review), scope of the PhD and expertise. However, as mentioned previously adherence in asthma, unlike in some chronic conditions, is well correlated with clinical outcomes for asthma (Murphy, Proeschal, et al., 2012). This PhD takes first steps in understanding nonadherence in CYP with problematic asthma which will lead to interventions which will include content addressing inhaler technique and measuring both adherence and clinical asthma outcomes.

Although this PhD used EMD as an objective measurement of adherence, EMDs which measure inhalation or inhaler techniques, as well as actuation (such as the INCA device), were not available for use in the clinical setting, at the beginning of this PhD. The best commercially available EMD to measure adherence, which included the time and date of each actuation, were already being used in the specialist hospital site (Smartinhaler™) which was approved for this PhD. Ideally for future studies EMDs would measure inhalation or inhaler technique in addition to adherence, as despite not being the focus of this PhD this is clearly of clinical importance. Indeed, a current study at The Royal Brompton Hospital is testing the feasibility and acceptability of a number of novel EMD devices with paediatric patients with asthma and clinical staff.

One further limitation of the PhD is the retrospective nature of some of the EMD adherence data, used as the basis for both the qualitative study and the BMQ-YPWA pilot study. As mentioned previously (Chapter 6 and Chapter 7) adherence data were collected prior to the start of each study and in some instances, they were up to two years old. Future studies would benefit from having a run-in phase where adherence is monitored over 3-6 months immediately prior to either an AMI interview or completion of any adherence measure e.g. BMQ-YPWA. This would mitigate the limitation of the retrospective data used within this study and would allow for removal of the first 10 days of the monitoring period in line with findings from Chapter 5. Due to small number of participants in both studies it was not possible to assess differences between patients who had more recent versus less recent adherence monitoring data. The



retrospective nature of the EMD data, as well as small sample size, also limited my ability to conduct meaningful reliability and validity psychometric testing of the newly adapted BMQ-YPWA.

Recruitment was an issue in both empirical studies which were conducted in an NHS setting (Chapter 6 and 7). As problematic asthma only accounts for 5-10% of patients with asthma, and only a proportion of patients have had adherence EMD collected at the Royal Brompton Hospital, the recruitment pool was relatively small. When conducting the qualitative study within this PhD, which was registered on the NIHR clinical research network portfolio, another site approached the study team to request to recruit on our behalf in the West Midlands. We were unable to take up this offer as the study was near completion at this point and the travel would not have been feasible from London. However, despite these difficulties the study did reach thematic saturation with 20 participants and a varied sample of patients were able to be recruited. Future research in problematic asthma with short recruitment windows would benefit from utilising the NIHR clinical research network portfolio support to adopt multiple sites within Greater London, to maximise recruitment and to increase generalisability of the study.

Recruitment was also challenging in the BMQ-YPWA adaptation study due to a limited time frame for data collection. The initial aims to conduct a validation study of BMQ adapted for young people with asthma needed to be modified due to lack of time, resources and difficulties of recruiting patients. Therefore, the data collected was used to illustrate the methodology for questionnaire validation and to explore patients' responses to the newly developed items. In retrospect the study should have started with the development of the first iteration of the BMQ-YPWA and then explored the acceptability of the questionnaire in a think-aloud task (Chapter 6.4.2). In this way the questionnaire could have been improved and ensured face validity prior to pilot testing. A think-aloud task was not conducted within this PhD as there were significant time restraints for this section of the PhD and, at the time of commencement of the pilot study we believed the qualitative work carried out in the same population would be adequate to ensure the applicability of this questionnaire.

#### **8.4 Implication for Research and Practice; and Future Research Questions**

Despite the limitations outlined above this PhD has clear implications for research and practice which will be discussed further in the following section. Finally, future research questions will be outlined to support these exploratory findings.

#### **8.4.1 Implications for Research**

Central to this PhD are key measurement issues for both adherence and asthma. Several chapters have highlighted the need for appropriate, objective, innovative measurement for asthma such as EMDs and an adapted beliefs about medicine questionnaire for young people with asthma (BMQ-YPWA). To accurately assess changes in adherence we must be sure that adherence is measured as stringently as possible. Similarly, researchers should consider their inclusion criteria for patients with asthma. As shown in this PhD's systematic review, more objective tools and expertise are needed as criteria for inclusion of participants into any type of research study. The PAPA including the e-CSM and NCF have been shown throughout this PhD to be appropriate for the investigation of adherence to ICS in children with asthma and indeed, to be a useful framework for future intervention development. Future research should use these findings and the PAPA to create a tailored intervention for this specific population exploring the use of the identified BCTs as a basis for this. Interventions should focus on increasing ICS necessity and decreasing SABA over-reliance, as well as encouraging parents to give practical support to their children. As indicated previously, exploration of both SABA and ICS will be important in the assessment of adherence in future research.

#### **8.4.2 Implications for Practice**

This PhD has highlighted the use of objective adherence measurement within clinical practice. The studies have not only used the percentage adherence generated by the EMDs but have further explored patterns of non-adherence relevant to clinicians and patients using these devices. Much like the AMI, health care professionals can use this data to enhance their discussions with patients about non-adherence. Similarly, the determinants raised within the qualitative study and summarised within the BMQ-YPWA can be explored with patients and normalised now that they are known.

Following these studies, it is now common practice for the specialist respiratory nurses at the Royal Brompton Hospital to not only look at overall adherence using the Smartinhaler™, but to calculate day of the week adherence and to look for changes to adherence over the monitoring period and gaps in adherence. These are then used for a discussion with the patient from a more-objective viewpoint. This encourages the patients to be more open in the discussion about their non-adherence and therefore enables a more useful personalised consultation about their barriers to adherence.

Within the duration of my PhD the NHS long-term plan has been published stating that innovative digital devices such as Smart Inhalers (meaning EMDs) will be trialled in an attempt to improve patient care and to monitor adherence, hence improving outcomes. As indicated in the above chapters this recommendation is supported by this PhD. However, the current work supports not only the use of EMDs for monitoring of adherence but for the basis of a non-judgemental open discussion with clinicians about patterns and determinants of non-adherence.

#### *8.4.2.1 Intervention development*

##### *8.4.2.1.1 Learnings from the PhD*

Interventions should be tailored to patients' specific practical and perceptual barriers to adherence to ICS and include relevant BCTs to target each factor. These could include BCTs summarised in Chapter 4: which include: prompts (e.g. reminders); feedback and monitoring (e.g. from a digital tool or clinician); pharmacological support (e.g. providing medication); instruction on how to perform a behaviour (e.g. appropriate inhaler and spacer technique or how to use an EMD) and information about antecedents (e.g. discussing triggers and causes of asthma). Although this BCT has not been used in previous interventions in asthma, reframing (Michie et al., 2013) ICS use as positive as it can be used in the privacy of patients' own homes to prevent social stigma by having to use a reliever inhaler publicly. Future research could test these techniques in a complex intervention based on PAPA. For further details of the specific findings from this PhD please see Table 18 below.

Table 18: Summary of content for future intervention development

<b>Systematic Review: What are the Most Effective Aspects of Interventions for Adherence to Preventative Medication in Children with Asthma?</b>			
<b>Findings</b>	<b>Target</b>	<b>BCT</b>	<b>Confidence in the finding</b>
Reminders to take ICS medication were often provided by electronic means such as EMD inhalers, website, smartphone app reminders or SMS message.	Child and parent	Prompts/cues	These were used in 75% of the effective high reliability intervention studies. Two non-effective interventions used prompts and cues however they were in the low reliability category. This BCT should be used in future interventions to target practical barriers for medication taking such as forgetting.
Feedback on adherence behaviour was often given by healthcare practitioners after a period of adherence monitoring (usually electronic monitoring) to the patient with parents present. Self-monitoring was often in relation to symptoms and patients' asthma action plans.	Delivered by health care practitioner to the child and parent	Feedback and monitoring	Feedback and monitoring was used in 63% of effective high reliability intervention studies. Three non-effective studies also used feedback on behaviour one of which was in the low reliability category. Two of the non-effectively but high reliability studies gave brief feedback on behaviour which was not given face-to-face (e.g. telephone). Feedback on behaviour and self-monitoring should be used in future interventions to target perceptual barriers to adherence.

<p>Including providing free medication to patients in countries without a national health service and providing upfront a supply of ICS medication to patients.</p>	<p>Delivered by health care practitioner to the child and parent</p>	<p>Pharmacological support</p>	<p>Pharmacological support was provided in 63% of effective high reliability intervention studies. Two non-effective studies used pharmacological support one of which was in the high reliability group but only provided prednisolone to patients rather than ICS. Again, the provision of ICS and support with medication would be recommended as part of a future complex intervention. In the UK this would consist of provision of a long-term prescription (e.g. more than one ICS inhaler per prescription) to target the practical barrier of cost and access/travelling to a pharmacy.</p>
<p>Patients were instructed how to use their inhaler and spacer appropriately and how to use an EMD where applicable</p>	<p>Delivered by health care practitioner to the child</p>	<p>Instruction on how to perform a behaviour</p>	<p>Instruction on how to perform a behaviour was used in 50% of effective high reliability intervention studies. Five non-effective studies used instruction on how to perform a behaviour all of which were in the low reliability category. This BCT would only be recommended in conjunction with demonstration of how to use inhaler/spacer/EMD and behavioural practice/rehearsal to increase the likelihood of addressing the practical barrier of their ability to use the devices.</p>
<p>Patients were told about the cause of asthma and what triggers asthma.</p>	<p>Delivered by health care</p>	<p>Information about antecedents</p>	<p>This BCT was only used in one effective high-reliability study and one non-effective low reliability study. The key difference between the interventions in how the BCT was enacted was that one (the</p>

	practitioner to the child		effective high-reliability study) was face-to-face and one study was website based (non-effective low reliability study). Although there is limited evidence from this systematic review information about the cause of asthma and asthma triggers should be included in a future interventions as patients often do not have a good level of illness coherence and understanding of how their ICS impact on their asthma (see below evidence from the qualitative study). This BCT would be used to target perceptual barriers related to knowledge and to increase necessity beliefs.
<b>The patients' perspective of non-adherence</b>			
<b>Findings</b>	<b>Target</b>	<b>BCT</b>	<b>Confidence in the finding</b>
Parental reminders were highlighted as important by children who reported being adherent and a lack of parental reminders was reported by children who were currently non-adherent as a reason for them forgetting their medication.	Parent	Prompts/cues	This lack of this BCT was mentioned as a barrier for non-adherence and as a facilitator for adherent children who were receiving parental reminders. In any future intervention this should be encouraged in addition to other reminders and prompts such as anchoring the behaviour with a behaviour already in their routine and independent of their parents. This BCT would be recommended for a future intervention but as it is only targeting forgetfulness (a

			practical barrier) it should be used in conjunction with additional perceptual targeted BCTs.
Patients reported relying heavily on their reliever rather than taking their ICS regularly however they also frequently reported feeling stigma for using reliever inhalers in public and when symptomatic frequently reported. However, stigma for ICS use was limited as this was often only taken in front of good friends or family at home or on sleepovers.	Child	Reframing	ICS use could be reframed positively as a treatment that can be used in the privacy of patients' own homes, which will reduce symptoms and the need to a reliever inhaler to prevent social stigma by having to use a reliever inhaler publicly.
Patients reporting now being adherent to their ICS described their realisation at how much they are able to do in terms of physical activity. Patients who were non-adherent conversely reported feeling different from others and again feeling stigmatised by limitations to their activity levels.	Child	Reframing and credible source	ICS can also be reframed as the treatment to enable patients to take part in activities that they are missing out on. This reframing could be presented by a patient of a similar age as a credible source for the patients. Although doctors should be a credible source for children perhaps the importance of peer groups particularly in adolescents could be utilised as a form of role modelling.

### 8.4.3 Future Research questions

The research presented in this thesis is the starting point for further exploration in this under examined group of patients, CYP with problematic asthma. As such the PhD has raised questions for future research, findings to be confirmed in additional studies and ideas for intervention development

#### 8.4.3.1 *Measurement tools*

EMD have been used throughout this PhD both to measure adherence and to explore underlying beliefs and barriers related to patterns of adherence. Future research should focus on the use of EMD as more than just a measurement tool. EMDs can add value to discussion about non-adherence and as an intervention tool in conjunction with interaction with a clinician. EMDs can also be used to measure SABA use which would complement the ICS adherence data to build a picture of the balance between the medications.

Future research could further adapt the BMQ for young people with asthma including reliever and preventer domains and complete the necessary psychometric testing for validation of the tool. The adapted BMQ-YPWA should first be explored within a talk aloud study before testing the questionnaire's reliability and validity in a large group of patients. A self-report questionnaire measuring beliefs relevant to adherence would be valuable both for research and practice.

#### 8.4.3.2 *Research exploring the problem of trivialisation of asthma*

The qualitative study (Chapter 6) outlined one theme particularly relevant to future research in the problematic asthma patient group. Patients reported an influential effect of trivialisation of asthma, in particular related to the severity of asthma, on their motivation to adhere to their daily ICS medication. Patients described this in relation to a lack understanding by both their wider family and the public about the seriousness of asthma as a condition. Trivialisation of asthma could be explored in future research. This could include the analysis of how asthma is presented through mediums such: theatre; television; film and news. Unlike many other serious conditions asthma is often portrayed as a condition of weakness, in characters who are nervous and unpopular and often using a SABA inhaler as opposed to an ICS inhaler. These sources often display poor inhaler technique and a lack of spacer use which has also been reported as a problem in other health conditions (e.g. the use of EpiPens). These portrayals used within the UK may influence non-adherence and poor asthma outcomes by increasing stigma felt by those



with asthma in this population, and therefore should be explored within future research. Indeed, Asthma UK have recently adopted and supported the use of images portraying patients using preventer rather than reliever inhalers.

#### *8.4.3.3 Methodology Recommendations and Next Steps*

##### *8.4.3.3.1 Drawing and visualisation of asthma and ICS*

The use of drawing within the qualitative study produced some data which may indicate the benefits of this methodology in certain circumstances as outlined in Chapter 6.4. The responses that were drawn were in relation to asthma and ICS understanding, in particular drawings of the lungs where illness coherence and understanding of preventer and reliever medication was generally found to be poor. There is a growing body of literature which suggests that visualisation of a chronic condition and of medications can increase illness coherence, necessity for medication (Jones, Fernandez, Grey, & Petrie, 2017) and adherence (Jones et al., 2018). Given the success of these type of studies, a similar visualisation of asthma and the effects for both ICS and SABA in the lungs may be a useful addition to a tailored adherence package. Indeed, a video animation for use in adults with asthma has recently been developed, by Professor Robert Horne and colleagues at UCL, to address illness and treatment beliefs. Initial pilot testing of the video has shown positive effects, particularly in patients who self-reported as not having asthma (Katzer, Wileman, Chan, Taylor, & Horne, 2018). Katzer et al. (2018) liken this “asthma naïve” group to newly diagnosed patients and suggest that this group would be appropriate to target with this type of intervention, as their beliefs may be the most adaptable. Given the poor understanding of asthma and ICS found within this PhD in children with asthma in tertiary care, these studies support the recommendation of this type of visual aid being developed and used within this population for newly referred patients (Chapter 6:).

##### *8.4.3.3.2 The use of Electronic Monitoring Devices in research*

Within this research the use of EMDs to measure and explore adherence was extremely useful. This type of adherence measurement allows for data to be shared with patients, to base interviews and therefore conclusions on objective data. For future research the selection of EMD is paramount as new devices are being developed year on year. Based on this PhD recommendations for use of an EMD such as the Smartinhaler can be made however patient choice, age and the device cost should be considered when selecting a device. Indeed, a recent focus group in this population exploring experience of using novel EMDs for adherence from both the patient and health care professional perspective concluded that “no one size fits all”

and that patient and healthcare provider needs should inform the choice of device (Mahkecha, Pearce, Chan, & Fleming, In press).

To date EMDs have been used in asthma predominantly to measure and intervene in preventer inhaler use however as mentioned within previous chapters measuring SABA use and patterns of SABA use will also be important in future research. Measuring both types of inhaler will allow researchers to consider the balance between medications and to illustrate and intervene on this balance with children and their families.

## **8.5 Conclusions**

The work presented in this PhD has explored patterns and modifiable determinants of non-adherence in young people with problematic asthma. Psychological theory (e-CSM, PAPA and BCTs) has been used as a basis for this research extending upon past research in adults and those with mild/moderate asthma severity. Methods and theory were explored within previously developed interventions for adherence to ICS children with asthma as an initial assessment of what had already been done and was effective. The systematic review found that in effective high-quality studies, the PAPA was more commonly addressed and BCTs were identified that were effective when used as part of a complex intervention. The PhD then went on to identify patterns of non-adherence and determinants of non-adherence through both quantitative and qualitative empirical studies. These studies revealed the worth of EMDs for exploring these behaviours with patients and that, as anticipated, distinct behavioural patterns are evident in different individuals and at different time points, related to low perceived necessity for ICS, a poor understanding of asthma and other identified themes. The qualitative study also revealed that unlike parental beliefs, young people's non-adherence is driven by low necessity and not high concerns and is not only related to forgetfulness. Given the important findings outlined by these extensive studies, a tool which can identify these beliefs quickly and accurately is needed. The adaptation of the BMQ-YPWA is the beginning of this essential work, however a larger further-validation study is needed. Future research in this area should focus on the perceptual and practical drivers of non-adherence outlined in this PhD when developing new tailored adherence support packages.

# Appendices

## Appendix 1: BCT Taxonomy (v1)

BCT Taxonomy (v1): 93 hierarchically-clustered techniques

Page	Grouping and BCTs	Page	Grouping and BCTs	Page	Grouping and BCTs
<b>1</b>	<b>1. Goals and planning</b> 1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behavior goal(s) 1.6. Discrepancy between current behavior and goal 1.7. Review outcome goal(s) 1.8. Behavioral contract 1.9. Commitment	<b>8</b>	<b>6. Comparison of behaviour</b> 6.1. Demonstration of the behavior 6.2. Social comparison 6.3. Information about others' approval	<b>16</b>	<b>12. Antecedents</b> 12.1. Restructuring the physical environment 12.2. Restructuring the social environment 12.3. Avoidance/reducing exposure to cues for the behavior 12.4. Distraction 12.5. Adding objects to the environment 12.6. Body changes
<b>3</b>	<b>2. Feedback and monitoring</b> 2.1. Monitoring of behavior by others without feedback 2.2. Feedback on behaviour 2.3. Self-monitoring of behaviour 2.4. Self-monitoring of outcome(s) of behaviour 2.5. Monitoring of outcome(s) of behavior without feedback 2.6. Biofeedback 2.7. Feedback on outcome(s) of behavior	<b>9</b>	<b>7. Associations</b> 7.1. Prompts/cues 7.2. Cue signalling reward 7.3. Reduce prompts/cues 7.4. Remove access to the reward 7.5. Remove aversive stimulus 7.6. Satiation 7.7. Exposure 7.8. Associative learning	<b>17</b>	<b>13. Identity</b> 13.1. Identification of self as role model 13.2. Framing/reframing 13.3. Incompatible beliefs 13.4. Valued self-identify 13.5. Identity associated with changed behavior
<b>5</b>	<b>3. Social support</b> 3.1. Social support (unspecified) 3.2. Social support (practical) 3.3. Social support (emotional)	<b>10</b>	<b>8. Repetition and substitution</b> 8.1. Behavioral practice/rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal 8.5. Overcorrection 8.6. Generalisation of target behavior 8.7. Graded tasks	<b>18</b>	<b>14. Scheduled consequences</b> 14.1. Behavior cost 14.2. Punishment 14.3. Remove reward 14.4. Reward approximation 14.5. Rewarding completion 14.6. Situation-specific reward 14.7. Reward incompatible behavior 14.8. Reward alternative behavior 14.9. Reduce reward frequency 14.10. Remove punishment
<b>6</b>	<b>4. Shaping knowledge</b> 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 4.4. Behavioral experiments	<b>11</b>	<b>9. Comparison of outcomes</b> 9.1. Credible source 9.2. Pros and cons 9.3. Comparative imagining of future outcomes	<b>19</b>	<b>15. Self-belief</b> 15.1. Verbal persuasion about capability 15.2. Mental rehearsal of successful performance 15.3. Focus on past success 15.4. Self-talk
<b>7</b>	<b>5. Natural consequences</b> 5.1. Information about health consequences 5.2. Saliency of consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.5. Anticipated regret 5.6. Information about emotional consequences	<b>12</b>	<b>10. Reward and threat</b> 10.1. Material incentive (behavior) 10.2. Material reward (behavior) 10.3. Non-specific reward 10.4. Social reward 10.5. Social incentive 10.6. Non-specific incentive 10.7. Self-incentive 10.8. Incentive (outcome) 10.9. Self-reward 10.10. Reward (outcome) 10.11. Future punishment	<b>19</b>	<b>16. Covert learning</b> 16.1. Imaginary punishment 16.2. Imaginary reward 16.3. Vicarious consequences
		<b>15</b>	<b>11. Regulation</b> 11.1. Pharmacological support 11.2. Reduce negative emotions 11.3. Conserving mental resources 11.4. Paradoxical instructions		



**Asthma UK Centre  
for Applied Research**

Royal Brompton & Harefield **NHS**  
NHS Foundation Trust

### **Adherence to Medication in Young People with Problematic Severe Asthma**

Your child has been invited to take part in a research study. Before you decide if you are happy for him/her to take part you need to understand why the research is being done and what it would involve for your child. Please take time to read the following information carefully. Talk to others including your family, friends, a doctor or nurse about the study if you wish.

If anything is not clear and you require more information before you decide whether or not your child should take part in the study, please telephone the study team on 020 78741297 and ask to speak to Ms Christina Pearce. Alternatively call Dr Fleming on 02073528121. You may want to visit the INVOLVE website (<http://www.invo.org.uk/>) which has information about being involved in research.

#### **What is the purpose of the study?**

The purpose of this study is to see why some children do not take their preventer asthma medication regularly. This study will help us to understand what areas doctors and patients should discuss together regarding children's preventer medication use. This study will ultimately help us to develop plans in the clinic to help adolescents to take their inhalers more often and so improve their health.

#### **Why has my son/daughter been invited?**

Your child has been invited to join our study because he/she has problematic severe asthma (meaning despite asthma medications, your child still has a lot of problems with asthma) and attends The Royal Brompton Hospital for treatment.

### **What are the benefits?**

We cannot promise the study will help your child with their asthma, although it may do. But by taking part, they will be providing information that may help other young people to gain better control of their problematic asthma in the future.

### **Does my child have to take part?**

No. It is up to you and your child to decide whether or not to take part. If you do agree to let him/her take part you will be asked by the researcher to sign a form to give your consent. You are free to withdraw your child from the study at any time without giving a reason. If you or your child decides to withdraw from the study or not take part it will not affect the care your child receives. Neither you nor your child would have to give a reason for withdrawing from the study.

Your child will be given information about the study appropriate for their age and will be asked to sign or write their name on the consent form. The researcher will spend time explaining the study to you and your child. **If your child does not want to take part or to be withdrawn from the study at any time, this will be respected by the researcher even if consent is given by you as their parent/legal guardian.**

### **What does the research involve?**

The research involves consenting for the researcher to access your child's medical records held by The Royal Brompton in relation to their asthma including their Smartinhaler™ data which has previously been collected. The researcher will then use this data to help guide an in-depth interview with your child regarding their asthma and their asthma medication use. The interview will be conducted at the hospital at a time that is convenient for them (and you) and this will be audio recorded for later analysis by the interviewer.

The interview will take approximately **30-45 minutes** dependant on how much your child has to say.

### **What if there is a problem or something goes wrong?**

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact Christina Pearce or Dr Louise Fleming using the contact details below.

If you remain unhappy, you can make a formal complaint through the National Health Service (NHS) complaints procedure. Details can be obtained through the Royal Brompton Hospitals Patient Advice and Liaison Service (PALS) on TEL: 020 7349 7715 or email: [pals@rbht.nhs.uk](mailto:pals@rbht.nhs.uk).

University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

### **Disclosure and confidentiality**

Although your child may want to share what they have disclosed within the interview with you the researcher will not be able to do this unless already agreed by your child. The researcher has agreed that the conversations they have with your child will be confidential. The only instance where information would be shared with your child's GP would be if your child was expressing thoughts about harming themselves or others.

### **Who has reviewed this study?**

The NHS National Research Ethics Service have reviewed and authorised this study (Ref: 16/NS/0082).

**How do I find out further information about the study?**

Please contact Christina Pearce, the researcher at University College London, 020 78741297 extension 227.

Dr Louise Fleming who is a consultant in Paediatric Respiriology at the Royal Brompton Hospital is in charge of the project and be contacted if necessary via switchboard on 020 7352 8121.

**Thank you for taking the time to consider this study.**



**Asthma UK Centre  
for Applied Research**

Royal Brompton & Harefield   
NHS Foundation Trust

## **Patient Information Sheet for Young People**

We are asking if you would like to take part in a research project to help us better understand why young people miss doses of their preventer inhalers. Before you decide if you want to join in, it is important to understand why the research is being done and what it will involve for you. So please consider this leaflet carefully. Talk about it with your family, friends, doctor or nurse if you want to.

### **Why are we doing this research?**

We are doing this research to gain a better understanding of why young people do not always take their preventer inhalers as prescribed by their doctors. We want to explore the reasons for this to help people to regularly take their inhalers and improve the control of their asthma.



**Why have I been chosen?** You have been invited to join our study because you are being seen by the doctors who have diagnosed you with problematic severe asthma at The Royal Brompton. This means that your asthma is not controlled by your asthma medications at the moment.

**Do I have to take part?** No. It is up to you to decide whether or not to take part. If at any time you don't want to do the research anymore, just tell a parent or guardian, or doctor or nurse. Nobody will be upset and you do not have to give a reason why you do not want to take part.

**What will I be asked to do?** If you decide to take part you will be asked if we can look at information about your asthma in your medical notes. You will also be asked to talk to a



researcher about your asthma and your how you use your inhaler. (But you don't have to if it is a bit too difficult for you).

**Will joining in help me?** We cannot promise the study will help you, although it may do. But by taking part, you will be providing information that may later help young people to gain better control of their problematic asthma in the future.

**What if there is a problem or something goes wrong?** If there is a problem and you wish to complain, or have any worries about this study then you can talk to a parent or guardian, your doctor, your nurse or the researcher (Christina Pearce on 02078741297), who will help you with any problems you have. Alternately Dr Louise Fleming may be contacted on 0207 3528121 (ext 2938).

**Will anyone else know I am taking part in this study?** No, no-one will know unless you say we can tell them. We will keep your information anonymously. This means we will only tell those who have a need or right to know. We will only send out information that has your name and address removed. With your permission we will let your GP know that you are taking part in the study.

**What will happen to the results of the study?** The results of our research will add to our overall understanding of preventer inhaler use in young people with severe asthma. We will publish these results to help other asthma teams and their patients, but without saying who was actually in the study. This information may help design new ways to discuss inhaler use with young people and to develop services to improve asthma control. The results will not affect the medical care you receive from the hospital. If you would like to find out more about what we learn from the study, please let us know by marking this on the consent form.

**Who is organising and funding the research?** This study has been developed by UCL and The Royal Brompton Hospital and is funded as a PhD study by Asthma UK Centre for Applied Research (AUKCAR- <http://www.aukcar.ac.uk/>).

**Please ask any questions if you need to.** If you have any questions that the person who looks after you cannot answer, you can email me on:

[christina.pearce.15@ucl.ac.uk](mailto:christina.pearce.15@ucl.ac.uk) or telephone me on 0207 8741297



We will try to answer your question or will arrange for you to speak to an appropriate person.

**Who has reviewed the study?** Before any research goes ahead it has to be checked by a Research Ethics Committee, which includes doctors as well as non-medical people. This group of people are independent from the University and the Hospital and they make sure that the research is fair. Your project has been checked and approved by NHS Scotland (Ref: 16/NS/0082).



for taking the time to read this information

## Appendix 4: NHS ethical approval for the qualitative study

### North of Scotland Research Ethics Service

Summerfield House  
2 Eday Road  
Aberdeen  
AB15 6RE

Telephone: 01224 558458  
Facsimile: 01224 558609  
Email: nosres@nhs.net



**Please note:** This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

16 August 2016

Professor Robert Horne  
Professor of Behavioural Medicine  
University College London  
Centre for Behavioural Medicine UCL School of Pharmacy Research department of Practice and Policy  
BM  
BMA/Tavistock House  
Tavistock Square  
LONDON  
WC1H 9JP

Dear Professor Horne

**Study title:** Adherence to Inhaled Corticosteroids in Young People with Problematic Severe Asthma  
**REC reference:** 16/NS/0082  
**IRAS project ID:** 188453

Thank you for your letter of 12 August 2016, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Carol Irvine, nosres@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

### Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

### **Conditions of the favourable opinion**

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, [www.hra.nhs.uk](http://www.hra.nhs.uk) or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

### Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact [hra.studyregistration@nhs.net](mailto:hra.studyregistration@nhs.net). The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

## Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, [www.hra.nhs.uk](http://www.hra.nhs.uk) or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

## Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact [hra.studyregistration@nhs.net](mailto:hra.studyregistration@nhs.net). The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

## **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

## Approved documents

The documents reviewed and approved by the Committee are:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only): Insurance Confirmation	1	18 July 2016
GP/consultant information sheets or letters: GP Patient Participation Letter	1	1 June 2016
Interview schedules or topic guides for participants: Topic Guide	1	21 April 2016
IRAS Application Form: IRAS Form 18072016	188453/988265/37/544	18 July 2016
IRAS Checklist XML: Checklist 15082016		15 August 2016
Letter from Funder: Studentship Funding	1	18 July 2016
1st Secretarial Confidentiality Agreement		January 2016
Cover Letter for REC	1	12 August 2016
Participant Consent Form: Young Person	2	28 July 2016
Participant Consent Form: Parent	2	28 July 2016
Participant Information Sheet (PIS): Young Person	2	28 July 2016
Participant Information Sheet (PIS): Parent	2	28 July 2016
Referee's report or other scientific critique report: Peer Review of original Studentship	1	31 May 2016
Research protocol or project proposal: Protocol Version 1	1	21 April 2016
Summary CV for Chief Investigator (CI): Rob Horne	1	19 January 2016
Summary CV for Student: Christina Pearce	1	12 April 2016
Summary CV for Supervisor (student research): Rob Horne	1	19 January 2016
Summary CV for Supervisor (student research): Louise Fleming		18 January 2016
Summary CV for Supervisor (student research): Andy Bush	1	18 January 2016

## Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

## After ethical review

### Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service 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>

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

<b>16/NS/0082</b>	<b>Please quote this number on all correspondence</b>
-------------------	---

With the Committee's best wishes for the success of this project.

Yours sincerely



**Professor Nigel Webster**  
Chair

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: Miss Emily Ikelle  
Mr Patrik Pettersson, Royal Bromton & Harefield Trust



**Health Research Authority**

Professor Robert Home  
Professor of Behavioural Medicine  
University College London  
Centre for Behavioural Medicine UCL School of Pharmacy  
Research department of Practice and Policy BM  
BMA/Tavistock House, Tavistock Square  
WC1H 9JP

Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)

30 August 2016

Dear Professor Home

**Letter of HRA Approval**

<b>Study title:</b>	<b>Adherence to Inhaled Corticosteroids in Young People with Problematic Severe Asthma</b>
<b>IRAS project ID:</b>	<b>188453</b>
<b>REC reference:</b>	<b>16/NS/0082</b>
<b>Sponsor</b>	<b>University College London</b>

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

**Participation of NHS Organisations in England**

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

*Appendix B* provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read *Appendix B* carefully, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.



## Appendix 6: Research and Development approval



Royal Brompton & Harefield   
NHS Foundation Trust

**Royal Brompton & Harefield NHS Foundation Trust**  
Research Office  
Chelsea Wing  
Sydney Street  
SW3 6NP  
[www.rbht.nhs.uk](http://www.rbht.nhs.uk)

28th September 2016

Dr Louise Fleming  
Consultant Respiratory Paediatrics  
Royal Brompton & Harefield NHS Foundation Trust

Dear Dr Fleming,

**Project Title:** Adherence to Inhaled Corticosteroids in Young People with Problematic Severe Asthma  
**R&D Ref:** 2016PL005B  
**REC Ref:** 16/NS/0082  
**IRAS No:** 188453  
**Study Sponsor:** University College London

Recruitment Target: 15  
Recruitment End Date: 31/03/2018  
Study End Date: 30/09/2018

### **Confirmation of Participation**

The project must be conducted as described in the protocol and in accordance with the supporting documentation provided by the Sponsor and the principles set out in the Research Governance Framework for Health and Social Care (April 2005, 2<sup>nd</sup> Edition, Department of Health (DoH)) and [RB&HFT Policies and procedures](#).

### **Study Amendments**

It is the responsibility of the Sponsor to ensure that HRA Policies and Procedures are followed concerning **all** study amendments.

Changes to the status of the project, including study suspension or premature termination, should be communicated to the Research Office.

### **Safety Reporting**

The research Sponsor, or the Chief Investigator (CI) or the local Principal Investigator (PI) at a research site, may take appropriate Urgent Safety Measures in order to protect research participants against any immediate hazard to their health or safety. The Research Office should be notified of such measures within the same time frame of notifying the REC. The notification should include reasons why the measures were taken and the plan for further action.



A lifetime of specialist care

All **patient related incidents** must be reported internally by the study team in line with the Trust's [Adverse Incident Management and Reporting Policy](#) via the Quality and Safety Department database [Datix](#). Where the incident is related to the patients' participation in research these should be marked "**research-related**".

In addition, **all** SAE/Rs must be reported to the study Sponsor and the main REC in line with the approved research protocol.

### **Audit**

Please note the Trust is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements. This responsibility is delegated to the Research Office and will be achieved by random audit of research projects ongoing in the Trust in accordance with RB&HFT Audit SOP.

### **Patient recruitment:**

You must ensure that monthly recruitment numbers (accruals) are uploaded to the CPMS Portal if you are the Chief Investigator (CI), or forwarded to the Chief Investigator or Recruitment Data Contact (RDC) if the CI is based in another organisation.

Yours sincerely



**Dr Jenny Rivers**  
Associate Director of Research

Cc: [christina.pearce.15@ucl.ac.uk](mailto:christina.pearce.15@ucl.ac.uk); [r.horne@ucl.ac.uk](mailto:r.horne@ucl.ac.uk)



**Problematic Severe Asthma Interview Topic Guide**

**Interviewer instructions:**

1. *Interviewer to introduce herself and the project including talking about AUKCAR; her affiliations and her experience of asthma*
2. *Read through the information sheet with the patient*
3. *Allow time to elicit/answer any questions the patient may have*
4. *Obtain written informed consent from both the child and the parent– complete two copies of consent form and give one to the patient or their parent/guardian for their records*

**Interview questions**

[Drawing materials will be present from the beginning of the interview.]

**Script**

What we are doing in this study is looking at patterns of inhaler use. What we find is that people vary in the way they take their inhalers. They might miss out doses or take it in a different way to what is on the label or their doctor has said to. Many people find a way of using their inhaler that suits them and sometimes this is different from what the doctor recommends. The problem is that some people don't want to tell the doctor what they actually do because they are concerned that the doctor might not be pleased.

I'll be asking lots of people similar questions and nobody including your doctors will know that it is you that has said the things in this room. I want to find out more because I

think the medical world needs a better understanding of how young people actually experience asthma and their asthma treatment. I have asthma myself and I have found my own way of using my treatment over the years.

As you know SmartInhalers record when you have taken your inhaler and I'd like to ask you about this pattern to understand why you use it that way.

1. [Dependant on the pattern of non-adherence shown within the SmartInhaler the participants will be asked specific questions regarding their inhaler use. E.g.]

- Have you ever taken your inhaler for 4 days then missed it for two days?
  - *Can you remember why you missed some days?*
  - *E.g. forgetting; not wanting to take it*
  - *How did you feel when you missed those days' doses?*
  - *E.g. better, worse, the same? Why do you think that is?*
  
- From looking at your smart inhaler data I can see that you tend to take your inhaler less at the weekend. Can you tell me a little bit about that?
  - *Why do you think that is?*
  - *What would help you to take it more at the weekends?*
  
- From looking at your smart inhaler data I can see that you do take your inhaler at least once on most days.
  - *What makes you take it once but not twice?*
  - *What might help you to take it in the morning and at night every day?*

**General Perceptual Questions about asthma and treatment**

2. What does having Asthma mean to you?
  - *What goes on inside the body in asthma?*
3. How does having asthma make you feel?
  - *angry, sad, embarrassed?*
4. What do you think the daily treatment does?
  - *What goes on inside the body when the daily treatment is used?*
5. How well do you understand how to take your inhalers?
  - *Using a spacer?*
  - *General inhaler use?*
6. What do you like/dislike about asthma daily treatments?
  - *What if anything, worries you about the daily treatment?*
  - *In the long-term; in the short term; side-effects if not mentioned*
7. How do the asthma inhaler treatments make you feel?
  - *angry, sad, embarrassed?*
8. How important is the daily treatment to you?
9. What do you use your blue inhaler for e.g. Ventolin?
  - *How often do you use it?*
  - *How do you use it compared to how you use your purple/daily inhaler?*

Specific Questions

Practicalities/ not intentional

10. What are the reasons that you forget to take your inhaler?

- *Can you remember and describe a recent situation when you forgot to take your inhaler? (For example in the last few weeks)*
- *What activities or other things might get in the way of you taking your inhaler?*

11. How do you remember to take your inhalers?

12. Some children and teenagers live between two parents or guardians home and have said that this can affect how they take their inhalers. Who do you live with?

- *What do your parents or family think of your asthma treatments?*
- *Do they get involved with the treatments? E.g. help you*

13. How often do you use your spacer?

- *What type is it/ can you describe it to me?*
- *What do you think about using a spacer?*
- *How do you find using a spacer with your inhaler?*

14. What aspects about the inhaler medicine itself might affect whether or not you take it?

- *E.g. taste, the size of the inhaler, ability to hold your breath; look of it*

Is there anything else you would like to say that we haven't already discussed?

**Thank you for taking part!**

## Appendix 8: SPEAK Asthma Feedback

### Patient Information for younger children:

- Specify which inhalers (morning & night-time inhalers)
- They may not know what 'questionnaire' means
- Replace medication with medicine for younger children
- They liked the 'Do I have to take part?' section and felt it would help younger people know they have a choice.
- Include 'nurse' as a person they can speak to if they change their mind.
- What is the Research Ethics Committee?
- They may not have an email address so you may want to leave a different way to contact you. Text was suggested.
- Who is the researcher?

### Patient Information for older children

- They wanted to know more information about who the researcher was. – photos sometimes help with this?
- First paragraph – which inhaler are you interested in finding out if they missed doses? (reliever or preventer?)
- Based on colours of inhaler the group here are using, they felt it would be better to use purple, red or yellow as the colour in the photo.
- In the Why have I been chosen section – they wanted to know what makes them come under the 'severe asthma' category.
- In the 'What will I be asked to do' section – include 'But you don't have to if it is a too difficult for you' at the end. (They were worried about it being traumatic for some children to speak with researchers about their inhaler use.)
- In the 'Joining in helping me' section one girl said that it may make them jealous. I suspect that it is because it touches a nerve with her asthma being uncontrolled. Maybe if the section emphasises their role on helping and makes clear that benefits would be for others in the future (as opposed to others rather than them now?) it may reduce that feeling – i.e. We cannot promise the study will help you. But by taking part, you will be providing information that may later help young people to gain better control of their problematic asthma in the future.
- What if there is a problem section – In general they really liked this section. Also suggested including a nurse as well as doctor as someone they could speak to (most will usually see the nurse).
- Will anyone else know I am taking part section – I am not sure one girl understood 'in confidence' – you may want to be clear about who the information would be shared with and they suggested using the word anonymous as it is more clear (They suggested saying something to the effect of You can stay anonymous if you want.)

- What will happen to the results – simplify this section (i.e. The results will not affect the medical care you receive from the hospital. If you would like to find out more about what we learn from the study, please let us know by marking this on the consent form.)
- Who/what is the Research Ethics Committee?
- Include text as a possible way of getting in touch with questions

#### Parental Consent Form:

- Q3. They felt the last part of this statement about medical care and legal rights was a very important point and needed to be emphasised more. Perhaps separate it into two sentences – i.e. If you decide not to take part, then your medical care or legal rights will not be affected.
- Q5. They found Q5. difficult and were put off by the way it was worded. They felt more comfortable with saying something like ‘I understand that if you become very worried about my safety or the safety of others because of any responses I provide on the questionnaire that the research team may contact my GP on my behalf.’
- They suggested separating the Young person’s agreement (assent form) into a different form so it wasn’t combined.

#### Consent Form:

- Overall they felt the wording could be simplified a bit to make it more understandable. Suggestions include:
- Q2. Change the word sufficient (as not everyone will understand it)
- Q3. Change participation to taking part (Also, see point above about emphasizing statement about rights).
- Q4. What is UCL?
- Q5. Change responses to answers (Also see suggestion above about wording)
- Q7. Not everyone will understand what you mean by audio recording.



## Appendix 9: Beliefs about Medicines Questionnaire

Beliefs about medicines questionnaire (BMQ) Horne, Weinman, Hankins, (1999)  
*Psychology and Health*, 14, 1-24

### *BMQ –Specific*

*Your views about medicines prescribed to you.*

- I would like to ask you about your personal views about medicines prescribed for your asthma.
- These are statements other people have made about their asthma medication.
- Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only cross one box per question.

#### 1) My health at present depends on my asthma medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

#### 2) Having to take asthma medication worries me

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

#### 3) My life would be impossible without my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

#### 4) Without my asthma medication I would be very ill

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5) I sometimes worry about the long-term effects of my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6) My asthma medication is mystery to me

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7) My health in the future will depend on my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8) My asthma medication disrupts my life

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9) I sometimes worry about becoming too dependent on my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10) My asthma medication protects me from becoming worse.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*BMQ-General*

- I would like to ask you about your personal views about medicines in general.
- These are statements other people have made about medicines in general.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only tick one box per question.

11) Doctors use too many medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12) People who take medicines should stop their treatment for a while every now and again.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

13) Most medicines are addictive.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14) Natural remedies are safer than medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

15) Medicines do more harm than good.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

16) All medicines are poisons

Strongly agree

agree

uncertain

disagree

strongly disagree

17) Doctors place too much trust on medicines

Strongly agree

agree

uncertain

disagree

strongly disagree

18) If doctors had more time with patients they would prescribe fewer medicines.

Strongly agree

agree

uncertain

disagree

strongly disagree

Appendix 10: Questionnaire pack including the BMQ-YPWA

Date:22/02/2018

BMQ- Young People With Asthma (YPWA)  
number.....

Version number: 1

Participant

## YOUR VIEWS ABOUT YOUR ASTHMA AND YOUR INHALERS

- We would like to ask you about your personal views about asthma and your inhalers. The questions will ask you separately about your Preventer and Reliever inhalers.
- Below are reasons why some young people with asthma at times do or don't use their inhalers. Do any of these statements apply to you? For each statement, please show how much you agree or disagree with the view.

**There are no right and wrong answers.  
We are just interested in your personal views**

Views about <b>your asthma</b>		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
Q1	Having asthma annoys me					
Q1	Having asthma symptoms like wheezing, coughing, chest tightness and difficulty breathing is normal for me					

Views about <b>your reliever inhaler*</b> *Reliever inhaler= blue		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
Q10	I use my reliever inhaler a lot more than I use my preventer inhaler					
Q10	I can feel my reliever inhaler working quickly so I rely on it					
Q11	I worry about the side effects of my reliever inhaler					
Q10	My reliever is the only inhaler that can help my asthma					
Q12	I feel embarrassed having to take my reliever inhaler					

Views about <b>your preventer inhaler*</b> Preventer inhaler= brown, orange, red, purple, white/red		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
Q11	My health, at present, depends on my preventer inhaler					
Q13	Having to use my preventer inhaler worries me					
Q14	My life would be impossible without my preventer inhaler					
Q15	Without my preventer inhaler I would be very ill					
Q12	I sometimes worry about the long-term effects of my preventer inhaler					

© Professor Rob Horne 1999

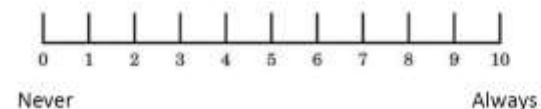
13	My preventer inhaler is a mystery to me					
14	My health in the future will depend on my preventer inhaler					
15	My preventer inhaler disrupts my life					
16	I sometimes worry about becoming too dependent on my preventer inhaler					
17	My preventer inhaler protects me from becoming worse					
18	My preventer inhaler gives me unpleasant side-effects					
19	Having to use preventer inhaler everyday annoys me					
20	I do not trust my preventer inhaler					
21	I don't notice a difference whether I take my preventer inhaler or not					
22	Nobody cares about asthma so why should I take my preventer inhaler					
23	When I feel well I don't think I need my preventer inhaler as much					
24	My asthma is still controlled without following all my doctor's instructions					

Practical issues related to <b>your preventer inhaler</b>		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
25	When I am very tired, I sometimes don't take my preventer inhaler					
26	I keep my preventer inhaler in the same place, so I can remember to take it					
27	My parent(s)/guardian(s) help me to remember to take my preventer inhaler					
28	I find my routine for taking my preventer inhaler is easily disrupted e.g at the weekend or during the school holidays					
29	I don't have a routine for taking my preventer inhaler					
30	I find it difficult to use my preventer inhaler with my spacer					

### **How much do I really use my preventer inhaler?**

Please put an **X** on the number that you agree with.

On a scale of 1-10 in general how often do you take your preventer inhaler (Seritide, Symbicort or other)?



### The Brief Illness Perception Questionnaire

For the following questions, please circle the number that best corresponds to your views:

<p><b>How much does your illness affect your life?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>no affect at all severely affects my life</p>
<p><b>How long do you think your illness will continue?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>a very short time forever</p>
<p><b>How much control do you feel you have over your illness?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>absolutely no control extreme amount of control</p>
<p><b>How much do you think your treatment can help your illness?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>not at all extremely helpful</p>
<p><b>How much do you experience symptoms from your illness?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>no symptoms at all many severe symptoms</p>
<p><b>How concerned are you about your illness?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>not at all concerned extremely concerned</p>
<p><b>How well do you feel you understand your illness?</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>don't understand at all understand very clearly</p>
<p><b>How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)</b></p> <p>0 1 2 3 4 5 6 7 8 9 10</p> <p>not at all affected emotionally extremely affected emotionally</p>
<p><b>Please list in rank-order the three most important factors that you believe caused <u>your illness</u>. <i>The most important causes for me:-</i></b></p> <p>1. _____</p> <p>2. _____</p> <p>3. _____</p>

© All rights reserved. For permission to use the scale please contact: [lizbroadbent@clear.net.nz](mailto:lizbroadbent@clear.net.nz)

## Take the Asthma Control Test™ (ACT) for people 12 yrs and older.

Write the number of each answer in the score box provided

1. In the past <b>4 weeks</b> , how much of the time did your <b>asthma</b> keep you from getting as much done at work, school or at home?	All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	SCORE
2. During the past <b>4 weeks</b> , how often have you had shortness of breath?	More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	
3. During the past <b>4 weeks</b> , how often did your <b>asthma</b> symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	
4. During the past <b>4 weeks</b> , how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	
5. How would you rate your <b>asthma</b> control during the <b>past 4 weeks</b> ?	Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	
											TOTAL

Copyright 2011, by QuinaryMetrics Incorporated.  
Asthma Control Test is a trademark of QuinaryMetrics Incorporated.

# Thank you for taking part!



Appendix 11: Ethical approval for the BMQ-YPWA study

**North of Scotland Research Ethics Service**

Summerfield House  
2 Eday Road  
Aberdeen  
AB15 6RE

Telephone: 01224 558458  
Facsimile: 01224 558609  
Email: nosres@nhs.net



**Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.**

23 March 2018

Miss Christina J C Pearce  
Centre for Behavioural Medicine UCL School of Pharmacy Research department of Practice  
and Policy BM  
BMA/Tavistock House  
Tavistock Square  
LONDON  
WC1H 9JP

Dear Miss Pearce

<b>Study title:</b>	<b>Adherence to Inhaled Corticosteroids in Young People with Problematic Severe Asthma</b>
<b>REC reference:</b>	<b>16/NS/0082</b>
<b>Amendment number:</b>	<b>1 (Study Ref) AM03 (REC Ref)</b>
<b>Amendment date:</b>	<b>10 August 2017</b>
<b>IRAS project ID:</b>	<b>188453</b>

Approval was sought for the following changes:

- Extension of the study to 31 May 2018 to allow for a follow-up set of questionnaires to be completed by the participants.
- Addition of Dr Amy Chan from University College London as the student's fourth supervisor.

The above amendment was reviewed by the Sub-Committee in correspondence.

**Ethical opinion**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

**Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/consultant information sheets or letters	2	5 February 2018
Notice of Substantial Amendment (non-CTIMP)	1 (Study Ref) AM03 (REC Ref)	10 August 2017
Appendix 1 Questionnaire Pack	1	22 February 2018
Major Ethics Amendment IRAS Sections	1	22 February 2018
Participant Consent Form: Parent	2	5 February 2018
Participant Consent Form: YP	2	5 February 2018
Participant Information Sheet (PIS): Parental	2	5 February 2018
Participant Information Sheet (PIS): YP	2	5 February 2018
Research protocol or project proposal	2	9 February 2018
Summary CV for supervisor (student research): Amy Chan		22 February 2018
Validated questionnaire: BMQ Asthma Preventer 2010	002	22 February 2018*

\* date received

### **Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

### **Working with NHS Care Organisations**

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

### **Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

<b>16/NS/0082: Please quote this number on all correspondence</b>
---

Yours sincerely



pp'd on behalf of  
Dr Ruth Stephenson  
Vice-Chair

## Amendment Categorisation and Implementation Information

Dear Professor Horne,

<b>IRAS Project ID:</b>	188453
<b>Short Study Title:</b>	Adherence to Asthma Medication in Young People with PSA
<b>Date complete amendment submission received:</b>	18 May 2018
<b>Amendment No./ Sponsor Ref:</b>	Non-Substantial Amendment 3
<b>Amendment Date:</b>	18 May 2018
<b>Amendment Type:</b>	Non-substantial
<b>Outcome of HRA and HCRW Assessment</b>	<b>This email also constitutes HRA and HCRW Approval for the amendment</b> , and you should not expect anything further.
<b>Implementation date in NHS organisations in England and Wales</b>	35 days from date amendment information together with this email, is supplied to participating organisations <b>(providing conditions are met)</b>

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](mailto:hra.amendments@nhs.net)
- Northern Ireland – [research.gateway@hscni.net](mailto:research.gateway@hscni.net)
- Scotland – [nhsg.NRSPCC@nhs.net](mailto:nhsg.NRSPCC@nhs.net)

- Wales – [research-permissions@wales.nhs.uk](mailto:research-permissions@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

**Richard Boyd**

**Health Research Authority**

Ground Floor | Skipton House | 80 London Road | London | SE1 6LH

**E.** [hra.amendments@nhs.net](mailto:hra.amendments@nhs.net)

**W.** [www.hra.nhs.uk](http://www.hra.nhs.uk)

Appendix 13: BMQ-YPWA internal validity item deletion data

Domain	Item Number	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Necessity Domain: Round 1	1.	0.42	0.60
	2.	0.27	0.63
	3.	0.39	0.61
	4.	0.54	0.57
	5.	0.48	0.60
	6. Having to use my preventer everyday annoys me	0.18	0.66
	7.	0.34	0.61
	8.	0.17	0.64
	9.	0.17	0.66
	10.	0.36	0.61
Necessity Domain: Round 2	1.	0.52	0.60
	2.	0.35	0.64
	3.	0.48	0.60
	4.	0.55	0.59
	5.	0.57	0.60
	7.	0.30	0.65
	8.	0.12	0.67

	9. When I feel well I don't think I need my preventer inhaler as much	-0.01	0.73
	10.	0.37	0.63
Concerns Domain:	1. Having to use my preventer inhaler worries me	0.74	0.79
	2.	0.68	0.79
	3.	0.61	0.81
	4.	0.65	0.80
	5.	0.37	0.85
	6.	0.60	0.81
	7.	0.67	0.82
Practicality Domain: Round 1	1.	0.28	0.04
	2. I keep my preventer inhaler in the same place, so I can remember to take it	-0.29	0.43
	3.	-0.47	0.48
	4.	0.47	-0.23
	5.	0.35	-0.07
	6.	0.21	0.11
Practicality Domain: Round 2	1.	0.40	0.22
	3. My parent(s)/ guardian(s) help me to remember to take my preventer inhaler	-0.50	0.67
	4.	0.53	0.07
	5.	0.45	0.19
	6.	0.21	0.39

Practicality Domain: Round 3	1.	0.48	0.58
	4.	0.59	0.49
	5.	0.54	0.55
	6. I find it difficult to use my preventer inhaler with my spacer	0.22	0.74



## References

- Abdou, J. K., Auyeung, V., Patel, J. P., & Arya, R. (2016). Adherence to long-term anticoagulation treatment, what is known and what the future might hold. *Br J Haematol*, *174*(1), 30-42. doi:10.1111/bjh.14134
- Abraham, C., & Michie, S. (2008). A taxonomy of behavior change techniques used in interventions. *Health Psychology*, *27*(3), 379-387. doi:10.1037/0278-6133.27.3.379
- Adair, J. G. (1984). The Hawthorne Effect - a Reconsideration of the Methodological Artifact. *Journal of Applied Psychology*, *69*(2), 334-345. doi:10.1037/0021-9010.69.2.334
- Adams, S. A., Leach, M. C., Feudtner, C., Miller, V. A., & Kenyon, C. C. (2017). Automated Adherence Reminders for High Risk Children With Asthma: A Research Protocol. *JMIR Res Protoc*, *6*(3), e48. doi:10.2196/resprot.6674
- Aikens, J. E., Nease, D. E., Nan, D. P., Klinkman, M. S., & Schwenk, T. L. (2005). Adherence to maintenance-phase antidepressant medication as a function of patient beliefs about medication. *Annals of Family Medicine*, *3*(1), 23-30. doi:10.1370/afm.238
- Ajzen, I. (1988). *Attitudes, personality and behavior*. Milton Keynes: Open University Press.
- Ajzen, I. (1991). The Theory of Planned Behavior. *Organizational Behavior and Human Decision Processes*, *50*(2), 179-211. doi:10.1016/0749-5978(91)90020-T
- Ajzen, I. (2002). Residual effects of past on later behavior: Habituation and reasoned action perspectives. *Personality and Social Psychology Review*, *6*(2), 107-122. doi:10.1207/S15327957pspr0602\_02
- Ajzen, I. (2005). *Attitudes, personality and behavior* (2nd ed. ed.). Maidenhead: Open University Press.
- Ajzen, I., & Fishbein, M. (1980). *Understanding attitudes and predicting social behavior*. Englewood Cliffs ; London: Prentice-Hall.
- Ajzen, I., & Madden, T. J. (1986). Prediction of Goal-Directed Behavior - Attitudes, Intentions, and Perceived Behavioral-Control. *Journal of Experimental Social Psychology*, *22*(5), 453-474. doi:10.1016/0022-1031(86)90045-4
- Alderwick, H., & Dixon, J. (2019). The NHS long term plan. *BMJ*, *364*, l84. doi:10.1136/bmj.l84
- Alsous, M., Hamdan, I., Saleh, M., McElnay, J., Horne, R., & Masri, A. (2018). Predictors of nonadherence in children and adolescents with epilepsy: A multimethod assessment approach. *Epilepsy Behav*, *85*, 205-211. doi:10.1016/j.yebeh.2018.06.022
- Anagnostou, K., Harrison, B., Iles, R., & Nasser, S. (2012). Risk factors for childhood asthma deaths from the UK Eastern Region Confidential Enquiry 2001–2006. *Primary Care Respiratory Journal*, *21*, 71. doi:10.4104/pcrj.2011.00097
- Andersson, M., Hedman, L., Bjerg, A., Forsberg, B., Lundback, B., & Ronmark, E. (2013). Remission and persistence of asthma followed from 7 to 19 years of age. *Pediatrics*, *132*(2), e435-442.
- Apter, A. J., Boston, R. C., George, M., Norfleet, A. L., Tenhave, T., Coyne, J. C., . . . Feldman, H. I. (2003). Modifiable barriers to adherence to inhaled steroids among adults with asthma: It's not just black and white. *Journal of Allergy and Clinical Immunology*, *111*(6), 1219-1226. doi:<https://doi.org/10.1067/mai.2003.1479>
- Arden, M. A., Drabble, S. J., O'Cathain, A., Hutchings, M., & Wildman, M. (2016). WS16.1 ACTiF study: understanding adherence to nebuliser treatment in adults with cystic fibrosis using the Theoretical Domains Framework. *Journal of Cystic Fibrosis*, *15*, S26. doi:[https://doi.org/10.1016/S1569-1993\(16\)30151-5](https://doi.org/10.1016/S1569-1993(16)30151-5)

- Axelsson, M., Cliffordson, C., Lundback, B., & Lotvall, J. (2013). The function of medication beliefs as mediators between personality traits and adherence behavior in people with asthma. *Patient Preference and Adherence*, 7, 1101-1109. doi:10.2147/Ppa.S49725
- Bacharier, L. B., Strunk, R. C., Mauger, D., White, D., Lemanske, R. F., Jr., & Sorkness, C. A. (2004). Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *American Journal of Respiratory & Critical Care Medicine*, 170(4), 426-432. doi:10.1164/rccm.200308-1178OC
- Bandura, A. (1977). *Social learning theory*. Englewood Cliffs ; London: Prentice-Hall.
- Bangsberg, D. R., Ragland, K., Monk, A., & Deeks, S. G. (2010). A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS*, 24(18), 2835-2840. doi:10.1097/QAD.0b013e328340a209
- Baren, J. M., Boudreaux, E. D., Brenner, B. E., Cydulka, R. K., Rowe, B. H., Clark, S., & Camargo, C. A. (2006). Randomized controlled trial of emergency department interventions to improve primary care follow-up for patients with acute asthma. *Chest*, 129(2), 257-265. doi:10.1378/chest.129.2.257
- Barrett, M. A., Humblet, O., Marcus, J. E., Henderson, K., Smith, T., Eid, N., . . . Sublett, J. L. (2017). Effect of a mobile health, sensor-driven asthma management platform on asthma control. *Ann Allergy Asthma Immunol*, 119(5), 415-421 e411. doi:10.1016/j.anai.2017.08.002
- Bartholomew, L. K., Parcel, G. S., & Kok, G. (1998). Intervention mapping: a process for developing theory- and evidence-based health education programs. *Health Education & Behavior*, 25(5), 545-563.
- Baum, A., & Poslusny, D. M. (1999). Health psychology: mapping biobehavioral contributions to health and illness. *Annu Rev Psychol*, 50, 137-163. doi:10.1146/annurev.psych.50.1.137
- Beasley, R., Perrin, K., Weatherall, M., & Wijesinghe, M. (2010). Call for withdrawal of LABA single-therapy inhaler in asthma. *Lancet*, 376(9743), 750-751. doi:10.1016/S0140-6736(10)61158-0
- Becker, M. H. (1974). *The health belief model and personal health behaviour*: Charles B. Slack.
- Becker, M. H., Radius, S. M., Rosenstock, I. M., Drachman, R. H., Schuberth, K. C., & Teets, K. C. (1978). Compliance with a medical regimen for asthma: a test of the health belief model. *Public Health Rep*, 93(3), 268-277.
- Bender, B., Wamboldt, F., O' Connor, S., Rand, C., Szeffler, S., Milgrom, H., & Wamboldt, M. (2000). Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma and Immunology*, 85(5), 416-421.
- Bender, B., Wamboldt, F., O'Connor, S. L., Rand, C., Szeffler, S., Milgrom, H., & Wamboldt, M. Z. (2000). Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma & Immunology*, 85(5), 416-421. doi:10.1016/S1081-1206(10)62557-4
- Bender, B., & Zhang, L. (2008). Negative affect, medication adherence, and asthma control in children. *J Allergy Clin Immunol*, 122(3), 490-495. doi:10.1016/j.jaci.2008.05.041
- Bisgaard, H., Le Roux, P., Bjamer, D., Dymek, A., Vermeulen, J. H., & Hultquist, C. (2006). Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest*, 130(6), 1733-1743. doi:10.1378/chest.130.6.1733
- Bland, J. M., Dumville, J. C., Ashby, R. L., Gabe, R., Stubbs, N., Adderley, U., . . . Cullum, N. A. (2015). Validation of the VEINES-QOL quality of life instrument in venous leg ulcers:

repeatability and validity study embedded in a randomised clinical trial. *Bmc Cardiovascular Disorders*, 15. doi:ARTN 85 10.1186/s12872-015-0080-7

- Bossley, C. J., Fleming, L., Gupta, A., Regamey, N., Frith, J., Oates, T., . . . Saglani, S. (2012). Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. *J Allergy Clin Immunol*, 129(4), 974-982 e913. doi:10.1016/j.jaci.2012.01.059
- Bousquet, J., Mantzouranis, E., Cruz, A. A., Ait-Khaled, N., Baena-Cagnani, C. E., Bleecker, E. R., . . . Zuberbier, T. (2010). Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol*, 126(5), 926-938. doi:10.1016/j.jaci.2010.07.019
- Bracken, M., Fleming, L., Hall, P., Van Stiphout, N., Bossley, C., Biggart, E., . . . Bush, A. (2009). The importance of nurse-led home visits in the assessment of children with problematic asthma. *Archives of Disease in Childhood*, 94(10), 780-784. doi:10.1136/adc.2008.152140
- Brandstetter, S., Finger, T., Fischer, W., Brandl, M., Bohmer, M., Pfeifer, M., & Apfelbacher, C. (2017). Differences in medication adherence are associated with beliefs about medicines in asthma and COPD. *Clinical and Translational Allergy*, 7. doi:ARTN 39 10.1186/s13601-017-0175-6
- British Thoracic Society; Scottish Intercollegiate Guidelines, N. (2019). *British guideline on the management of asthma : a national clinical guideline* (Revised edition. ed.).
- Broadbent, E., Petrie, K. J., Main, J., & Weinman, J. (2006). The Brief Illness Perception Questionnaire. *J Psychosom Res*, 60(6), 631-637. doi:10.1016/j.jpsychores.2005.10.020
- Broadbent, E., Schoones, J. W., Tiemensma, J., & Kaptein, A. A. (2018). A systematic review of patients' drawing of illness: Implications for research using the Common Sense Model. *Health Psychol Rev*, 1-139. doi:10.1080/17437199.2018.1558088
- Brooks, C. M., Richards, J. M., Kohler, C. L., Soong, S. J., Martin, B., Windsor, R. A., & Bailey, W. C. (1994). Assessing adherence to asthma medication and inhaler regimens: a psychometric analysis of adult self-report scales. *Med Care*, 32(3), 298-307.
- Bruzzese, J. M., Carcone, A. I., Lam, P., Ellis, D. A., & Naar-King, S. (2014). Adherence to Asthma Medication Regimens in Urban African American Adolescents: Application of Self-Determination Theory. *Health Psychology*, 33(5), 461-464. doi:10.1037/a0033510
- Buelo, A., McLean, S., Julious, S., Flores-Kim, J., Bush, A., Henderson, J., . . . Pinnock, H. (2018). At-risk children with asthma (ARC): a systematic review. *Thorax*, 73(9), 813. doi:10.1136/thoraxjnl-2017-210939
- Burgess, S. W., Sly, P. D., & Devadason, S. G. (2010). Providing Feedback on Adherence Increases Use of Preventive Medication by Asthmatic Children. *Journal of Asthma*, 47(2), 198-201. doi:10.3109/02770900903483840
- Burgess, S. W., Wilson, S. S., Cooper, D. M., Sly, P. D., & Devadason, S. G. (2006). In vitro evaluation of an asthma dosing device: the smart-inhaler. *Respir Med*, 100(5), 841-845. doi:10.1016/j.rmed.2005.09.004
- Bush, A. (2018). Management of asthma in children. *Minerva Pediatrica*, 70(5), 444-457. doi:10.23736/S0026-4946.18.05351-3
- Bush, A. (2019). Pathophysiological Mechanisms of Asthma. *Frontiers in Pediatrics*, 7, 68. doi:10.3389/fped.2019.00068
- Bush, A., & Fleming, L. (2016). Is asthma overdiagnosed? *Archives of Disease in Childhood*, 101(8), 688-689. doi:10.1136/archdischild-2015-309053

- Bush, A., Grigg, J., & Saglani, S. (2014). Managing wheeze in preschool children. *Bmj-British Medical Journal*, *348*. doi:ARTN g15  
10.1136/bmj.g15
- Bush, A., Hedlin, G., Carlsen, K. H., de Benedictis, F., Lodrup-Carlsen, K., & Wilson, N. (2008). Severe childhood asthma: a common international approach? *Lancet*, *372*(9643), 1019-1021. doi:Doi 10.1016/S0140-6736(08)61422-1
- Bush, A., & Pavord, I. (2011). Following Nero: fiddle while Rome burns, or is there a better way? *Thorax*, *66*(5), 367. doi:10.1136/thx.2011.160861
- Bush, A., & Saglani, S. (2010). Management of severe asthma in children. *Lancet*, *376*(9743), 814-825. doi:Doi 10.1016/S0140-6736(10)61054-9
- Bush, A., & Saglani, S. (2020). Medical algorithm: Diagnosis and treatment of preschool asthma. *Allergy*. doi:10.1111/all.14172
- Bush, A., & Zar, H. J. (2011). WHO universal definition of severe asthma. *Curr Opin Allergy Clin Immunol*, *11*(2), 115-121. doi:10.1097/ACI.0b013e32834487ae
- Byer, B., & Myers, L. B. (2000). Psychological correlates of adherence to medication in asthma. *Psychology, Health & Medicine*, *5*(4), 389-393. doi:10.1080/713690213
- Byrne, P. M., Jenkins, C., & Bateman, E. D. (2017). The paradoxes of asthma management: time for a new approach? *European Respiratory Journal*, *50*(3), 1701103. doi:10.1183/13993003.01103-2017
- Caffarelli, C., Garrubba, M., Greco, C., Mastroilli, C., & Dascola, C. P. (2016). Asthma and Food Allergy in Children: is There a Connection or interaction? *Frontiers in Pediatrics*, *4*. doi:ARTN 34 10.3389/fped.2016.00034
- Cajigal, S., Wells, K. E., Peterson, E. L., Ahmedani, B. K., Yang, J. J., Kumar, R., . . . Williams, L. K. (2017). Predictive Properties of the Asthma Control Test and Its Component Questions for Severe Asthma Exacerbations. *Journal of Allergy and Clinical Immunology: In Practice*, *5*(1), 121-127 e122. doi:10.1016/j.jaip.2016.06.025
- Calnan, M., Montaner, D., & Horne, R. (2005). How acceptable are innovative health-care technologies? A survey of public beliefs and attitudes in England and Wales. *Soc Sci Med*, *60*(9), 1937-1948. doi:10.1016/j.socscimed.2004.08.058
- Cane, J., O'Connor, D., & Michie, S. (2012). Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implementation Science*, *7*, 37. doi:10.1186/1748-5908-7-37
- Canino, G., Shrout, P., Vila, D., Ramirez, R., & Rand, C. (2016). Effectiveness of a multi-level asthma intervention in increasing controller medication use: a randomized control trial. *Journal of Asthma*, *53*(3), 301-310. doi:10.3109/02770903.2015.1057846
- Cashin, G. H., Small, S. P., & Solberg, S. M. (2008). The Lived Experience of Fathers Who Have Children With Asthma: A Phenomenological Study. *Journal of Pediatric Nursing*, *23*(5), 372-385. doi:<https://doi.org/10.1016/j.pedn.2007.08.001>
- Chan, A., Harrison, J., Black, P., Mitchell, E., & Foster, J. (2015). Using Electronic Monitoring Devices to Measure Inhaler Adherence: A Practical Guide for Clinicians. *Journal of Allergy and Clinical Immunology: In Practice*, *3*(3), 335-349 e335. doi:<http://dx.doi.org/10.1016/j.jaip.2015.01.024>
- Chan, A. H., Stewart, A. W., Harrison, J., Camargo, C. A., Jr., Black, P. N., & Mitchell, E. A. (2015). The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med*, *3*(3), 210-219. doi:10.1016/S2213-2600(15)00008-9
- Chapman, S., Dale, P., Svedsater, H., Stynes, G., Vyas, N., Price, D., & Horne, R. (2017). Modelling the effect of beliefs about asthma medication and treatment intrusiveness on adherence and preference for once-daily vs. twice-daily

medication. *Npj Primary Care Respiratory Medicine*, 27. doi:ARTN 61  
10.1038/s41533-017-0061-7

- Chapman, S. C., Horne, R., Chater, A., Hukins, D., & Smithson, W. H. (2014). Patients' perspectives on antiepileptic medication: relationships between beliefs about medicines and adherence among patients with epilepsy in UK primary care. *Epilepsy Behav*, 31, 312-320. doi:10.1016/j.yebeh.2013.10.016
- Chapman, S. C. E., Horne, R., Eade, R., Balestrini, S., Rush, J., & Sisodiya, S. M. (2015). Applying a perceptions and practicalities approach to understanding nonadherence to antiepileptic drugs. *Epilepsia*, 56(9), 1398-1407. doi:10.1111/epi.13097
- Chater, A. M., Parham, R., Riley, S., Hutchison, A. J., & Horne, R. (2014). Profiling patient attitudes to phosphate binding medication: A route to personalising treatment and adherence support. *Psychology & Health*, 29(12), 1407-1420. doi:10.1080/08870446.2014.942663
- Chatkin, J. M., Blanco, D. C., Scaglia, N., Wagner, M. B., & Fritscher, C. C. (2006). Impact of a low-cost and simple intervention in enhancing treatment adherence in a Brazilian asthma sample. *Journal of Asthma*, 43(4), 263-266. doi:10.1080/02770900600620459
- Chung, K. F., Wenzel, S. E., Brozek, J. L., Bush, A., Castro, M., Sterk, P. J., . . . Teague, W. G. (2014). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*, 43(2), 343-373. doi:10.1183/09031936.00202013
- Clark, E. M., Gould, V. C., Tobias, J. H., & Horne, R. (2016). Natural history, reasons for, and impact of low/non-adherence to medications for osteoporosis in a cohort of community-dwelling older women already established on medication: a 2-year follow-up study. *Osteoporosis International*, 27(2), 579-590. doi:10.1007/s00198-015-3271-2
- Clatworthy, J., Bowskill, R., Parham, R., Rank, T., Scott, J., & Horne, R. (2009). Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. *J Affect Disord*, 116(1-2), 51-55. doi:10.1016/j.jad.2008.11.004
- Clin-e-cal. (2018). Retrieved from <https://clin-e-cal.com/rafi-tone/>
- Cohen, J. L., Mann, D. M., Wisnivesky, J. P., Home, R., Leventhal, H., Musumeci-Szabo, T. J., & Halm, E. A. (2009). Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol*, 103(4), 325-331.
- British National Formulary (2019). British National Formulary (online). Retrieved from <http://www.medicinescomplete.com>
- Conn, K. M., Halterman, J. S., Fisher, S. G., Yoos, H. L., Chin, N. P., & Szilagyi, P. G. (2005). Parental beliefs about medications and medication adherence among urban children with asthma. *Ambul Pediatr*, 5(5), 306-310. doi:10.1367/A05-004R1.1
- Conn, K. M., Halterman, J. S., Lynch, K., & Cabana, M. D. (2007). The impact of parents' medication beliefs on asthma management. *Pediatrics*, 120(3), e521-526. doi:10.1542/peds.2006-3023
- Conn, V. S., & Ruppap, T. M. (2017). Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. *Prev Med*, 99, 269-276. doi:10.1016/j.ympmed.2017.03.008
- Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2013). Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud*, 50(5), 587-592. doi:10.1016/j.ijnurstu.2012.09.010
- Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M., & Medical Research Council, G. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*, 337, a1655. doi:10.1136/bmj.a1655

- Craig, R., & Mindell, J. (2010). *The Health Survey for England*. Retrieved from
- Crawshaw, J., Auyeung, V., Ashworth, L., Norton, S., & Weinman, J. (2017). Healthcare provider-led interventions to support medication adherence following ACS: a meta-analysis. *Open Heart*, 4(2), e000685. doi:10.1136/openhrt-2017-000685
- Davis, J., Trudo, F., Siddall, J., & Small, M. (2018). Burden of asthma among patients adherent to ICS/LABA: A real-world study. *Journal of Asthma*, 1-9.
- de Groot, E. P., Kreggemeijer, W. J., & Brand, P. L. P. (2015). Getting the basics right resolves most cases of uncontrolled and problematic asthma. *Acta Paediatr*, 104(9), 916-921. doi:10.1111/apa.13059
- De Simoni, A., Horne, R., Fleming, L., Bush, A., & Griffiths, C. (2017). What do adolescents with asthma really think about adherence to inhalers? Insights from a qualitative analysis of a UK online forum. *BMJ Open*, 7(6pe), e015245. doi:10.1136/bmjopen-2016-015245
- De Smet, B. D., Erickson, S. R., & Kirking, D. M. (2006). Self-Reported Adherence in Patients with Asthma. *Annals of Pharmacotherapy*, 40(3), 414-420. doi:10.1345/aph.1G475
- Deci, E. L., & Ryan, R. M. (1985). *Intrinsic motivation and self-determination in human behavior*. New York: Plenum.
- Del Giacco, S. R., Firinu, D., Bjermer, L., & Carlsen, K. H. (2015). Exercise and asthma: an overview. *European Clinical Respiratory Journal*, 2(1). doi:ARTN 27984 10.3402/ecrj.v2.27984
- Desager, K., Vermeulen, F., & Bodart, E. (2018). Adherence to asthma treatment in childhood and adolescence - a narrative literature review. *Acta Clin Belg*, 73(5), 348-355. doi:10.1080/17843286.2017.1409684
- DiMatteo, M. R., Haskard, K. B., & Williams, S. L. (2007). Health beliefs, disease severity, and patient adherence: a meta-analysis. *Med Care*, 45(6), 521-528. doi:10.1097/MLR.0b013e318032937e
- Dozier, A., Aligne, C. A., & Schlabach, M. B. (2006). What Is Asthma Control? Discrepancies Between Parents' Perceptions and Official Definitions. *Journal of School Health*, 76(6), 215-218. doi:10.1111/j.1746-1561.2006.00099.x
- Drabble, S. J., O'Cathain, A., Arden, M. A., Hutchings, M., Beever, D., & Wildman, M. (2019). When Is Forgetting Not Forgetting? A Discursive Analysis of Differences in Forgetting Talk Between Adults With Cystic Fibrosis With Different Levels of Adherence to Nebulizer Treatments. *Qual Health Res*, 1049732319856580. doi:10.1177/1049732319856580
- Durand, H., Hayes, P., Harhen, B., Conneely, A., Finn, D. P., Casey, M., . . . Molloy, G. J. (2018). Medication adherence for resistant hypertension: Assessing theoretical predictors of adherence using direct and indirect adherence measures. *British Journal of Health Psychology*, 23(4), 949-966. doi:10.1111/bjhp.12332
- Durham, S. (1998). ABC of allergies. Summer hay fever. *BMJ*, 316(7134), 843-845.
- E.D. Bateman, S.S. Hurd, P.J. Barnes, J. Bousquet, J.M. Drazen, J.M. FitzGerald, . . . Zar., H. J. (2018). Global strategy for asthma management and prevention: GINA executive summary. *European Respiratory Journal*, 51. doi:10.1183/13993003.51387-2007
- Effective Practice and Organisation of Care (EPOC). (2015). EPOC Resources for review authors. *Oslo: Norwegian Knowledge Centre for the Health Services*. Retrieved from <http://epoc.cochrane.org/epoc-specific-resources-review-authors>
- Elliott, R. A., Barber, N., & Horne, R. (2005). Cost-effectiveness of adherence-enhancing interventions: a quality assessment of the evidence. *Annals of Pharmacotherapy*, 39(3), 508-515. doi:10.1345/aph.1E398
- Emilsson, M., Berndtsson, I., Lotvall, J., Millqvist, E., Lundgren, J., Johansson, A., & Brink, E. (2011). The influence of personality traits and beliefs about medicines on

- adherence to asthma treatment. *Prim Care Respir J*, 20(2), 141-147.  
doi:10.4104/pcrj.2011.00005
- Eney R.D, & E.O, G. (1976). Compliance of Chronic Asthmatics With Oral Administration of Theophylline as Measured by Serum and Salivary Levels. *Paediatrics*, 57(4), 513-517.
- Engelkes, M., Janssens, H. M., de Jongste, J. C., Sturkenboom, M. C., & Verhamme, K. M. (2015). Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J*, 45(2), 396-407. doi:10.1183/09031936.00075614
- National Insititue of Health and Care Excellence (2017a). Asthma: diagnosis and monitoring. In *Asthma: diagnosis and monitoring of asthma in adults, children and young people*. London.
- National Insititue of Health and Care Excellence (2017b). *Smart inhaler for asthma*. Retrieved from nice.org.uk/guidance/mib90
- Fernandes, P. T., Salgado, P. C., Noronha, A. L., Barbosa, F. D., Souza, E. A., Sander, J. W., & Li, L. M. (2007). Prejudice towards chronic diseases: comparison among epilepsy, AIDS and diabetes. *Seizure*, 16(4), 320-323. doi:10.1016/j.seizure.2007.01.008
- Fishbein, M., & Ajzen, I. (1975). *Belief, attitude, intention and behavior : an introduction to theory and research*. Reading, Mass. ; London: Addison-Wesley.
- FitzGerald, J. M. (2011). Targeting lung attacks. *Thorax*, 66(5), 365. doi:10.1136/thx.2010.156760
- Fleming, L., Tsartsali, L., Wilson, N., Regamey, N., & Bush, A. (2012). Sputum inflammatory phenotypes are not stable in children with asthma. *Thorax*, 67(8), 675. doi:10.1136/thoraxjnl-2011-201064
- Fleming, M., Fitton, C. A., Steiner, M. F. C., McLay, J. S., Clark, D., King, A., . . . Pell, J. P. (2019). Educational and health outcomes of children treated for asthma: Scotland-wide record linkage study of 683 716 children. *Eur Respir J*, 54(3). doi:10.1183/13993003.02309-2018
- Fogg, B. J. (2009). *A behavior model for persuasive design*. Paper presented at the 4th international Conference on Persuasive Technology Claremont, California.
- Folkman, S. (1984). Personal Control and Stress and Coping Processes - a Theoretical-Analysis. *J Pers Soc Psychol*, 46(4), 839-852. doi:Doi 10.1037/0022-3514.46.4.839
- Foot, H., La Caze, A., Gujral, G., & Cottrell, N. (2016). The necessity-concerns framework predicts adherence to medication in multiple illness conditions: A meta-analysis. *Patient Education & Counseling*, 99(5), 706-717. doi:10.1016/j.pec.2015.11.004
- British Lung Foundation (2019). Asthma Statistics. Retrieved from <https://statistics.blf.org.uk/asthma>
- Francis, J. J., O'Connor, D., & Curran, J. (2012). Theories of behaviour change synthesised into a set of theoretical groupings: introducing a thematic series on the theoretical domains framework. *Implementation Science*, 7. doi:Artn 35 10.1186/1748-5908-7-35
- French, D. (2010). *Health psychology* (2nd ed. ed.). Oxford: Wiley-Blackwell.
- Gamble, J., Stevenson, M., & Heaney, L. G. (2011). A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med*, 105(9), 1308-1315. doi:10.1016/j.rmed.2011.03.019
- Garcia-Marcos, P. W., Brand, P. L. P., Kaptein, A. A., & Klok, T. (2016). Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma? *Journal of Asthma*, 53(10), 1085-1089. doi:10.1080/02770903.2016.1180699
- Gardner, B. (2015). A review and analysis of the use of 'habit' in understanding, predicting and influencing health-related behaviour. *Health Psychol Rev*, 9(3), 277-295. doi:10.1080/17437199.2013.876238

- Garrett, J., Fenwick, J. M., Taylor, G., Mitchell, E., Stewart, J., & Rea, H. (1994). Prospective controlled evaluation of the effect of a community based asthma education centre in a multiracial working class neighbourhood. *Thorax*, *49*(10), 976-983.
- Gautier, C., & Charpin, D. (2017). Environmental triggers and avoidance in the management of asthma. *Journal of Asthma and Allergy*, *10*, 47-56. doi:10.2147/Jaa.S121276
- George, D., Mallery, P., & George, D. S. f. W. s. b. s. (2012). *IBM SPSS statistics 19 step by step : a simple guide and reference* (12th ed. / Darren George, Paul Mallery. ed.). Boston, Mass. ; London: Pearson.
- George K.E, Ryan D.M, Keevil B, Niven R, & SJ., F. (2017). A pilot study to investigate the use of serum inhaled corticosteroid concentration as a potential marker of treatment adherence in severe asthma. *Journal of Clinical Immunology*, *139*(3), 1037-1039. doi: 10.1016/j.jaci.2016.08.037
- GINA. (2019). A Pocket Guide for Asthma Management and Prevention. Retrieved from <https://ginasthma.org/wp-content/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf>
- GINA., A. (2012). *Guide for asthma management and Prevention Update*. <http://www.ginasthma.org2012>.
- Giraud, V., & Allaert, F. A. (2009). Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): the SYSTER survey. *Eur Rev Med Pharmacol Sci*, *13*(5), 323-330.
- Given, C. W., Given, B. A., Gallin, R. S., & Condon, J. W. (1983). Development of Scales to Measure Beliefs of Diabetic-Patients. *Research in Nursing & Health*, *6*(3), 127-141. doi:DOI 10.1002/nur.4770060306
- Guendelman, S., Meade, K., Benson, M., Chen, Y. Q., & Samuels, S. (2002). Improving asthma outcomes and self-management behaviors of inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary. *Arch Pediatr Adolesc Med*, *156*(2), 114-120.
- Guenette, L., Breton, M. C., Gregoire, J. P., Jobin, M. S., Bolduc, Y., Boulet, L. P., . . . Moisan, J. (2015). Effectiveness of an asthma integrated care program on asthma control and adherence to inhaled corticosteroids. *J Asthma*, *52*(6), 638-645. doi:10.3109/02770903.2014.999084
- Gupta, A., Steinfeld, J., Price, R., Azmi, J., Bradford, E., & Yancey, S. (2018). Mepolizumab for severe eosinophilic asthma: a comparison of efficacy in children, adolescents, and adults. *European Respiratory Journal*, *52*(suppl 62), PA5447. doi:10.1183/13993003.congress-2018.PA5447
- Gupta, R., Sheikh, A., Strachan, D. P., & Anderson, H. R. (2004). Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy*, *34*(4), 520-526. doi:10.1111/j.1365-2222.2004.1935.x
- Gustafson, D., Wise, M., Bhattacharya, A., Pulvermacher, A., Shanovich, K., Phillips, B., . . . Kim, J. S. (2012). The Effects of Combining Web-Based eHealth With Telephone Nurse Case Management for Pediatric Asthma Control: A Randomized Controlled Trial. *Journal of Medical Internet Research*, *14*(4), 41-59. doi:10.2196/jmir.1964
- Hagger, M. S., Koch, S., Chatzisarantis, N. L. D., & Orbell, S. (2017). The common sense model of self-regulation: Meta-analysis and test of a process model. *Psychol Bull*, *143*(11), 1117-1154. doi:10.1037/bul0000118
- Halm, E. A., Mora, P., & Leventhal, H. (2006). No symptoms, no asthma: the acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. *Chest*, *129*(3), 573-580. doi:10.1378/chest.129.3.573
- Hamelmann, E. (2018). Long-acting muscarinic antagonists for the treatment of asthma in children-a new kid in town. *Allergo J Int*, *27*(7), 220-227. doi:10.1007/s40629-018-0066-y



- Hamilton-West, K. (2011). *Psychobiological processes in health and illness*. Los Angeles: SAGE.
- Hand, C. H., & Bradley, C. (1996). Health beliefs of adults with asthma: Toward an understanding of the difference between symptomatic and preventive use of inhaler treatment. *Journal of Asthma, 33*(5), 331-338.
- Harris, K., Mosler, G., Williams, S. A., Whitehouse, A., Raine, R., & Grigg, J. (2017). Asthma control in London secondary school children. *J Asthma, 54*(10), 1033-1040. doi:10.1080/02770903.2017.1299757
- Hazell, B., & Robson, R. (2015). *Pharmaceutical waste reduction in the NHS* (Version 1). Retrieved from <https://www.england.nhs.uk/wp-content/uploads/2015/06/pharmaceutical-waste-reduction.pdf>
- Heaney, L. G., Busby, J., Bradding, P., Chaudhuri, R., Mansur, A. H., Niven, R., . . . Medical Research Council, U. K. R. A. S. P. (2018). Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Non-Adherence in Severe Asthma. *American Journal of Respiratory & Critical Care Medicine*. doi:10.1164/rccm.201806-1182OC
- Heaney, L. G., & Horne, R. (2012). Non-adherence in difficult asthma: time to take it seriously. *Thorax, 67*(3), 268-270. doi:10.1136/thoraxjnl-2011-200257
- Hederos, C. A., Janson, S., & Hedlin, G. (2005). Group discussions with parents have long-term positive effects on the management of asthma with good cost-benefit. *Acta Paediatr, 94*(5), 602-608. doi:10.1111/j.1651-2227.2005.tb01946.x
- Hedlin, G., Bush, A., Lodrup Carlsen, K., Wennergren, G., De Benedictis, F. M., Melen, E., . . . Problematic Severe Asthma in Childhood Initiative, g. (2010). Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. *Eur Respir J, 36*(1), 196-201. doi:10.1183/09031936.00104809
- Heller, M. K., Chapman, S. C., & Horne, R. (2017). No blank slates: Pre-existing schemas about pharmaceuticals predict memory for side effects. *Psychology & Health, 32*(4), 402-421. doi:10.1080/08870446.2016.1273355
- Heller, M. K., Chapman, S. C. E., & Horne, R. (2015). Beliefs about medication predict the misattribution of a common symptom as a medication side effect — Evidence from an analogue online study. *J Psychosom Res, 79*(6), 519-529. doi:<https://doi.org/10.1016/j.jpsychores.2015.10.003>
- Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., . . . Cochrane Statistical Methods, G. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343*, d5928. doi:10.1136/bmj.d5928
- Hilliard, M. E., Eakin, M. N., Borrelli, B., Green, A., & Riekert, K. A. (2015). Medication beliefs mediate between depressive symptoms and medication adherence in cystic fibrosis. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association, 34*(5), 496-504. doi:10.1037/hea0000136
- Hoch, H., Kempe, A., Brinton, J., & Szeffler, S. (2018). Feasibility of medication monitoring sensors in high risk asthmatic children. *J Asthma, 1-3*. doi:10.1080/02770903.2018.1446979
- Holgate, S. T. (2008). Pathogenesis of asthma. *Clinical and Experimental Allergy, 38*(6), 872-897. doi:10.1111/j.1365-2222.2008.02971.x
- Holley, S., Morris, R., Knibb, R., Latter, S., Liossi, C., Mitchell, F., & Roberts, G. (2017). Barriers and facilitators to asthma self-management in adolescents: A systematic review of qualitative and quantitative studies. *Pediatr Pulmonol, 52*(4), 430-442. doi:10.1002/ppul.23556
- Holmes, E. A. F., Hughes, D. A., & Morrison, V. L. (2014). Predicting Adherence to Medications Using Health Psychology Theories: A Systematic Review of 20 Years of Empirical Research. *Value in Health, 17*(8), 863-876. doi:<https://doi.org/10.1016/j.jval.2014.08.2671>

- Holmes, M. S., D'Arcy, S., Costello, R. W., & Reilly, R. B. (2014). Acoustic Analysis of Inhaler Sounds From Community-Dwelling Asthmatic Patients for Automatic Assessment of Adherence. *IEEE J Transl Eng Health Med*, 2, 2700210. doi:10.1109/JTEHM.2014.2310480
- Hoo, Z. H., Gardner, B., Arden, M. A., Waterhouse, S., Walters, S. J., Campbell, M. J., . . . Wildman, M. J. (2019). Role of habit in treatment adherence among adults with cystic fibrosis. *Thorax*, 74(2), 197-199. doi:10.1136/thoraxjnl-2017-211453
- Horne, R. (1997). Representations of medication and treatment: advances in theory and measurement. In K. J. Petrie & J. Weinman (Eds.), *Perceptions of Health and Illness: Current Research and Applications* (pp. 155-187). London: Harwood Academic.
- Horne, R. (2001). Compliance, adherence and concordance. In G. Harding & K. Taylor (Eds.), *Pharmacy practice* London: Taylor & Francis.
- Horne, R. (2003). Treatment perceptions and self-regulation. In *The self-regulation of health and illness behaviour* (pp. 138-153). London: Routledge
- Horne, R. (2005). *Concordance, adherence and compliance in medicine taking : report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO)*. [London]: NCCSDO.
- Horne, R. (2006). Compliance, adherence, and concordance: implications for asthma treatment. *Chest*, 130(1 Suppl), 65S-72S. doi:10.1378/chest.130.1\_suppl.65S
- Horne, R. (2012). Improving adherence with asthma therapies. In R. Polosa, G. Papale, & S. T. Holgate (Eds.), *Advances in Asthma Management* (pp. 132-142). London: Future Medicine.
- Horne, R. (2017). Decisions about medicines: scientific evidence in context. *The Academy of Medical Sciences*. Retrieved from <https://acmedsci.ac.uk/file-download/80849939>
- Horne, R., Chapman, S. C. E., Parham, R., Freemantle, N., Forbes, A., & Cooper, V. (2013). Understanding Patients' Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework. *PLoS One*, 8(12). doi:ARTN e80633 10.1371/journal.pone.0080633
- Horne, R., Cooper, V., Wileman, V., & Chan, A. (2019). Supporting adherence to medicines for long-term conditions: A perceptions and practicalities approach based on an extended common-sense model. *European Psychologist*, 24(1), 82-96. doi:10.1027/1016-9040/a000353
- Horne, R., & Weinman, J. (1998). Predicting Treatment Adherence: An Overview of Theoretical Models. In L. Myers & K. Midence (Eds.), *Adherence to treatment in medical conditions*. Australia ; United Kingdom: Harwood Academic.
- Horne, R., & Weinman, J. (1999). Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res*, 47(6), 555-567. doi:Doi 10.1016/S0022-3999(99)00057-4
- Horne, R., & Weinman, J. (2002). Self-regulation and self-management in asthma: Exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychology & Health*, 17(1), 17-32. doi:10.1080/08870440290001502
- Horne, R., Weinman, J., & Hankins, M. (1999). The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & Health*, 14(1), 1-24. doi:Doi 10.1080/08870449908407311
- Horspool, M. J., Julious, S. A., Boote, J., Bradburn, M. J., Cooper, C. L., Davis, S., . . . VanStaa, T. (2013). Preventing and lessening exacerbations of asthma in school-age children associated with a new term (PLEASANT): study protocol for a cluster randomised control trial. *Trials [Electronic Resource]*, 14, 297.

- Howard, S., Lang, A., Sharples, S., & Shaw, D. (2017). See I told you I was taking it! - Attitudes of adolescents with asthma towards a device monitoring their inhaler use: Implications for future design. *Applied Ergonomics*, *58*, 224-237. doi:10.1016/j.apergo.2016.06.018
- Huvanandana, J., Reddel, H., Nguyen, C., Foster, J., Frey, U., & Thamrin, C. (2018). Clustering of adherence variability metrics and clinical outcomes in asthma. *European Respiratory Journal*, *52*. doi:10.1183/13993003.congress-2018.PA5030
- Hyrkas-Palmu, H., Ikaheimo, T. M., Laatikainen, T., Jousilahti, P., Jaakkola, M. S., & Jaakkola, J. J. K. (2018). Cold weather increases respiratory symptoms and functional disability especially among patients with asthma and allergic rhinitis. *Scientific Reports*, *8*. doi:ARTN 10131 10.1038/s41598-018-28466-y
- Ivanova, J. I., Birnbaum, H. G., Hsieh, M., Yu, A. P., Seal, B., van der Molen, T., . . . Colice, G. L. (2008). Adherence to inhaled corticosteroid use and local adverse events in persistent asthma. *Am J Manag Care*, *14*(12), 801-809.
- Jackson, C., Eliasson, L., Barber, N., & Weinman, J. (2014). Applying COM-B to medication adherence: a suggested framework for research and interventions. *European Health Psychologist*, *16*(1), 7-17.
- James, A. (1993). *Childhood identities : self and social relationships in the experience of the child*. Edinburgh: Edinburgh University Press.
- Jamison, J., Sutton, S., Mant, J., & De Simoni, A. (2018). Online stroke forum as source of data for qualitative research: insights from a comparison with patients' interviews. *BMJ Open*, *8*(3), e020133. doi:10.1136/bmjopen-2017-020133
- Jan, R. L., Wang, J. Y., Huang, M. C., Tseng, S. M., Su, H. J., & Liu, L. F. (2007). An internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. *Telemedicine Journal and E-Health*, *13*(3), 257-268. doi:<http://dx.doi.org/10.1089/tmj.2006.0053>
- Janezic, A., Locatelli, I., & Kos, M. (2017). Criterion validity of 8-item Morisky Medication Adherence Scale in patients with asthma. *PLoS One*, *12*(11), e0187835. doi:10.1371/journal.pone.0187835
- Jochmann, A., Artusio, L., Jamalzadeh, A., Nagakumar, P., Delgado-Eckert, E., Saglani, S., . . . Fleming, L. J. (2017). Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children. *Eur Respir J*, *50*(6). doi:10.1183/13993003.00910-2017
- Jochmann, A., Nagakumar, P., Hall, P., Jamalzadeh, A., Artusio, L., Saglani, S., . . . Fleming, L. (2015). Improvement in asthma control and airway inflammation during a period of electronic monitoring. *European Respiratory Journal*, *46*, no pagination. doi:<http://dx.doi.org/10.1183/13993003.congress2015.OA4775>
- Johnson, K. B., Patterson, B. L., Ho, Y. X., Chen, Q., Nian, H., Davison, C. L., . . . Mulvaney, S. A. (2016). The feasibility of text reminders to improve medication adherence in adolescents with asthma. *J Am Med Inform Assoc*, *23*(3), 449-455. doi:10.1093/jamia/ocv158
- Johnson, M. (1995). Pharmacology of long-acting beta-agonists. *Ann Allergy Asthma Immunol*, *75*(2), 177-179.
- Jones, A. S. K., Coetzee, B., Kagee, A., Fernandez, J., Cleveland, E., Thomas, M., & Petrie, K. J. (2018). The Use of a Brief, Active Visualisation Intervention to Improve Adherence to Antiretroviral Therapy in Non-adherent Patients in South Africa. *AIDS Behav*. doi:10.1007/s10461-018-2292-1
- Jones, A. S. K., Fernandez, J., Grey, A., & Petrie, K. J. (2017). The Impact of 3-D Models versus Animations on Perceptions of Osteoporosis and Treatment Motivation: A Randomised Trial. *Annals of Behavioral Medicine*, *51*(6), 899-911. doi:10.1007/s12160-017-9913-1

- Joost, R., Dorje, F., Schwitulla, J., Eckardt, K. U., & Hugo, C. (2014). Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study. *Nephrol Dial Transplant*, *29*(8), 1597-1607. doi:10.1093/ndt/gfu207
- Jorup, C., Lythgoe, D., & Bisgaard, H. (2018). Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. *Eur Respir J*, *51*(1). doi:10.1183/13993003.01688-2017
- Julious, S. A., Horspool, M. J., Davis, S., Bradburn, M., Norman, P., Shephard, N., . . . Bortolami, O. (2016). PLEASANT: Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term - a cluster randomised controlled trial and economic evaluation. *Health Technol Assess*, *20*(93), 1-154. doi:10.3310/hta20930
- Kaplan, A., & Price, D. (2020). Treatment Adherence in Adolescents with Asthma. *Journal of Asthma and Allergy*, *13*, 39-49. doi:10.2147/JAA.S233268
- Kaptein, A. A., Hughes, B. M., Scharloo, M., Fischer, M. J., Snoei, L., Weinman, J., & Rabe, K. F. (2008). Illness perceptions about asthma are determinants of outcome. *Journal of Asthma*, *45*(6), 459-464. doi:10.1080/02770900802040043
- Katz, I. T., Ryu, A. E., Onuegbu, A. G., Psaros, C., Weiser, S. D., Bangsberg, D. R., & Tsai, A. C. (2013). Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. *J Int AIDS Soc*, *16*(3 Suppl 2), 18640. doi:10.7448/IAS.16.3.18640
- Katzer, C. B., Wileman, V., Chan, A. H. Y., Taylor, S. J. C., & Horne, R. (2018). Reframing asthma and inhaled corticosteroids (ICS) to modify treatment beliefs: an online randomised controlled trial. *European Respiratory Journal*, *52*(suppl 62), OA1644. doi:10.1183/13993003.congress-2018.OA1644
- Kew, K. M., & Dahri, K. (2016). Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev*(1), CD011721. doi:10.1002/14651858.CD011721.pub2
- Klok, T., Brand, P. L., Bomhof-Roordink, H., Duiverman, E. J., & Kaptein, A. A. (2011). Parental illness perceptions and medication perceptions in childhood asthma, a focus group study. *Acta Paediatr*, *100*(2), 248-252. doi:10.1111/j.1651-2227.2010.02024.x
- Klok, T., Kaptein, A., & Brand, P. (2013). Improving adherence in paediatric respiratory disease. *Breathe*, *9*(4), 268-277.
- Klok, T., Kaptein, A. A., & Brand, P. L. P. (2015). Non-adherence in children with asthma reviewed: The need for improvement of asthma care and medical education. *Pediatr Allergy Immunol*, *26*(3), 197-205. doi:10.1111/pai.12362
- Klok, T., Kaptein, A. A., Duiverman, E. J., & Brand, P. L. (2012). High inhaled corticosteroids adherence in childhood asthma: the role of medication beliefs. *Eur Respir J*, *40*(5), 1149-1155. doi:10.1183/09031936.00191511
- Klok, T., Kaptein, A. A., Duiverman, E. J., & Brand, P. L. (2015). Long-term adherence to inhaled corticosteroids in children with asthma: Observational study. *Respir Med*, *109*(9), 1114-1119. doi:10.1016/j.rmed.2015.07.016
- Konstantinou, G. N. (2012). Pragmatic trials: how to adjust for the 'Hawthorne effect'? *Thorax*, *67*(6), 562; author reply 562. doi:10.1136/thoraxjnl-2011-200657
- Koster, E. S., Philbert, D., de Vries, T. W., van Dijk, L., & Bouvy, M. L. (2015). "I just forget to take it": asthma self-management needs and preferences in adolescents. *J Asthma*, *52*(8), 831-837. doi:10.3109/02770903.2015.1020388

- Koster, E. S., Raaijmakers, J. A., Vijverberg, S. J., & Maitland-van der Zee, A. H. (2011). Inhaled corticosteroid adherence in paediatric patients: the PACMAN cohort study. *Pharmacoepidemiol Drug Saf*, 20(10), 1064-1072. doi:10.1002/pds.2228
- Laba, T. L., Jan, S., Zwar, N. A., Roughead, E., Marks, G. B., Flynn, A. W., . . . Reddel, H. K. (2019). Cost-Related Underuse of Medicines for Asthma-Opportunities for Improving Adherence. *J Allergy Clin Immunol Pract*, 7(7), 2298-2306 e2212. doi:10.1016/j.jaip.2019.03.024
- Lakhanpaul, M., Bird, D., Culley, L., Hudson, N., Robertson, N., Johal, N., . . . Johnson, M. (2014). *The use of a collaborative structured methodology for the development of a multifaceted intervention programme for the management of asthma (the MIA project), tailored to the needs of children and families of South Asian origin: a community-based, participatory study*. Retrieved from Southampton (UK): <https://www.ncbi.nlm.nih.gov/pubmed/25642522>
- Lally, P., Van Jaarsveld, C. H. M., Potts, H. W. W., & Wardle, J. (2010). How are habits formed: Modelling habit formation in the real world. *European Journal of Social Psychology*, 40(6), 998-1009. doi:10.1002/ejsp.674
- Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer Pub. Co.
- Lee, J., Tay, T. R., Radhakrishna, N., Hore-Lacy, F., Mackay, A., Hoy, R., . . . Hew, M. (2018). Nonadherence in the era of severe asthma biologics and thermoplasty. *Eur Respir J*, 51(4). doi:10.1183/13993003.01836-2017
- Lee, S. J., Pincus, K. J., & Williams, A. A. (2016). Behavioral influences on prescription inhaler acquisition for persistent asthma in a patient-centered medical home. *Research in Social & Administrative Pharmacy*, 12(5), 789-793. doi:10.1016/j.sapharm.2015.11.007
- Lemanske, R. F., & Busse, W. W. (2006). Asthma: Factors underlying inception, exacerbation, and disease progression. *Journal of Allergy and Clinical Immunology*, 117(2), S456-S461. doi:10.1016/j.jaci.2005.07.006
- Lenney, W., Bush, A., Fitzgerald, D. A., Fletcher, M., Ostrem, A., Pedersen, S., . . . Zar, H. J. (2018). Improving the global diagnosis and management of asthma in children. *Thorax*, 73(7), 662. doi:10.1136/thoraxjnl-2018-211626
- Leventhal, H., Diefenbach, M., & Leventhal, E. A. (1992). Illness Cognition - Using Common-Sense to Understand Treatment Adherence and Affect Cognition Interactions. *Cognitive Therapy and Research*, 16(2), 143-163. doi:Doi 10.1007/Bf01173486
- Leventhal, H., Nerenz, D. R., & Steele, J. (1984). Illness representations and coping with health threats. In A. Baum, S. E. Taylor, & J. E. Singer (Eds.), *Handbook of Psychology and Health Volume IV: social psychological aspects of health* (Vol. IV, pp. 219-252). Hillsdale: Erlbaum.
- Lisy, K., & Porritt, K. (2016). Narrative Synthesis: Considerations and challenges. 14(4), 201. doi:10.1097/01.XEB.0000511348.97198.8c
- Lombardi, C., Savi, E., Ridolo, E., Passalacqua, G., & Canonica, G. W. (2017). Is allergic sensitization relevant in severe asthma? Which allergens may be culprits? *World Allergy Organization Journal*, 10. doi:ARTN 2 10.1186/s40413-016-0138-8
- Lotsch, F., Auer-Hackenberg, L., Groger, M., Rehman, K., Morrison, V., Holmes, E., . . . Ramharter, M. (2015). Adherence of patients to long-term medication: a cross-sectional study of antihypertensive regimens in Austria. *Wien Klin Wochenschr*, 127(9-10), 379-384. doi:10.1007/s00508-015-0782-y
- Luskin, A. T., Chipps, B. E., Rasouliyan, L., Miller, D. P., Haselkorn, T., & Dorenbaum, A. (2014). Impact of Asthma Exacerbations and Asthma Triggers on Asthma-related

- Quality of Life in Patients with Severe or Difficult-to-Treat Asthma. *Journal of Allergy and Clinical Immunology-in Practice*, 2(5), 544-+. doi:10.1016/j.jaip.2014.02.011
- Luyster, F. S., Dunbar-Jacob, J., Aloia, M. S., Martire, L. M., Buysse, D. J., & Strollo, P. J. (2016). Patient and Partner Experiences With Obstructive Sleep Apnea and CPAP Treatment: A Qualitative Analysis. *Behav Sleep Med*, 14(1), 67-84. doi:10.1080/15402002.2014.946597
- Lycett, H. (2017). *Behavioural science foundations for effective digital interventions: a systematic review*. Paper presented at the European Society for Patient Adherence, Compliance, and Persistence ESPACOMP, Budapest. [http://www.espacomp.eu/pdf/171116\\_ESPACOMP\\_program.pdf](http://www.espacomp.eu/pdf/171116_ESPACOMP_program.pdf)
- Maddux, J. E. (1997). Habit, health, and happiness. *Journal of Sport & Exercise Psychology*, 19(4), 331-346. doi:DOI 10.1123/jsep.19.4.331
- Mahkecha, S., Pearce, C. J., Chan, A. H., & Fleming, L. (In press). Assessment of novel electronic adherence monitoring devices in children with asthma. *BMJ Open*.
- Masoli, M., Fabian, D., Holt, S., Beasley, R., & Global Initiative for Asthma, P. (2004). The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*, 59(5), 469-478. doi:10.1111/j.1398-9995.2004.00526.x
- McBride, C. M., Emmons, K. M., & Lipkus, I. M. (2003). Understanding the potential of teachable moments: The case of smoking cessation. *Health Education Research*, 18(2), 156-170.
- McCullough, A. R., Ryan, C., O'Neill, B., Bradley, J. M., Elborn, J. S., & Hughes, C. M. (2015). Defining the content and delivery of an intervention to Change Adherence to treatment in Bronchiectasis (CAN-BE): a qualitative approach incorporating the Theoretical Domains Framework, behavioural change techniques and stakeholder expert panels. *BMC Health Services Research*, 15(1), 342. doi:10.1186/s12913-015-1004-z
- McNally, K. A., Rohan, J., Schluchter, M., Riekert, K. A., Vavrek, P., Schmidt, A., . . . Drotar, D. (2009). Adherence to combined montelukast and fluticasone treatment in economically disadvantaged african american youth with asthma. *Journal of Asthma*, 46(9), 921-927.
- McQuaid, E. L., Everhart, R. S., Seifer, R., Kopel, S. J., Mitchell, D. K., Klein, R. B., . . . Canino, G. (2012). Medication adherence among Latino and non-Latino white children with asthma. *Pediatrics*, 129(6), e1404-1410. doi:10.1542/peds.2011-1391
- McQuaid, E. L., Kopel, S. J., Klein, R. B., & Fritz, G. K. (2003). Medication Adherence in Pediatric Asthma: Reasoning, Responsibility, and Behavior. *Journal of Pediatric Psychology*, 28(5), 323-333. doi:10.1093/jpepsy/jsg022
- Menard, S., Jbilou, J., & Lauzier, S. (2018). Family caregivers' reported nonadherence to the controller medication of asthma in children in Casablanca (Morocco): Extent and associated factors. *J Asthma*, 1-11. doi:10.1080/02770903.2017.1414235
- Menckeberg, T. T., Bouvy, M. L., Bracke, M., Kaptein, A. A., Leufkens, H. G., Raaijmakers, J. A., & Horne, R. (2008). Beliefs about medicines predict refill adherence to inhaled corticosteroids. *J Psychosom Res*, 64(1), 47-54. doi:10.1016/j.jpsychores.2007.07.016
- Merchant, R., R, I., R, Q., Email Merchant, R., dignityhealth, M., & org. (2016). Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. *Journal of Allergy and Clinical Immunology: In Practice*, 4(3), 455-463. doi:<http://dx.doi.org/10.1016/j.jaip.2015.11.022>
- Mes, M. A., Chan, A. H. Y., Wileman, V., Katzer, C. B., Goodbourn, M., Towndrow, S., . . . Horne, R. (2019). Patient involvement in questionnaire design: tackling response error and burden. *J Pharm Policy Pract*, 12, 17. doi:10.1186/s40545-019-0175-0

- Mes, M. A., Katzer, C. B., Chan, A. H. Y., Wileman, V., Taylor, S. J. C., & Horne, R. (2018). Pharmacists and medication adherence in asthma: a systematic review and meta-analysis. *Eur Respir J*, *52*(2). doi:10.1183/13993003.00485-2018
- Michie, S., Johnston, M., Abraham, C., Lawton, R., Parker, D., Walker, A., & Grp, P. T. (2005). Making psychological theory useful for implementing evidence based practice: a consensus approach. *Quality & Safety in Health Care*, *14*(1), 26-33. doi:10.1136/qshc.2004.011155
- Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., . . . Wood, C. E. (2013). The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of Behavioral Medicine*, *46*(1), 81-95. doi:10.1007/s12160-013-9486-6
- Michie, S., van Stralen, M. M., & West, R. (2011). The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science*, *6*. doi:Artn 42 10.1186/1748-5908-6-42
- Moore, M., & Meltzer, L. J. (2008). The sleepy adolescent: causes and consequences of sleepiness in teens. *Paediatr Respir Rev*, *9*(2), 114-120; quiz 120-111. doi:10.1016/j.prrv.2008.01.001
- Morisky, D. E., Ang, A., Krousel-Wood, M., & Ward, H. J. (2008). Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)*, *10*(5), 348-354.
- Morisky, D. E., Green, L. W., & Levine, D. M. (1986). Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*, *24*(1), 67-74.
- Morisky, D. E., Kominski, G. F., Afifi, A. A., & Kotlerman, J. B. (2009). The Effects of a Disease Management Program on Self-Reported Health Behaviors and Health Outcomes: Evidence From the "Florida: A Healthy State (FAHS)" Medicaid Program. *Health Education & Behavior*, *36*(3), 505-517. doi:10.1177/1090198107311279
- Morton, R. W., Elphick, H. E., Rigby, A. S., Daw, W. J., King, D. A., Smith, L. J., & Everard, M. L. (2017). STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. *Thorax*, *72*(4), 347-354. doi:10.1136/thoraxjnl-2015-208171
- Morton, R. W., Everard, M. L., & Elphick, H. E. (2014). Adherence in childhood asthma: the elephant in the room. *Archives of Disease in Childhood*, *99*(10), 949-953.
- Mosnaim, G., Li, H., Martin, M., Richardson, D., Belice, P. J., Avery, E., . . . Powell, L. (2013). The Impact of Peer Support and mp3 Messaging on Adherence to Inhaled Corticosteroids in Minority Adolescents with Asthma: A Randomized, Controlled Trial. *Journal of Allergy and Clinical Immunology: In Practice*, *1*(5), 485-493. doi:<http://dx.doi.org/10.1016/j.jaip.2013.06.010>
- Moss-Morris, R., Weinman, J., Petrie, K. J., Horne, R., Cameron, L. D., & Buick, D. (2002). The revised Illness Perception Questionnaire (IPQ-R). *Psychology & Health*, *17*(1), 1-16. doi:10.1080/08870440290001494
- Mukherjee, M., Stoddart, A., Gupta, R. P., Nwaru, B. I., Farr, A., Heaven, M., . . . Sheikh, A. (2016). The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med*, *14*(1), 113. doi:10.1186/s12916-016-0657-8
- Murphy, A. C., Proeschal, A., Brightling, C. E., Wardlaw, A. J., Pavord, I., Bradding, P., & Green, R. H. (2012). The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax*, *67*(8), 751-753. doi:10.1136/thoraxjnl-2011-201096

- Murray, M., & Chamberlain, K. (1999). *Qualitative health psychology : theories and methods*. London ; Thousand Oaks, Calif.: Sage Publications.
- Nagakumar, P., & Thomas, H. (2017). Management of problematic severe asthma in children. *Paediatrics and Child Health, 27*(7), 318-323. doi:10.1016/j.paed.2017.03.002
- Nathan, R. A., Sorkness, C. A., Kosinski, M., Schatz, M., Li, J. T., Marcus, P., . . . Pendergraft, T. B. (2004). Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol, 113*(1), 59-65. doi:10.1016/j.jaci.2003.09.008
- National Asthma, E., & Prevention, P. (2007). Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol, 120*(5 Suppl), S94-138. doi:10.1016/j.jaci.2007.09.043
- National Collaborating Centre for Primary Care UK. (2009). *Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence*. Retrieved from <https://www.nice.org.uk/guidance/cg76/resources/medicines-adherence-involving-patients-in-decisions-about-prescribed-medicines-and-supporting-adherence-975631782085>
- National Review of Asthma Deaths (NRAD). (2014). *British Journal of General Practice, 64*(628), 564. doi:<http://dx.doi.org/10.3399/bjgp14X682237>
- Network, B. T. S. S. I. G. (2016). *British guideline on the management of asthma : Quick Reference Guide* (Revised edition. ed.).
- The Global Asthma Network (2018). *The Global Asthma Report*. Retrieved from Auckland, New Zealand:
- Newby, C., Heaney, L. G., Menzies-Gow, A., Niven, R. M., Mansur, A., Bucknall, C., . . . British Thoracic Society Severe Refractory Asthma, N. (2014). Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS One, 9*(7), e102987. doi:10.1371/journal.pone.0102987
- Ngahane, B. H., Pefura-Yone, E. W., Mama, M., Tengang, B., Nganda, M. M., Wandji, A., . . . Kuaban, C. (2016). Evaluation of factors affecting adherence to asthma controller therapy in chest clinics in a sub-Saharan African setting: a cross-sectional study. *Afr Health Sci, 16*(1), 194-200. doi:10.4314/ahs.v16i1.26
- Normansell, R., Kew, K. M., & Stovold, E. (2017). Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database of Systematic Reviews*(4). doi:ARTN CD012226 10.1002/14651858.CD012226.pub2
- Nunes, V., Neilson, J., O'flynn, N., Calvert, N., Kuntze, S., Smithson, H., . . . Crome, P. (2009). *Clinical guidelines and evidence review for medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence*. Retrieved from London::
- NVivo qualitative data analysis software*. (2015). (Vol. 11).
- O'Byrne, P., Bateman, E. D., FitzGerald, J. M., Barnes, P. J., Zhong, N., Alagappan, V. K. T., . . . Reddel, H. K. (2019). Efficacy of As-Needed Budesonide/Formoterol for Reducing Severe Exacerbations in Adolescents with Mild Asthma: Pooled Subgroup Analysis of the SYGMA 1 and 2 Trials. In *D105. IMPROVING PEDIATRIC ASTHMA CONTROL AND OUTCOMES* (pp. A7191-A7191): American Thoracic Society.
- Ogden, J. (2012). *Health psychology : a textbook* (5th ed. ed.). Maidenhead: McGraw-Hill/Open University Press.
- Orrell-Valente, J. K., Jarlsberg, L. G., Hill, L. G., & Cabana, M. D. (2008). At what age do children start taking daily asthma medicines on their own? *Pediatrics, 122*(6), e1186-1192. doi:10.1542/peds.2008-0292



- Orrell-Valente, J. K., Jarlsberg, L. G., Rait, M. A., Thyne, S. M., Rubash, T., & Cabana, M. D. (2007). Parents' specific concerns about daily asthma medications for children. *J Asthma*, *44*(5), 385-390. doi:10.1080/02770900701364221
- Ovchinnikova, L., Smith, L., & Bosnic-Anticevich, S. (2011). Inhaler Technique Maintenance: Gaining an Understanding from the Patient's Perspective. *Journal of Asthma*, *48*(6), 616-624. doi:10.3109/02770903.2011.580032
- Papadopoulos, N. G., Christodoulou, I., Rohde, G., Agache, I., Almqvist, C., Bruno, A., . . . Zuberbier, T. (2011). Viruses and bacteria in acute asthma exacerbations - A GA2LEN-DARE\* systematic review. *Allergy*, *66*(4), 458-468. doi:10.1111/j.1398-9995.2010.02505.x
- Pavord, I. D., Beasley, R., Agusti, A., Anderson, G. P., Bel, E., Brusselle, G., . . . Bush, A. (2018). After asthma: redefining airways diseases. *Lancet*, *391*(10118), 350-400. doi:10.1016/S0140-6736(17)30879-6
- Pearce, C., Chan, A., Horne, R., Fleming, L., Bush, A., & Jamalzadeh, A. (2018). "It's Like Trying to Fit a Piece into an Already Not Working Puzzle": Non Adherence to Inhaled Corticosteroids in Young People with Problematic Asthma: A Qualitative Study. *International Journal of Behavioral Medicine*, *25*, S191-S191.
- Pearce, C. J., & Fleming, L. (2018). Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. *Expert Rev Clin Immunol*, *14*(12), 1055-1063. doi:10.1080/1744666X.2018.1532290
- Pearce, C. J., Jochmann, A., Bush, A., Horne, R., & Fleming, L. (2016). *Patterns of nonadherence in children with severe asthma*. Paper presented at the European Respiratory Society, London.
- Penza-Clyve, S. M., Mansell, C., & McQuaid, E. L. (2004). Why don't children take their asthma medications? A qualitative analysis of children's perspectives on adherence. *J Asthma*, *41*(2), 189-197.
- Petrie, K. J., Perry, K., Broadbent, E., & Weinman, J. (2012). A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *Br J Health Psychol*, *17*(1), 74-84. doi:10.1111/j.2044-8287.2011.02033.x
- Petrie, K. J., & Weinmann, J. A. (2013). *Perceptions of Health and Illness*. In. New York: Routledge.
- Phillips, L. A., Leventhal, H., & Leventhal, E. A. (2013). Assessing theoretical predictors of long-term medication adherence: Patients' treatment-related beliefs, experiential feedback and habit development. *Psychology & Health*, *28*(10), 1135-1151. doi:10.1080/08870446.2013.793798
- Poniaman, D., Wisnivesky, J. P., Leventhal, H., Musumeci-Szabo, T. J., & Halm, E. A. (2009). Impact of positive and negative beliefs about inhaled corticosteroids on adherence in inner-city asthmatic patients. *Ann Allergy Asthma Immunol*, *103*(1), 38-42. doi:10.1016/S1081-1206(10)60141-X
- Prestwich, A., Conner, M., & Kenworthy, J. (2017). *Health behavior change : theories, methods and interventions* (1st ed.). Abindon Oxfordshire: Routledge.
- Prestwich, A., Webb, T. L., & Conner, M. (2015). Using theory to develop and test interventions to promote changes in health behaviour: evidence, issues, and recommendations. *Current Opinion in Psychology*, *5*, 1-5. doi:<https://doi.org/10.1016/j.copsyc.2015.02.011>
- Pridmore, P., & Bendelow, G. (1995). Images of health: exploring beliefs of children using the 'draw-and-write' technique. *Health Education Journal*, *54*(4), 473-488. doi:10.1177/001789699505400410

- Puranik, S., Forno, E., Bush, A., & Celedon, J. C. (2017). Predicting Severe Asthma Exacerbations in Children. *American Journal of Respiratory and Critical Care Medicine*, 195(7), 854-859. doi:10.1164/rccm.201606-1213PP
- Radhakrishna, R. B. (2007). Tips for developing and testing questionnaires/instruments. *Journal of extension*, 45(1), 1-4.
- Raissy, H. H., & Kelly, H. W. (2017). Tiotropium Bromide in Children and Adolescents with Asthma. *Pediatric Drugs*, 19(6), 533-538. doi:10.1007/s40272-017-0258-9
- Rand, C. S., & Wise, R. A. (1994). Measuring adherence to asthma medication regimens. *American Journal of Respiratory & Critical Care Medicine*, 149(2 Pt 2), S69-76; discussion S77-68.
- Rao, D., Feldman, B. J., Fredericksen, R. J., Crane, P. K., Simoni, J. M., Kitahata, M. M., & Crane, H. M. (2012). A Structural Equation Model of HIV-Related Stigma, Depressive Symptoms, and Medication Adherence. *AIDS Behav*, 16(3), 711-716. doi:10.1007/s10461-011-9915-0
- Richards, L. (2005). *Handling qualitative data: a practical guide*. London: Sage Publications.
- Ritchie, J. A., Lewis, J., McNaughton Nicholls, C., & Ormston, R. (2013). *Qualitative research practice: a guide for social science students and researchers* (Second edition. ed.). London: SAGE Publications.
- Ritschl, V., Lackner, A., Boström, C., Mosor, E., Lehner, M., Omara, M., . . . Stamm, T. A. (2018). I do not want to suppress the natural process of inflammation: new insights on factors associated with non-adherence in rheumatoid arthritis. *Arthritis Research & Therapy*, 20(1), 234. doi:10.1186/s13075-018-1732-7
- Robinson, D. S., Campbell, D. A., Durham, S. R., Pfeiffer, J., Barnes, P. J., Chung, K. F., . . . Lung, I. (2003). Systematic assessment of difficult-to-treat asthma. *Eur Respir J*, 22(3), 478-483.
- Rosenstock, I. M. (1974). Historical origins of the health belief model. *Health education monographs*, 2(4), 328-335.
- Royal College of Physicians. (2014). *Why asthma still kills : the National review of asthma deaths (NRAD). Confidential enquiry report* (9781860165313 (paperback) : No price 781860165320 (ebook) : Retrieved from London:
- Ryan R, & Hill S.H. (2016). How to GRADE the quality of the evidence. 3. Retrieved from <http://cccr.org/author-resources>.
- Ryan, S., & Carr, A. (2010). Chapter 5 - Applying the biopsychosocial model to the management of rheumatic disease. In K. Dziedzic & A. Hammond (Eds.), *Rheumatology* (pp. 63-75). Edinburgh: Churchill Livingstone.
- Sandberg, S., Paton, J. Y., Ahola, S., McCann, D. C., McGuinness, D., Hillary, C. R., & Oja, H. (2000). The role of acute and chronic stress in asthma attacks in children. *Lancet*, 356(9234), 982-987. doi:Doi 10.1016/S0140-6736(00)02715-X
- Santos Pde, M., D'Oliveira, A., Jr., Noblat Lde, A., Machado, A. S., Noblat, A. C., & Cruz, A. A. (2008). Predictors of adherence to treatment in patients with severe asthma treated at a referral center in Bahia, Brazil. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisiologia*, 34(12), 995-1002.
- Shah, R., Hagell, A., & Cheung, R. (2019). *International comparisons of health and wellbeing in adolescence and early adulthood*. Retrieved from [https://www.nuffieldtrust.org.uk/files/2019-02/1550657729\\_nt-ayph-adolescent-health-report-web.pdf](https://www.nuffieldtrust.org.uk/files/2019-02/1550657729_nt-ayph-adolescent-health-report-web.pdf)
- Sharples, J., Gupta, A., Fleming, L., Bossley, C. J., Bracken-King, M., Hall, P., . . . Saglani, S. (2012). Long-term effectiveness of a staged assessment for paediatric problematic severe asthma. *Eur Respir J*, 40(1), 264-267. doi:10.1183/09031936.00209511

- Shields, M. D., F, A. L., Rivey, M. P., & McElnay, J. C. (2018). Mobile direct observation of therapy (MDOT) - A rapid systematic review and pilot study in children with asthma. *PLoS One*, *13*(2), e0190031. doi:10.1371/journal.pone.0190031
- Simmons, M. S., Nides, M. A., Kleerup, E. C., Chapman, K. R., Milgrom, H., Rand, C. S., . . . Tashkin, D. P. (1997). Validation of the Doser, a new device for monitoring metered dose inhaler use, and comparison with the thermistorbased Nebulizer Chronolog. *American Journal of Respiratory & Critical Care Medicine*, *155*, A260.
- Simoni, J. M., Frick, P. A., & Huang, B. (2006). A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy [American Psychological Association doi:10.1037/0278-6133.25.1.74]. Retrieved
- Simoni, J. M., Frick, P. A., Lockhart, D., & Liebovitz, D. (2002). Mediators of social support and antiretroviral adherence among an indigent population in New York City. *Aids Patient Care and Stds*, *16*(9), 431-439. doi:Doi 10.1089/108729102760330272
- Sofianou, A., Martynenko, M., Wolf, M. S., Wisnivesky, J. P., Krauskopf, K., Wilson, E. A. H., . . . Federman, A. D. (2013). Asthma Beliefs Are Associated with Medication Adherence in Older Asthmatics. *Journal of General Internal Medicine*, *28*(1), 67-73. doi:10.1007/s11606-012-2160-z
- Sporik, R., Chapman, M. D., & Platts-mills, T. A. E. (1992). House Dust Mite Exposure as a Cause of Asthma. *Clinical and Experimental Allergy*, *22*(10), 897-906. doi:DOI 10.1111/j.1365-2222.1992.tb02062.x
- Stergachis, A., Gardner, J. S., Anderson, M. T., & Sullivan, S. D. (2002). Improving pediatric asthma outcomes in the community setting: does pharmaceutical care make a difference? *Journal of the American Pharmaceutical Association*, *42*(5), 743-752.
- Stewart, A. C., Gannon, K. N., Beresford, F., & Fleming, L. (2018). Adolescent and caregivers' experiences of electronic adherence assessment in paediatric problematic severe asthma. *J Child Health Care*, *22*(2), 238-250. doi:10.1177/1367493517753082
- Suissa, S., & Ernst, P. (2001). Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol*, *107*(6), 937-944. doi:10.1067/mai.2001.115653
- Suissa, S., Ernst, P., Benayoun, S., Baltzan, M., & Cai, B. (2000). Low-dose inhaled corticosteroids and the prevention of death from asthma. *New England Journal of Medicine*, *343*(5), 332-336. doi:Doi 10.1056/Nejm200008033430504
- Suissa, S., Ernst, P., Boivin, J. F., Horwitz, R. I., Habbick, B., Cockroft, D., . . . Spitzer, W. O. (1994). A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *American Journal of Respiratory & Critical Care Medicine*, *149*(3 Pt 1), 604-610. doi:10.1164/ajrccm.149.3.8118625
- Sulaiman, I., Greene, G., MacHale, E., Seheult, J., Mokoka, M., D'Arcy, S., . . . Costello, R. W. (2018). A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *Eur Respir J*, *51*(1). doi:10.1183/13993003.01126-2017
- Sulaiman, I., Mac Hale, E., Holmes, M., Hughes, C., D'Arcy, S., Taylor, T., . . . Costello, R. W. (2016). A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma. *BMJ Open*, *6*(1), e009350. doi:10.1136/bmjopen-2015-009350
- Sulaiman, I., Seheult, J., MacHale, E., Boland, F., O'Dwyer, S. M., Rapcan, V., . . . Costello, R. W. (2016). A Method to Calculate Adherence to Inhaled Therapy that Reflects the Changes in Clinical Features of Asthma. *Ann Am Thorac Soc*, *13*(11), 1894-1903. doi:10.1513/AnnalsATS.201603-222OC
- Taylor, S., Epiphaniou, E., Pearce, G., Parke, H., Schwappach, A., & al., e. (2014). A rapid synthesis of the evidence on interventions supporting self-management for people

- /with long-term conditions : PRISMS - Practical systematic Review of Self-Management Support for long-term conditions. *Health Services and Delivery Research*, 2(53).
- Taylor, T. E., Zigel, Y., Egan, C., Hughes, F., Costello, R. W., & Reilly, R. B. (2018). Objective Assessment of Patient Inhaler User Technique Using an Audio-Based Classification Approach. *Sci Rep*, 8(1), 2164. doi:10.1038/s41598-018-20523-w
- Teach, S. J., Crain, E. F., Quint, D. M., Hylan, M. L., & Joseph, J. G. (2006). Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency department-based randomized clinical trial. *Arch Pediatr Adolesc Med*, 160(5), 535-541. doi:10.1001/archpedi.160.5.535
- Thøgersen, J. (1995). Understanding of consumer behavior as a prerequisite for environmental protection. *Journal of Consumer Policy*, 18, 345-385. doi:10.1007/BF01024160
- Trachtenberg, F., Vichinsky, E., Foote, D., Pakbaz, Z., Mednick, L., Sobota, A., . . . Neufeld, E. J. (2012). Beliefs about chelation among thalassemia patients. *Health and Quality of Life Outcomes*, 10(148). doi:10.1186/1477-7525-10-148
- Tran, N., Coffman, J. M., Sumino, K., & Cabana, M. D. (2014). Patient reminder systems and asthma medication adherence: a systematic review. *J Asthma*, 51(5), 536-543. doi:10.3109/02770903.2014.888572
- Turan, B., Hatcher, A. M., Weiser, S. D., Johnson, M. O., Rice, W. S., & Turan, J. M. (2017). Framing Mechanisms Linking HIV-Related Stigma, Adherence to Treatment, and Health Outcomes. *American Journal of Public Health*, 107(6), 863-869. doi:10.2105/Ajph.2017.303744
- Turi, K. N., Gebretsadik, T., Lee, R. L., Hartert, T. V., Evans, A. M., Stone, C., . . . Wu, P. (2018). Seasonal patterns of Asthma medication fills among diverse populations of the United States. *J Asthma*, 55(7), 764-770. doi:10.1080/02770903.2017.1362426
- Turpin, D. L. (2005). CONSORT and QUOROM guidelines for reporting randomized clinical trials and systematic reviews. *Am J Orthod Dentofacial Orthop*, 128(6), 681-685; discussion 686. doi:10.1016/j.ajodo.2005.10.010
- Asthma UK, (2019). Asthma facts and statistics. Retrieved from <https://www.asthma.org.uk/about/media/facts-and-statistics/>
- Ullmann, N., Mirra, V., Di Marco, A., Pavone, M., Porcaro, F., Negro, V., . . . Cutrera, R. (2018). Asthma: Differential Diagnosis and Comorbidities. *Frontiers in Pediatrics*, 6. doi:ARTN 27610.3389/fped.2018.00276
- van Dalen, C., Harding, E., Parkin, J., Cheng, S., Pearce, N., & Douwes, J. (2008). Suitability of forced expiratory volume in 1 second/forced vital capacity vs percentage of predicted forced expiratory volume in 1 second for the classification of asthma severity in adolescents. *Arch Pediatr Adolesc Med*, 162(12), 1169-1174. doi:10.1001/archpedi.162.12.1169
- van Es, S. M., Nagelkerke, A. F., Colland, V. T., Scholten, R., & Bouter, L. M. (2001). An intervention programme using the ASE-model aimed at enhancing adherence in adolescents with asthma. *Patient Education and Counseling*, 44(3), 193-203. doi:10.1016/s0738-3991(00)00195-6
- van Servellen, G., & Lombardi, E. (2005). Supportive relationships and medication adherence in HIV-infected, low-income Latinos. *Western Journal of Nursing Research*, 27(8), 1023-1039. doi:10.1177/0193945905279446
- Van Someren, M., Barnard, Y. F., & Sandberg, J. A. C. (1994). Practical procedures in obtaining think aloud protocols. In *The think aloud method : a practical guide to modelling cognitive processes* (pp. 41-48). London: Academic Press.
- Van Steenis, M. N. A., Drienaar, J. A., Bensing, J. M., Van Hulten, R., Souverein, P. C., Van Dijk, L., . . . Van Dulmen, A. M. (2014). Relationship between medication beliefs,

- self-reported and refill adherence, and symptoms in patients with asthma using inhaled corticosteroids. *Patient Preference and Adherence*, 8, 83-91. doi:10.2147/Ppa.S44185
- Vasbinder, E. C., Goossens, L. M., Rutten-van Molken, M. P., de Winter, B. C., van Dijk, L., Vulto, A. G., . . . van den Bemt, P. M. (2016). e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC): a randomised controlled trial. *Eur Respir J*. doi:10.1183/13993003.01698-2015
- Verplanken, B., & Orbell, S. (2003). Reflections on past behavior: A self-report index of habit strength. *Journal of Applied Social Psychology*, 33(6), 1313-1330. doi:DOI 10.1111/j.1559-1816.2003.tb01951.x
- Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppert, T., . . . Team, A. B. C. P. (2012). A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*, 73(5), 691-705. doi:10.1111/j.1365-2125.2012.04167.x
- Vrijens, B., Dima, A., Van Ganse, E., van Boven, J., Eakin, M., Foster, J., . . . Price, D. (2016). What We Mean When We Talk About Adherence in Respiratory Medicine. *Journal of Allergy and Clinical Immunology: In Practice*, 4(5), 802-812. doi:<http://dx.doi.org/10.1016/j.jaip.2016.05.019>
- Watkinson, A., Chapman, S. C. E., & Horne, R. (2017). Beliefs About Pharmaceutical Medicines and Natural Remedies Explain Individual Variation in Placebo Analgesia. *The Journal of Pain*, 18(8), 908-922. doi:<https://doi.org/10.1016/j.jpain.2017.02.435>
- Weinberger, M., & Hendeles, L. (1996). Theophylline in Asthma. *New England Journal of Medicine*, 334(21), 1380-1388. doi:10.1056/NEJM199605233342107
- Weinman, J., Petrie, K. J., Moss-Morris, R., & Horne, R. (1996). The illness perception questionnaire: A new method for assessing the cognitive representation of illness. *Psychology & Health*, 11(3), 431-445. doi:Doi 10.1080/08870449608400270
- Wenzel, S. E. (2006). Asthma: defining of the persistent adult phenotypes. *Lancet*, 368(9537), 804-813. doi:Doi 10.1016/S0140-6736(06)69290-8
- Wenzel, S. E. (2012). Asthma phenotypes: the evolution from clinical to molecular approaches. *Nature Medicine*, 18(5), 716-725. doi:10.1038/nm.2678
- WHO. WHO Mortality Database. . Retrieved from <http://www.who.int/whosis/mort/download/en/>
- Wiecha, J. M., Adams, W. G., Rybin, D., Rizzodepaoli, M., Keller, J., & Clay, J. M. (2015). Evaluation of a web-based asthma self-management system: a randomised controlled pilot trial. *BMC Pulmonary Medicine*, 15, 17.
- Williams, L. K., Peterson, E. L., Wells, K., Ahmedani, B. K., Kumar, R., Burchard, E. G., . . . Pladevall, M. (2011). Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol*, 128(6), 1185-1191 e1182. doi:10.1016/j.jaci.2011.09.011
- Wolfe, I., Thompson, M., Gill, P., Tamburlini, G., Blair, M., van den Bruel, A., . . . McKee, M. (2013). Health services for children in western Europe. *Lancet*, 381(9873), 1224-1234. doi:10.1016/S0140-6736(12)62085-6
- Wood, W., & Neal, D. T. (2009). The habitual consumer. *Journal of Consumer Psychology*, 19(4), 579-592. doi:10.1016/j.jcps.2009.08.003
- Wu, A. C., Butler, M. G., Li, L., Fung, V., Kharbanda, E. O., Larkin, E. K., . . . Soumerai, S. B. (2015). Primary Adherence to Controller Medications for Asthma Is Poor. *Annals of the American Thoracic Society*, 12(2), 161-166. doi:10.1513/AnnalsATS.201410-459OC
- Yilmaz, O., Eroglu, N., Ozalp, D., & Yuksel, H. (2012). Beliefs about Medications in Asthmatic Children Presenting to Emergency Department and Their Parents. *Journal of Asthma*, 49(3), 282-287. doi:10.3109/02770903.2011.654021