

THE EFFECT OF ORGANOLEPTIC PROPERTIES OF
MEDICINES ON MEDICATION ADHERENCE IN
CHILDREN WITH CHRONIC ILLNESSES

SIMON P BRYSON

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ABSTRACT

The development of age appropriate paediatric formulations, particularly those suitable for young children, presents challenges with only limited knowledge available on the acceptability of different medicines and how this affects medication adherence.

This thesis describes studies conducted at Alder Hey Children's Hospital, Liverpool UK, with the aim of determining which factors relating to dose form and organoleptic properties of a medicinal product influence medication adherence in chronically ill children. The research was conducted in two phases comprising 70 chronically ill children aged between 3 and 11 years, 70 primary caregivers, and 33 hospital clinical and technical staff.

Phase one, the CHIMP study (Children's Medication Preferences), investigated children's preferences in terms of the organoleptic properties of medicines, and factors which influence these preferences and medication adherence.

The data generated in the CHIMP study was used to construct a Medication Adherence Prediction Tool (MedAPT), in the form of a questionnaire, which was the subject of a second study (MedAPT), to qualify the prediction tool, in which adherence predictions derived from children and primary caregiver's questionnaire response data were statistically evaluated against adherence measurement generated from pharmacy medication refill data.

The developed MedAPT questionnaire correctly predicted medication adherence/non-adherence in 79.4% of children. It is envisaged that, following further confirmation of the MedAPT as a prediction tool, this may be used in clinical practice as a predictor of adherence, and as a means of focussing resources and interventions to address non-adherence.

This thesis provides an original contribution to knowledge by providing evidence of those factors affecting medication adherence, methodology to predict adherence, and an evidence base to focus pharmaceutical product development towards the production of medicines which are acceptable to the child.

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Preface

This thesis contains five chapters, representing two empirical studies. Chapter 1 contains the introduction and literature review, which provide an overview of medication adherence, health related behaviour and factors affecting adherence in children, with a focus on the organoleptic properties of medicines. Chapter 2 presents the children's medication adherence preferences study (CHIMP), an assessment of child, parent/carer and healthcare professional involvement, preferences, beliefs and behaviours in medication prescribing and medication taking by the child. Chapter 3 describes the development of a medication adherence prediction model, which was the subject of a medication adherence study described in chapter 4. Finally, a general discussion is presented in chapter 5.

DEDICATION

It is with pride and loving affection that I dedicate this thesis to the memory of my mum and dad, Josie and Peter Bryson, my unwavering supporters, who never got the chance to see me complete this chapter of my life.

ACKNOWLEDGEMENTS

Undertaking this PhD has been a fulfilling, yet often overwhelming, learning process. Reaching the finish line would not have been possible without the support and guidance that I received from so many people.

To my supervisors, Dr. Angela Macadam and Professor Paul Gard, thank you for your continuous guidance and endless encouragement throughout. Your advice and commitment towards my research and in writing this thesis were vital. I will miss my trips to Brighton to meet with you both. In my moments of self-doubt and lacking direction our meetings were a source of motivation and focus.

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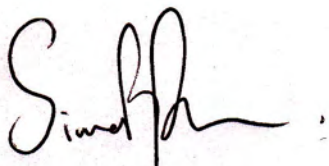
To all the staff at Alder Hey Children's NHS foundation trust who supported my research, from the pharmacy team led by Catrin Barker to each of the clinical teams who gave me access to their patients, and generously gave their time and expertise in meetings and focus groups, I give you my sincere thanks.

This study would not have been possible without the cooperation of the people who are at the heart of this research. To the children and parents who kindly agreed to participate in my research at often difficult times. I give my heartfelt thanks to each of you.

And finally, my family. To my children, Ellen, Hannah and Max, who won't remember a time before PhD, and to my wife Rachel, thank you for putting up with the additional stresses my research has placed on our already hectic lives. Your support throughout this seemingly never-ending research process has allowed me to keep going and reach the finish line. I'm looking forward to having the extra time to spend with you, and promise I won't do anything like this again!

DECLARATION

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

A handwritten signature in black ink, appearing to read 'Simon P Bryson', with a stylized flourish at the end.

Simon P Bryson

20 October 2014

Abbreviations

Adacc	Adherent acceptable (CHIMP adherence category)
Adcop	Adherent with coping mechanisms (CHIMP adherence category)
ADME	Adsorption, Distribution, Metabolism, Elimination
AHCNHSFT	Alder Hey Children's NHS Foundation Trust
BBQ	Beliefs and Behaviour Questionnaire
BPCA	Better Pharmaceuticals for Children Act
CDER	US FDA Center for Drugs Evaluation and Research
CHIMP	Children's Medication Preferences Study
CMA	Cumulative Measure of Adherence
CPMP	Committee for Proprietary Medicinal Products
DCMA	Dose CMA
EMA	European Medicines Agency (formerly EMEA)
EMEA	European Medicines Evaluation Agency (now know as EMA)
FWG	Formulation Working Group (of the EMA)
HBM	Health Belief Model
HLC	Health Locus of Control
MedAPT	Medication Adherence Prediction Tool
MEMS	Medication Event Monitoring System
MDT	Multi-Disciplinary Team
MHRA	UK Medicines and Healthcare Products Regulatory Agency
Nadal	Non-adherent always (CHIMP adherence category)
Nadso	Non-adherent sometimes (CHIMP adherence category)
NHS	National Health Service UK
NRES	National Research Ethics Service
PDCO	Paediatric Committee (of EMA)
PIC	Participants Identification code
PIP	Paediatric Investigation Plan
PUMA	Paediatric Use Marketing Authorisation
PREA	Paediatric Research Equity Act
SIA	Single Interval Compliance

TRA	Theory of Reasoned Action
TPB	Theory of Planned Behaviour
UoB	University of Brighton
US FDA	United States of America Food and Drugs Administration

1. Overview of medication adherence, health related behaviour and factors affecting adherence in children

1.1. Introduction

Within the paediatric healthcare community which is comprised of medical practitioners, parents and carers, the pharmaceutical industry, society and the child themselves, there appears to be agreement that children are disadvantaged in terms of the availability of safe and effective, easy to use, convenient, nice tasting medicines which have been appropriately developed and studied with them in mind. Rather they have been tested and formulated for adults. This is reported in a number of reviews (Matsui, 2007; Ernest et al.,2007; Nunn and Williams, 2005; Standing and Tuleu, 2005; Pawar and Kumar, 2002).

Approximately 90% of babies in neonatal intensive care, 70% of patients in paediatric intensive care, and almost 70% of all children in hospital in Europe receive at least one unlicensed or off-label medicine during a hospital stay (Ernest et al.,2007). A similar picture was reported by Janet Woodcock, Director of the Center for Drugs Evaluation and Research (CDER) within the United States Food and Drug Administration (FDA) in 2001 (Woodcock, 2001), who commented that only a small fraction of all drugs marketed and used as therapies for children in the United States of America (USA) have been studied in paediatric patients, and a majority of marketed drugs are not labelled, or are insufficiently labelled, for use in paediatric patients. Safety and dosage information for the youngest paediatric age groups is particularly difficult to find on product labelling, due largely to a lack of clinical data.

In addition to the limited availability of critical safety and efficacy information, there is an absence of age-adapted formulations, due to the lack of paediatric studies. This presents this vulnerable patient population with the increased risks of adverse events and dosing errors (Costello et al., 2007) as medical professionals seek to modify adult medicines for use in children, and ultimately this can lead to the ineffective treatment of the underlying disease or condition. Inconsistencies in definition and subsequent reporting of medication errors,

together with the extensive use of off-label or extemporaneous preparations, which can evade the pharmacovigilance mechanisms established for licensed products, make it difficult to place a precise figure on error rate. However, some studies have been conducted, and the reported figures suggest that the error rate can be as high as 26.3% and between 0.2% and 5.6% of errors are potentially lethal, mainly as a consequence of dosing calculation errors (Costello et al., 2007).

A further challenge to the medication-assisted treatment of children is the patient's adherence to the medication regime. Whilst differences exist in the methods of measuring adherence and non-adherence and the scientific rigor of the data generated, there is a recognised problem of adherence to medication in paediatrics. Reported figures for non-adherence are within the range 25% to 70% (Fiese and Everhart, 2006; Gardiner and Dvorkin, 2006; Costello, Wong and Nunn, 2004; Cohn et al., 2003), in conditions ranging from acne to oral chemotherapy (Costello, Wong and Nunn, 2004). These figures are, on average, higher in children than reported figures from adult studies, and an effect on clinical outcome has been observed. Cohn et al. (2003) reviewed the effects of medication delivery systems on adherence of children with asthma, and found that increased illness, exacerbations and visits to the emergency department were demonstrated in patients who are non-adherent to their treatment regimens. The association between non-adherence and adverse clinical outcome is also reported in patients with cardiovascular disease (Ho, Bryson and Rumsfeld, 2009).

The reasons why there is a lack of optimised paediatric medicines is, as Baber and Smyth describe in their 2005 report (Baber and Smyth, 2005), both complex and multi-factorial. They describe the challenges in investigating medicines to the same standard as is performed with adults where the disease burden is much less in children than adults, with the resultant challenge in generating equally high-quality data from studies in children. Furthermore, there is a perception which exists that the market for most paediatric medicines is comparatively small with a low return on investment, that regulatory demands are too demanding within

this heterogeneous population (where organ maturation plays a key role in the adsorption, distribution, metabolism and elimination (ADME) of the medicinal product), and that the ethical difficulties associated with studies in children present a significant barrier to clinical development.

The development of age appropriate paediatric formulations, particularly those suitable for young children, presents challenges with only limited knowledge available. Some general information is available within the Committee for Human Medicinal Products (CHMP) 'reflection paper' on "Formulations of choice for the paediatric population" EMEA/CHMP/PEG/194810/2005 adopted by CHMP on 21 September 2006, however, there are knowledge gaps on the acceptability of different dosage forms, administration volumes, dosage form size, taste, and the acceptability and safety of formulation excipients in relation to the age and development status of the child.

More research and clinical feedback will be valuable since if a formulation has poor patient acceptability, it affects compliance, prescribing practices, commercial viability and clinical outcome.

The chapter explores the evidence of contributing factors, which may affect medication adherence in children, with particular emphasis on the children's medication preferences in terms of the medicine's organoleptic properties. Organoleptic is defined as being "able to stimulate an organ, especially a sense organ" (Collins English Dictionary online, 2014). In the context of medicines, organoleptic properties encompass the senses of taste, touch/mouth feel, smell, appearance or sound.

1.2. Definition of adherence

Medication compliance with a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. The most widely quoted definition is provided by Haynes (2002), who defined compliance as, "the extent to which a person's behaviour (in terms of

taking medication, following diets, or executing lifestyle changes) coincides with medical or health advice” Adherence is the extent to which an individual ‘changes’ their health behaviour to coincide with medical advice.

The word "adherence" is preferred by many health care providers, because "compliance" suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on a therapeutic alliance (an agreement between patients and health professionals to work together) or contract established between the patient and the physician.

The definition of adherence brings together three important elements, as described by Rapoff (1999). Firstly, the definition captures the behavioural aspects in achieving adherence, whereby the patient is required to follow the instructions in taking medication in the prescribed manner, and/or following specified diets, or executing certain lifestyle changes. Secondly, the word “extent” is an “important qualifier” which suggests that adherence is not an absolute term, and may be the result of a number of different actions, which are not strictly within the requirements specified in the prescription. Thirdly, the element of concordance (the degree to which clinical advice and health behaviour agrees) is implicit, by assessing whether the patient’s behaviour coincides with the treatment protocol. This aspect does imply that there is a standard for determining whether adherence is acceptable or not. The extent to which non-adherence may produce unacceptable clinical outcomes, requires data on a case by case basis, making a gold standard for concordance a challenge.

The first question facing a researcher embarking on assessing medication adherence is to define non-adherence i.e. is a patient considered non-adherent if they miss one single dose within the measurement period, or do not take their daily dose at the correct time of day, or are they considered adherent providing they take their medication for example at least 90% of the time, or within a few hours of the expected time? Estimates of non-adherence in the literature show considerable variability (Fiese and Everhart, 2006; Gardiner and Dvorkin, 2006; Costello, Wong and Nunn, 2004; Cohn et al., 2003), reflecting the variance in the measurement methodology used and the criterion set by the researcher for

classifying patients as non-adherent (Rapoff 1998). It is therefore important to clearly state the non-adherence classification criteria for each medication adherence study within the study methodology, to enable accurate interpretation of the study findings. The criteria for the studies within this thesis are described in sections 2.2.6. and 4.2.4.1., and defined non-adherence as, at least one missed dose. The purpose of this approach was to avoid a value judgement of the percentage of adherence which could be considered acceptable. Each medication for each patient was assessed with the same non-adherence measurement criteria of at least one missed dose equating to non-adherence.

Additionally, the concept of acceptability is an important aspect, which requires consideration, as a potential contributing factor in achieving medication adherence. A medicine, which is considered by the child to be acceptable, is one which is acceptable in terms of its organoleptic properties, to the extent that the child will willingly take it, without the need for coping mechanisms to be used. Coping mechanisms being the broad term for the strategies used by parents and carers to facilitate administration, and include taste masking, psychological interventions including persuasion techniques and physical force.

1.3. Incidence of non-adherence

The reported non-adherence figures are predominantly from studies conducted in the developed world, with most articles reporting work conducted in the USA, Canada and the UK. The picture which emerges on reviewing the available literature is of a widespread problem which is particularly common in patients with chronic illnesses e.g. cystic fibrosis, epilepsy, asthma and diabetes, for whom the extended treatment regimes and multiple medications combine to present a challenging discipline for children to follow (Butz, 2006; Penza-Clyve, Mansell and McQuaid, 2004; Quittner, 2000). Periods of symptomatic remission can present a confusing scenario, and has resulted in the cessation of medication, for example the stopping of daily inhaled steroids when the child is feeling better in the hope that this will prevent the adverse effects of the medication (Gardiner

and Dvorkin 2006). Parental or carer support is therefore cited across the literature as a key factor in assuring medication adherence in children (James 2008; Colland et al., 2004; Cohn et al.,2003).

1.4. Psychology of health related behaviour

The degree to which a patient acts upon and follows the medical advice they are given by a healthcare professional is a matter of concern for all clinical specialities (Osterberg and Blaschke, 2005). By understanding the reasons behind patients' behaviours and beliefs towards treatment and adherence, interventions can be developed to improve adherence.

The nature and extent of non-adherent behaviour, and the factors, which characterise the behaviour of the non-adherent patient, are complex. There are no behaviour theories of adherence or non-adherence, however health-related behaviour models, have been used to predict the relationship between the patients' beliefs and their health related behaviour (George et al., 2006).

The health-related behaviour models are based on either social or illness cognition. The main social cognition models are: The Health Belief Model; The Theory of Reasoned Action; Theory of Planned Behaviour; Health Locus of Control; Self-Efficacy; Attribution Theory. Illness cognition is modelled in the Self Regulatory Model (George et al., 2006; Rapoff, 1998).

1.4.1. The Health Belief Model (HBM)

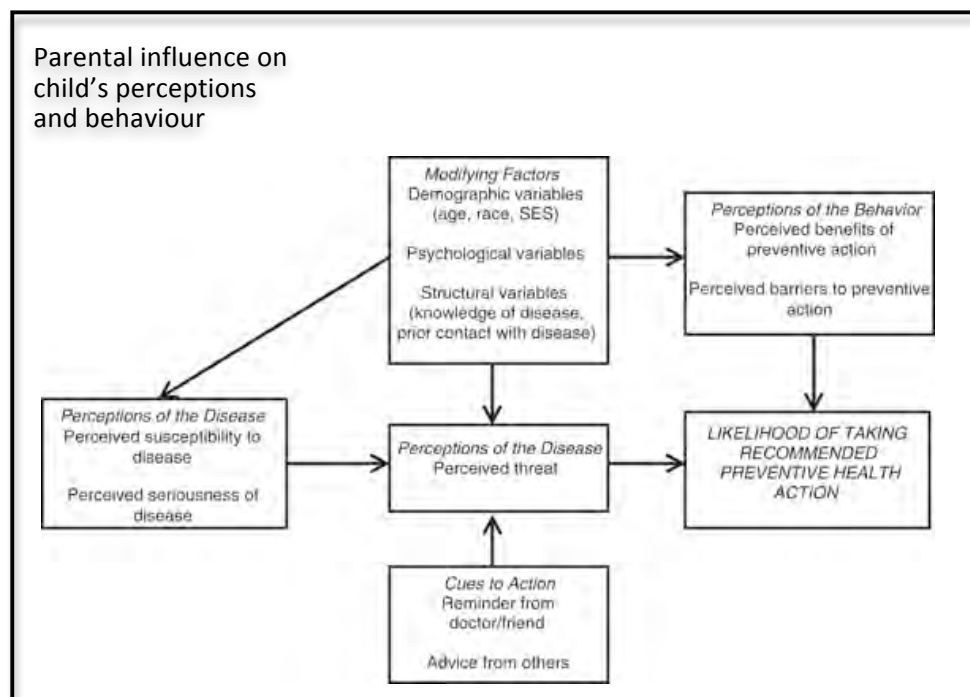
This is one of the most widely used theories of health behaviour, originally developed in the 1950's to provide a basis to explain why people did not take advantage of preventative health services. It was later extended to adherence to prescribed medical regimes from the 1970s (Rapoff, 1998; Rosenstock, 1974).

The HBM includes a series of variables to characterise adherence: The patients' perceived susceptibility to illness; The perceived severity of the consequences of

the illness; The perceived benefits of the prescribed treatment; The perceived barriers of adhering including a cost-benefit evaluation by the patient; Cues to action, which are internal (e.g. disease symptoms) or external stimuli (e.g. promotion of the treatment by others) that trigger action; Health motivation is the readiness of the individual to be concerned about health matters.

The HBM has been adapted for use with paediatric populations by Bush and Iannotti (1990) to create the Children's Health Belief Model (CHBM), see figure 1.1. The model includes similar dimensions to the HBM with the additional emphasis placed on the influence of the parent/carer on the child's behaviour.

Figure 1.1. The children's Health Belief Model, (adapted from Bush and Iannotti, 1990)



Despite the extensive use of the HBM model within literature and in the contribution this has made to future health related behaviour research, the HBM has received criticism due to its limitations in conceptual aspects. There have

been variations in the way HBM constructs have been conceptualized and measured. The model assumes an individual can be objective about health risks, where people tend to underestimate their own health risks. A patients' response to symptoms has a dynamic profile which the HBM is unlikely to address. Finally, the HBM fails to suggest strategies to alter health beliefs (Rapoff, 1998).

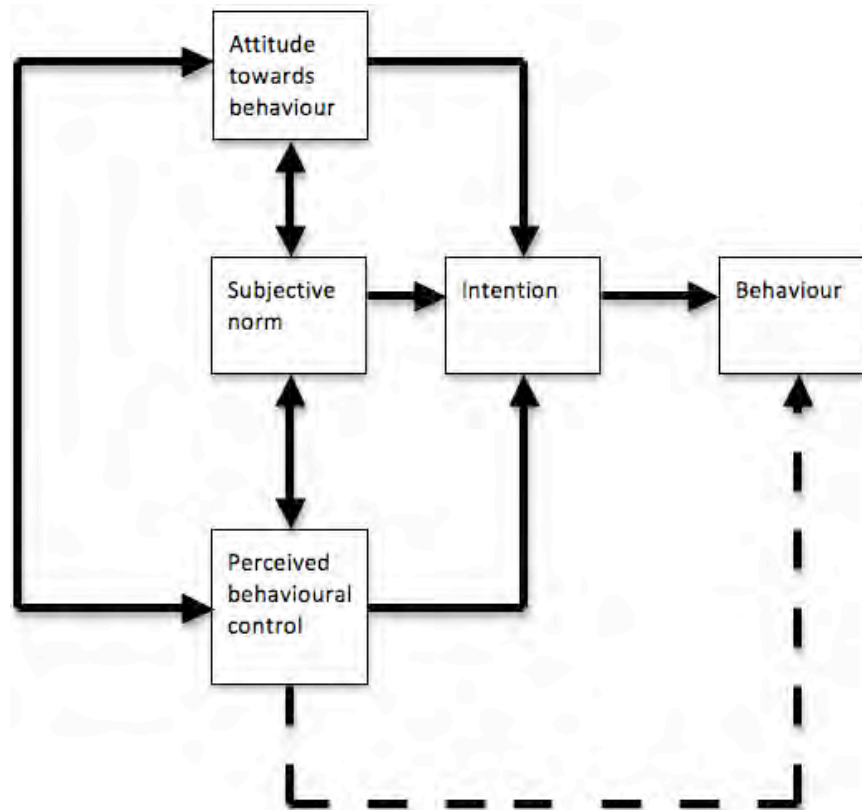
1.4.2. Theory of Reasoned Action (TRA) and Theory of Planned Behaviour (TPB)

The TRA was originally introduced in 1967 to help explain why measures of attitude were poor predictors of behaviour, and to improve the use of measures of attitude (Rapoff, 1998, Fishbein, 1967). Not specific to health, but widely used in this context, the TRA proposed that measures of one's attitude were more likely to predict behavioural outcomes when the attitudinal measures and outcome behaviours specify: the action or behaviour being performed; the target of the action; the context; the time frame. Therefore attitude is more likely to predict behaviours if the specificity of the measures of both attitude and behaviour match across the four elements. The main concepts of TRA are that the behaviours are predicted by intentions, which are determined by attitudes towards the behaviour and subjective norms concerning the behaviour. The attitudes are defined as the product of the beliefs regarding the likely outcome and the perceived value of the outcome.

Intentions are determined by three major factors: 1) Attitude towards the behaviour, 2) Subjective norms and 3) Perceived behavioural control and barriers. The subjective norms are defined as the person's beliefs regarding the views of the important people in the person's life regarding the behaviour and their motivation to support these views, to meet their expectations (Rapoff, 1998).

The perceived behavioural control and perceived barriers were the two key predictors added to the TRA to form the TPB (Ajzen, 1985), Figure 1.2.

Figure 1.2. TPB model (adapted from Ajzen, 1991)



Studies which have used TRA/TPB to predict health related behaviours, have concentrated on adults, in areas including exercise, mammography screening and condom use (Rapoff, 1998).

There is evidence from meta-analytical and systematic reviews that both the TRA and the TPB are superior to that of the HBM in predicting health-related behaviour (Godin et al., 2008). In addition the additional constructs within the TPB mean that it is able to predict a greater percentage of overall behavioural variance than the TRA.

The TPB and TRA have been used in studies with children. One such study was conducted by Stewart Trost and colleagues (Trost, Saunders and Ward, 2002). They evaluated the determinants of physical activity in middle school children in Australia using the TRA and TPB models to predict moderate to vigorous physical activity. Although the model demonstrated an acceptable fit, both the TRA and

TPB accounted for only a small percentage of variance in activity. They concluded that the TRA and TPB as a framework for physical activity interventions was limited in children, although the TPB, with its additional constructs, was a better predictor of intentions and physical activity.

1.4.3. Health Locus of Control (HLC)

The HLC was developed by Barbara Wallston and her colleagues in the late 1970s. The theory assumes that health related behaviours are a function of a person's belief or expectancy of the amount of control that they have over health events (Wallston et al., 1976). People may be divided into those who believe they have control over health events (internal locus of control) and those who believe that control resides outside of their sphere of control (external locus of control).

HLC measures people's expectancy beliefs along three general dimensions: 'internal', which characterises people who believe they are in control of their health behaviour; 'powerful others', which characterises people who believe the medically qualified people are in control of their health; and 'fate' types, who believe that health is a function of divine intervention, beyond the control of them or medical professionals.

The value of HLC in medication adherence research was reviewed by Fotheringham and Sawyer in 1995. They concluded that there is value in the HLC in medication adherence with both children and adults, whereby patients with internal HLC orientations show better adherence than those with external HLC orientations (Fotheringham and Sawyer 1995).

1.4.4. Self-Efficacy

The self-efficacy theory, or social cognitive theory is a theory of human behaviour originated by Albert Bandura, which is based on a 'person's perceived self-efficacy', which assumes a relationship between a person's belief in their

capability in carrying out a behaviour and the likelihood of that behaviour being achieved (Rapoff, 1998).

Self-efficacy has been demonstrated to be a predictor of health-related behaviour in adults in studies including breast screening, smoking cessation and physical exercise (Rapoff, 1998; Bandura, 1997).

Self-efficacy is acknowledged, even by the most vocal critics, as a useful and influential theory in psychology (Rapoff, 1998). Whilst not a health related study, Bandura's 2001 study demonstrates the value of the theory with children. Bandura conducted a study with 272 children to evaluate self-efficacy as shapers of children's aspirations and career trajectories. The study concluded that children's perceived efficacy rather than their actual academic achievement is the key determinant of their perceived occupational self-efficacy and preferred choice of career.

1.4.5. Attribution Theory

"Attribution theory deals with how the social perceiver uses information to arrive at causal explanations for events. It examines what information is gathered and how it is combined to form a causal judgment" (Fiske and Taylor, 1991). It explains how people explain their actions by searching for reasons to explain threats or changes as a means of controlling events.

Children have been shown to possess the ability to attribute, or explain events, although no studies within a health context were identified in the literature.

1.4.6. Summary of social cognition models

The social cognition models are limited in their ability to explain what may be considered irrational behaviour. The models are based on the assumption that the patients' behaviour is rational.

1.4.7. Illness cognition – The self regulatory model of illness behaviour

The self-regulatory model was developed by Howard and Elaine Leventhal, and Michael Diefenbach in the 1980s, as a means of understanding illness behaviour (Leventhal, Diefenbach and Leventhal, 1992). The model characterises the patient as an active participant in the process of achieving a goal or ideal health state, and reflects their attempt to 'close the gap' between their existing health state and their goal.

Leventhal's model incorporates three variables affecting the health behaviour following a health threat event: 1) *Cognitive representation* along the 5 key aspects of identity, cause, time-line, consequence and control; 2) *Coping procedure* or action planning stage; 3) *Appraisal* stage whereby the individual assesses success and adapts if necessary. There are emotional reactions along these phases, which can result at any stage, and which may provoke coping plans and appraisals.

Methodological limitations with the model have since been highlighted by Leventhal, with the lack of supporting data and lack of standardised measurement to enable comparison across studies (Leventhal and Cameron 1987). The development and validation of standardised questionnaires have since addressed the deficiencies, including the validation Beliefs and Behaviour questionnaire developed by George et al. (2006).

1.5. Non-adherence factors

Rapoff highlights three main areas of focus as correlates of adherence: patient/family factors, disease factors and regimen factors (Rapoff, 1998). Similarly, Mitchell and Selmes (2007) summarise the factors into patient factors, Illness factors and clinician factors. Rapoff and Mitchell both propose patient factors and Illness or disease factors, however for the third factor Mitchell places emphasis on the clinician's role within the drug regimen suggested by Rapoff.

Gardiner and Dvorkin (2006) propose a number of adherence factors, which may be addressed as improvement strategies in medication adherence in children, namely:

- using simplified drug regimens (e.g., once-daily dosing)
- pleasant-tasting medicines
- liquid or other non tablet formulations
- regular phone contact between parents and physicians
- reminders
- information counselling
- self-management plans, and other forms of individualized supervision or attention
- Physicians encouraging adherence by providing a clearly written explanation or patient information sheets detailing dosage, schedule, duration, common side effects and associated coping strategies
- Child participation in the design of the treatment plan

Furthermore, Costello, Wong and Nunn (2004) and Carter, Taylor and Levenson (2003) concluded that the provision of information, therapy management, parental monitoring and behaviour modification such as reward provision were found to be effective strategies in improving adherence.

The improvement strategies, which have been claimed within literature to positively enhance medication adherence in children, can be condensed into six key areas:

- i. Provision of Information
- ii. Practical aspects – reminders
- iii. Supervision/management plans – including child participation
- iv. Reward or behaviour modification
- v. Dosing or administration regime complexity
- vi. Medication specific factors

Items i and ii are considered under section 1.5.1., patient factors. Items iii, iv and v are discussed in section 1.5.3., regimen factors. Medication specific factors (vi) are discussed within a dedicated section 1.7., medication specific factors.

1.5.1 Patient factors

The patients' role in non-adherence may be intentional or non-intentional. Non-intentional non-adherence may result from all or a combination of:

misunderstanding instructions, due to lack of knowledge, information or ability to understand; external distractions; forgetting (Mitchell and Selmes, 2007; Lehane and McCarthy, 2007; George et al., 2006). The inability of the patient to access the medication, for example if they cannot open the packet, is a further non-intentional barrier to adherence.

Intentional non-adherence is the result of the patients' deliberate act and decision not to follow their treatment as instructed. Concerns about side effects, the stigma of taking medication, lack of perceived benefits, daily routine adjustment and concerns about cost, dependency and medication availability have been indicated as possible behavioural factors in intentional non-adherence (Mitchell and Selmes, 2007; George et al., 2006; Rapoff, 1998).

Refusal of medication on poor palatability grounds, whilst this may be considered justifiable, is intentional non-adherence.

Provision of information regarding the medication and the underlying condition, plays an important role in ensuring that patient, parent/carer's concerns regarding drug therapy effectiveness and side effects are clearly acknowledged and addressed. A patients' understanding of their condition, and the need for treatment is positively related to adherence. Adherence, satisfaction and understanding are, in turn related to the amount and type of information given. Studies have shown that patients who understand the purpose of their medication are twice as likely to routinely collect their prescription from pharmacy, than those who do not understand (Mitchell and Selmes, 2007; Daltroy, Katz and Morlino, 1991).

A lack of understanding of the importance of medication in assisting the treatment of the underlying condition can result in the inconsistent use of prescribed medication (Penza-Clyve, Mansell and McQuaid, 2004). Concerns regarding side effects of medication, and periods of symptomatic remission have been shown to result in the patient stopping their medication (Penza-Clyve, Mansell and McQuaid, 2004)

In addition to not wanting to take their medication, children sometimes exhibit non-intentional non-adherence by forgetting to take their medication (Penza-Clyve, Mansell and McQuaid, 2004; Cohn et al., 2003), in particular when they are out of routine. Practical reminders from parents or carers or alarm clocks or pagers have shown success, however, there is a fine line between positive support and encouragement and being seen to be 'nagging' as has been reported by some children in the Penza-Clyve study (Penza-Clyve, Mansell and McQuaid, 2004).

A systematic review of Hanghoj and Boisen (2014) identified similar patient factors. Hanghoj and Boisen evaluated "Self-reported barriers to medication adherence among chronically ill adolescents". They identified the five key themes of physical wellbeing, forgetting by coincidence, striving for normality, peer influence and parental influence across a number of chronic illnesses.

Reward/behaviour modification has reportedly had some success through the offer of rewards if the child takes the medication. (Costello, Wong and Nunn, 2004; Penza-Clyve, Mansell and McQuaid, 2004; Da Costa et al., 1997). Da Costa describes a token system, which involves the children earning points for taking their medications, exchanging points for privileges, and a loss of privileges for 1 day when they failed to take their medication. This mechanism was successful in Da Costa's study with children receiving Asthma medication.

The efficacy of behaviour management as an intervention to enhance medication adherence in children was identified in the systemic literature review of Dean, Walters and Hall (2010). They reviewed interventions to enhance medication adherence in children and adolescents with chronic illnesses. Their findings

suggest that educational interventions alone were insufficient to improve medication adherence in children, and that introduction of behavioural therapies were more likely to prove beneficial in promoting adherence.

1.5.2. Illness factors

The duration, symptoms and perceived severity of the underlying condition can be factors in adherence. Illnesses with a longer duration have been shown to be associated with lower medication adherence, and adherence has also been shown to deteriorate with time (Rapoff, 1998).

Periods of symptomatic remission can present a confusing scenario and has resulted in the cessation of medication, for example the stopping of daily, inhaled steroids when the child is feeling better in the hope that this will prevent the adverse effects of the medication (Gardiner and Dvorkin, 2006). Gardiner and Dvorkin's work has demonstrated the alignment between the presence of symptoms and medication adherence, however, increased illness, exacerbations and visits to the emergency department have been demonstrated in patients who are non-adherent to their treatment regimens (Cohn et al., 2003) and as stated by Rapoff, one could reasonably assume an increase in adherence in an attempt to alleviate symptoms in these severe cases (Rapoff, 1998).

Adherence has been shown to be significantly positively correlated with a patients' beliefs in the severity of the disease to be treated. Di Matteo, Haskard and Williams' (2007) meta-analysis, comprising 116 studies, showed higher adherence with increasing disease conditions for patients with less serious illnesses. For patients with more serious conditions, worse adherence is associated with poorer health (evaluated objectively). A similar pattern was shown to exist when health status is rated by patients themselves, and by parents in paediatric samples (Di Matteo, Haskard and Williams, 2007).

The results suggested that the objective severity of patients' disease conditions, and their awareness of this severity, provides information to predict their

adherence. Patients who are most severely ill with serious diseases may be at greatest risk for non-adherence to treatment (DiMatteo, Haskard and Williams, 2007).

1.5.3. Regimen factors

In general, a simpler and less intrusive regime is more easily understood, reduces confusion, and should facilitate adherence. Children have reported medication annoyances in relation to their medication regime (Penza-Clyve, Mansell and McQuaid, 2004) namely: Children complained about feeling tied down to their medication schedule and reported being woken in the night to take their medication, making them 'hyper' and presenting a subsequent problem in getting back off to sleep.

Implementation of a sustainable and effective treatment programme is essential. It is important that the physician, patient and parent/carer jointly devise a management plan with which each is confident of clinical outcome and adherence.

Buchanan et al. (2012) studied barriers to medication adherence in HIV-infected children. Based on reporting from the children and caregivers, they identified lack of agreement contributing to more than half of the studied barriers, indicating discrepancies between children's and caregivers' perceptions of factors that influence medication-taking. The findings suggest a need for interventions that involve both child and caregiver in the tasks of remembering when to administer the child's medications, sustaining adherence, and appropriately transitioning medication responsibility to the youth or older child.

A number of studies cite the importance of family involvement in allocating adequate time, resources and practical arrangements in enabling medical appointment attendance and dietary and medication adherence (James, 2008; Fiese and Everhart, 2006; Colland et al., 2004; Costello, Wong and Nunn, 2004; Cohn et al., 2003).

1.6. Measuring medication adherence

There are a number of methods for measuring medication adherence, which involve either direct or indirect measurement, or estimation.

1.6.1. Direct methods

1.6.1.1. Drug assays

Drug assay methods involve the analysis of a sample of a patient's bodily fluid (serum, urine and saliva) for the presence of the active drug, drug metabolite or pharmacological marker (inert substances added to some medicines to facilitate detection in bodily fluids).

Knowledge of the clinical pharmacokinetics of the medication being analysed is required in order to accurately interpret the assay results to avoid inaccuracies. The absorption, distribution, metabolism and excretion of the active drug, metabolite and pharmacological marker must be understood to enable accurate calculation.

Drug assays are quantifiable methods, which provide direct data on medication adherence. There are certain disadvantages with this approach, which can include the invasive nature of taking body fluid samples from patients who, in the case of children, may not wish to be subjected to what is seen as an unnecessarily painful procedure (Rapoff, 1998). There are also ethical requirements of notifying patients of the reason for sampling and analysis and gaining consent. In gaining permission through the informed consent process there is the potential for reactivity bias to occur, whereby patients may alter their behaviour to achieve better results (Hawkshead and Krousel-Wood, 2007).

1.6.1.2. Direct observation

Direct observation involves the observation of the patient's medication-taking behaviour by the researcher. This form of measurement is limited by the practical ability of the researcher or clinician to access the patient at each dosing

event. This method is rare (Rapoff and Barnard, 1991) and most commonly used as an adherence improvement technique or means of assessing a patient's technique, skills or ability to follow the process necessary for adherence, rather than an objective method of assessing adherence due to reactivity bias (Rapoff, 1998), whereby the individual alters their behaviour as they know their performance is being assessed.

1.6.2. Indirect methods

1.6.2.1. Pill counts

Pill counts are a straightforward, inexpensive method of assessing adherence, calculated as the difference between the number of dosage units dispensed, and the number remaining in the container on the subsequent count during a scheduled or unannounced visit to the patient. The method is reliant upon the dose removed having been ingested and not discarded or "dumped". Studies have been conducted to evaluate the reliability of pill counts and have concluded that this method most often overestimates adherence (Rapoff, 1998), and some have recommended that investigators cease using this method as a measure of adherence (Bond and Hussar, 1991). However, there is value in the uncomplicated nature of the methodology and the ability to compare adherence across a wide range of medication regimens and patient samples.

1.6.2.2. Pharmacy prescription refill (repeat dispensing)

Pharmacy prescription refill, also known as repeat dispensing, is a methodology, which evaluates the patient's replenishment of their medication through a pharmacy, by comparing the frequency and timing with which a patient presents a prescription for refill, with the expected frequency and timing if they were taking the medicine in accordance with the dosing instructions.

The methodology requires the patient to consistently receiving the medication being studied, from the same pharmacy. If the patient refills their medication being measured from multiple sources, this method is practically limited unless all of the pharmacies used by the patient are known, and can be monitored.

With the increasing use of computerised pharmacy medication systems, the access to significant quantities of prescription refill data, prescription refill is being increasingly used as a source of adherence information (Vink et al., 2009; Steiner and Prochazka, 1997).

1.6.2.3. Electronic monitors

This methodology involves the integration of electronic devices into the medicine container, which records the date and time of container opening or dose dispensing from the container.

Several products are available to monitor different dosage forms including the Medication Event Monitoring System (MEMS) of the Aprex Corporation, USA. The cap device is a child resistant cap, which fits to the neck of a standard pill bottle and monitors removal and replacement of the cap.

Electronic monitor methodology has limitations similar to pill counts, in that electronic medication monitoring devices cannot assure that a dose that was removed was actually consumed or administered correctly. In addition to no medication taken when the container is opened, errors may be introduced when a patient removes multiple doses during one opening and only one event is recorded for the multiple doses taken (Samet et al., 2001). Despite the limitations, electronically measured adherence has been more highly associated with clinical outcomes than self-report (Liu et al., 2001) and pill counts (Namkoong et al., 1999).

The technology may be limited for larger studies with a standard bottle cap costing between £5 and £30 per unit, and the electronic data reader from £200, dependent upon the technology provider.

1.6.2.4. Provider estimates

Provider estimates generally involve global ratings by clinicians of the extent to which their patients are adherent to a particular medication regime. Such ratings are inexpensive and simple to administer. Clinician estimates are not accurate, however there is some evidence to suggest they are more accurate than estimates of patient or parental self-report (Rapoff and Christophersen, 1982).

1.6.2.5. Patient or parental self-report

Patient or parent/carer self-reporting is a commonly used, simple, relatively non-intrusive and inexpensive method of studying medication-taking behaviour (Fialko et al., 2008; Rapoff, 1998).

Methods of patient self-reporting include: Structured patient interviews; Patient Diaries; validated, adherence specific questionnaires incorporating global rating scales (Rapoff, 1998).

Patient interviews have the benefit of enabling the interviewer to offer explanation to the patient, or explore the responses in further depth. The accuracy of the data or information derived from the interview can be affected by the skills of the interviewer, which means the method is prone to interviewer bias (Fialko et al., 2008; Rapoff, 1998).

Medication adherence scales or questionnaires are an inexpensive means of identifying medication non-adherence in clinical practice. There are a number of validated tools described in the literature, however, as Lavsa, Holzworth and Ansani (2011) state in their paper entitled "Selection of a validated scale for measuring adherence", no gold standard exists, and no single medication adherence scale is universally applicable.

According to Lavsa, Ansani and Holzworth (2011), the key criteria to be considered in selecting an adherence scale include: validation in the target population; length and time of administration; Internal consistency; ability to detect barriers to adherence; ability to detect self-efficacy; sensitivity; specificity.

The six main medication adherence scales are: The Medication Adherence Questionnaire (MAQ); The Self-Efficacy for Appropriate Medication Use Scale (SEAMS); The Brief Medication Questionnaire (BMQ); The Hill-Bone Compliance Scale; The Medication Adherence Rating Scale (MARS); The Beliefs and Behaviour Questionnaire (BBQ).

1.6.2.5.1. The Medication Adherence Questionnaire (MAQ)

The MAQ was the first published medication adherence scale. It was developed and published by Morisky, Green and Levine (1986).

The MAQ scale is based on the belief that medication non-adherence can occur when patients forget, are careless, stop taking their medication when feeling better, or stop taking their medication when feeling worse. The questions is structured to take account of patients' general desire to answer "yes" when asked questions, whereby answering yes identifies non-adherent behaviours.

The scale was originally validated by Morisky, Green and Levine (1986), in patients with hypertension. It has since been validated in patients with dyslipidemia, human immunodeficiency virus infection, Parkinson's disease, depression, type 2 diabetes, heart failure, and coronary artery disease.

The main advantages of the MAQ are the simplicity of questions and the ease of scoring. The original 1986 MAQ was a 4-item questionnaire, and more recently an 8-item self-reported scale has been developed (Morisky et al. 2008), which is currently only validated in patients with hypertension. Each yes answer receives 1 point and the total is added. The predictive value of the scale is higher for those scoring high compared (indicative of non-adherent behaviour), with low medication adherence. A disadvantage of MAQ is that it does not assess patient self-efficacy.

Overall, MAQ is a simple scale to administer and score and is validated in many populations, making it a good tool to assess adherence across patient populations at the point of care.

1.6.2.5.2. The Self-Efficacy for Appropriate Medication Use Scale (SEAMS)

The psychological theory of self-efficacy, described in section 1.4.4. is based on a person's perceived self-efficacy, which assumes a relationship between a person's belief in their capability in carrying out a behaviour and the likelihood of that behaviour being achieved.

Risser, Jacobson and Kripalani (2007) found self-efficacy to be an important predictor of medication adherence, and based on this concept developed SEAMS to incorporate the measurement of self-efficacy in evaluating medication adherence.

SEAMS was originally developed as a 21-item scale that was reduced to 13 items. Each item is assessed using a three-point Likert-type scale (1, not confident; 2, somewhat confident; and 3, very confident). SEAMS has been validated in patients with chronic disease including coronary heart disease and related conditions such as hypertension, hypercholesterolemia, and diabetes.

Overall, SEAMS is constructed to measure self-efficacy barriers to adherence, and allow responses via a three-point response scale, it is somewhat limited by its inability to quickly score at the point of care. SEAMS is useful in a medication management clinic setting dedicated to focusing on medication adherence, where time is available for administering, scoring, and reviewing the survey with patients (Lavsa, Ansani and Holzworth, 2011).

1.6.2.5.3. The Brief Medication Questionnaire (BMQ)

BMQ was constructed by Svarstad et al. (1999), with the aim of creating a tool that is quick to administer, sensitive, and able to detect different types of non-adherence.

The scale consists of a five-item regimen screen to detect repeat and sporadic non-adherence, a two-item belief screen to assess beliefs about drug efficacy and troublesome effects, and a two-item recall screen to identify difficulties in remembering medication-taking. BMQ was initially validated in patients prescribed the angiotensin-converting-enzyme inhibitors (ACEi) enalapril or captopril, but has also been used for patients with diabetes, depression, and other chronic diseases (Lavsa, Ansani and Holzworth, 2011). The instrument makes improvements in the sensitivity and specificity beyond that of existing adherence scales, and allows assessment of barriers to adherence.

Although the instrument assesses three important aspects (regimen, beliefs, and recall) accurately, scoring at the point of care is difficult. In addition, BMQ requires specific medication regimens to be listed by the patient and assumes this list is comprehensive. As with the SEAMS instrument, the scale may also be useful in a clinic setting with dedicated time to review medication lists and medication adherence.

1.6.2.5.4. The Hill-Bone Compliance Scale

The Hill-Bone Compliance Scale was developed by Kim, Bone and Levine (2000) to provide a simple method for health care professionals to determine patient-reported compliance levels.

It was originally validated in an urban black population, however it was later assessed in broader community based patients attending an internal medicine clinic (Krousel-Wood et al., 2005).

The scale contains 14 items in three subscales that assess medication adherence, sodium intake, and appointment attendance. Each item is scored on a four-point Likert-type scale.

The Hill-Bone Compliance Scale determines barriers to non-adherence such as forgetfulness and adverse effects, making it similar to the MAQ. However, the nine adherence questions of the Hill-Bone Compliance Scale are worded specifically in regard to high blood pressure medications. Additionally, two questions pertain to keeping appointments and three questions pertain to sodium intake, thus limiting the ability to generalise across patient populations.

Overall, the scale is useful in cardiovascular practice or cardiovascular clinic setting, and the medication adherence subscale has also been validated in patients with inflammatory bowel disease.

1.6.2.5.5. The Medication Adherence Rating Scale (MARS)

MARS was created by Thompson, Kulkarni and Sergejew (2000), for assessment of adherence in psychiatric patients. The scale includes 10 items and has been validated in patients with schizophrenia and schizoaffective disorder, or patients who are delusional (Fialko et al., 2008). The scale has also been used in patients with bipolar disorder.

Development of MARS built upon questions from MAQ and another commonly used psychiatric adherence survey, 'Depression Item Access', validated in schizophrenia (Lavsa, Ansani and Holzworth, 2011).

MARS examines adherence behaviours and attitudes toward medication with relatively simplistic scoring. However, it is limited in application to chronic mental illness. MARS is useful in psychiatric practices or psychiatric clinic settings.

1.6.2.5.6. The Beliefs and Behaviour Questionnaire (BBQ)

George et al. have developed and validated the BBQ (George et al. 2006). The questionnaire is based upon the Becker and Maiman HBM, developed in the 1970's as an expansion of the work of Kasl and Cobb (1966) who looked at the HBM's variables to sick-role behaviour (Becker and Maiman, 1975; Becker, Drachman and Kirscht, 1974).

In the original HBM, fear of the severity of illness and negative attributions associated with the course of action was the focus. People sought health prevention because they did not want to get sick. Becker et al. (1974) propose that positive aspects can draw people to better health choices. For example, people may seek preventive health care because they perceive it will make them feel better. This counters HBM's position that people seek preventive health care to avoid negative consequences (Rosenstock, 1966). In the first example they move toward comfort. In the second they move away from discomfort (Becker, Drachman and Kirscht, 1974; Becker and Maiman, 1975).

The questionnaire was validated to screen for non-adherence in adults with chronic ailments. It is a 30 item beliefs and behaviour questionnaire, which measures the beliefs, experiences and adherent behaviour, on a series of five-point Likert-type scales. A Likert scale is a commonly used scale in questionnaire based research, developed by Likert in 1932 (McLeod, 2008). In its final form, the Likert scale allows the individual to express how much they agree or disagree with a particular statement e.g. Strongly agree, agree, don't know, disagree, strongly agree.

1.6.2.5.7. Use of medication adherence scales in children

Each of the medication adherence scales described in 1.6.2.5., have been developed and validated within the adult population. None of the scales have yet been validated for use in children.

Given the emphasis of the rating scales on self-efficacy and control over medication taking events, the use of the medication adherence scales may be limited with younger children who are generally more subjected to parental influence and control. Logically, the instruments should be applicable in older children, however this would require validation. As discussed within section 1.4.3 “Health Locus of Control”, there is value in the HLC in medication adherence with children, whereby patients with internal HLC orientations (exhibiting internal control) show better adherence than those with external HLC (control resides with ‘others’) orientations (Fotheringham and Sawyer 1995). The medication adherence scales may be applicable where children possess internal HLC orientations.

Given the importance of adherence to treatment in childhood chronic illness for effective clinical care, there is a clear need to develop effective and valid instruments for the measurement of adherence in children.

1.7. Medication specific factors

There are a range of medication-specific factors, including the organoleptic properties of taste and palatability, and the nature of the delivery system, which have been shown to affect medication adherence (Squires et al., 2013; Hames et al., 2008; Cheng and Ratnapalan, 2007; Pieroni and Torry, 2007; Matsui, 2007; Steele, Russo and Thomas, 2006; Holland 2006; Martinez, 2006; Holas et al., 2005; Britten et al., 2004; Colland et al., 2004; Penza-Clyve, Mansell and McQuaid, 2004; Cohn et al., 2003; Quittner, 2000; Angelilli et.al., 2000; Hutto and Bratton, 1999; Nahata, 1999).

The Organoleptic properties of a medicine include taste, touch/mouth feel, smell, appearance and sound. Furthermore, the taste modality can be further classified as sweet, salty, sour, bitter, and more recently a fifth form, Umami (Matsui, 2007). Umami is a Japanese word meaning savoury, a "deliciousness" factor deriving specifically from detection of the natural amino acid, glutamic

acid, or glutamates common in meats, cheese, broth, stock, and other protein-heavy foods.

1.7.1. Assessment of taste and how this affects medication adherence in children

The Collins English Dictionary (1992) defines 'taste' as the sense by which the qualities and flavour of a substance are distinguished by the taste buds. 'Taste bud' being defined as any of the sensory organs on the surface of the tongue, by means of which the sensation of taste is experienced. 'Palatable' is defined as pleasant, acceptable or satisfactory. The commonly held definition of taste as defined in Collins (1992) is misleading. Flavour results from an inter-play of the sensations of taste via the taste buds of the mouth, smell/aroma via the olfactory nerves and tactile sensations. Taste alone does not constitute flavour.

Children's responses to certain tastes can differ markedly to those of adults as described by Baber (2005). The sense of smell in neonates in particular is very different than in adults. Minna Huotilainen (2003) explains that the developing foetus is exposed, via the amniotic fluid, to a rich array of fragrances typical to the mother's diet throughout pregnancy. It has been shown that neonates express preference to these tastes and can even differentiate human breast milk distinct from cow's milk, and furthermore the neonate can recognise milk from his/her own mother compared to breast milk from mothers who gave birth on the same day.

From birth the child is exposed to further influences, which will shape their taste preferences. Holland (2006) describes the concept of representation-mediated potentiation of odour and flavour aversion, whereby aversion to a particular smell is greater when the smell plus flavour are paired with a particular event like illness. Similar associative experience-based learning may go some way to explaining flavour and smell preferences

The senses of taste and smell evolved to help humans reject harmful foods and seek beneficial and pleasurable foods (Birch and Dietz, 2008). Infants and children have been reported to have a preference for sweet-tasting substances (Matsui, 2007; Southall and Schwartz, 2007), which decreases during late adolescence to resemble that of adults. It is suggested that this heightened preference for sweet tasting substances, which is evident globally, evolved to attract them to high-energy-foods during maximal growth (Birch and Dietz, 2008).

The child has been shown to have an aversion to bitter taste, which appears from an early age (Mennella et al. 2013), which is likely to manifest in decreased acceptance and palatability (Squires et al., 2013; Matsui, 2007). This aversion response probably evolved to protect the child from ingesting poisons (Birch and Dietz 2008). Indeed bittering agents like Denatonium Benzoate, trademark Bitrex® from the company MacFarlan Smith is used as a human aversive. Due to its overwhelming bitter taste, it helps to prevent accidental poisonings of toxic household products (Sibert and Frude, 1991). The study observed the responses of young children to Denatonium Benzoate (Bitrex) in order to assess the potential of this bittering agent in the prevention of accidental poisoning. Thirty-three children aged 17-36 months were offered orange juice containing Bitrex (in a concentration of 10 parts per million). Of the 30 children who took some of this juice, only seven were willing to take more than 10 grammes. The highly unpalatable nature of Bitrex has been used in commercial products as a measure to limit accidental poisoning of toxic substances.

In addition to the changes in taste preferences observed during the development of the child from birth through adolescence to adulthood, some inherited differences have been reported in the literature. Mennella, Pepino and Reed (2005) demonstrated that genotypic differences in the taste gene TAS2R38 was associated with the sensitivity of children to the bitter tasting propylthiouracil (PROP) and sucrose preferences.

Multi-cultural differences in experience-based taste learning and its impact on taste perceptions and associations with medicinal value are explored by Pieroni and Torry (2007). They evaluated the taste perceptions of five commonly used herbal remedies, namely mint, garlic, ginger, cinnamon and cloves among the Gujarati, Kashmiri and English ethnic groups.

The main cross-cultural differences in taste perceptions regarded the perception of the spicy taste of ginger, garlic, and cinnamon, of the bitter taste of ginger, the sweet taste of mint, and of the sour taste of garlic. Among Kashmiris, ginger was frequently considered to be helpful for healing infections and muscular-skeletal and digestive disorders, mint was chosen for healing digestive and respiratory troubles, garlic for blood system disorders, and cinnamon was perceived to be efficacious for infectious diseases. Among the Gujarati and Kashmiri groups there was evidence of a strong link between the bitter and spicy tastes of ginger, garlic, cloves, and cinnamon and their perceived medicinal properties, whereas there was a far less obvious link between the sweet taste of mint and cinnamon and their perceived medicinal properties, although the link did exist among some members of the Gujarati group. Within the autochthonous English group there was no clear link between taste and the medicinal properties of the remedies observed. The study showed that links between taste perceptions and the medicinal uses of herbal remedies may be understood through individual experiences and cultural background, which may shape the perception of the taste and flavour of a substance.

Some studies cite palatability as an important factor in influencing medication adherence in children (Squires et al., 2013; Ernest et al., 2007; Matsui, 2007; Costello, Wong and Nunn, 2004), and although this is widely accepted, the idea lacks broad empirical confirmation, with formal studies limited in scope. A common belief that has pervaded medication adherence research for many years is that if you make a medicine sweet and 'pleasant-tasting', a child is more likely to accept taking the medicine and hence more likely to take it, and therefore adhere to the medication regime. However, as Squires et al. (2013) point out in their systematic literature review on palatability of oral dosage forms in children,

“there is a limited evidence base regarding the correlation between palatability of oral dosage forms and treatment adherence in paediatric patients”.

A review of the palatability studies reported in the literature are summarised in table 1.1.

Table 1.1. Studies assessing the palatability of medicines in the paediatric population [Adapted from Matsui, 2007]

Medications	Age (yrs)	Results
2 pivampicillin mixtures	1-7 (clinical condition)	Taste more improved with banana than cocoa-peppermint
2 penicillin formulations	3-10 (clinical condition)	No difference in taste scores between 2 suspensions
Azithromycin vs one of 5 alternate antibiotics	4-12 (healthy)	Taste rating for azithromycin higher than other medications
Brand and generic antibiotic susp.	3-14 (clinical condition)	Brand names didn't necessarily taste better than generic
4 antistaph. antibiotics	6-12 (healthy)	Cloxacillin taste scores lowest
4 antibiotics effective against β lactamase-producing bacteria	4-9 (healthy)	Taste score of azithromycin highest
11 antimicrobial suspensions used for treatment of otitis media	Adult Physicians and children	14 of 16 children ranked 3 antibiotics in same order as adults
Azithromycin, cefprozil, cefixime, amox./ clavulanate	5-9 (healthy)	Palatability score for cefixime higher than other three
4 antibiotics effective against β lactamase-producing bacteria	5-8 (healthy)	More children selected cefixime as best-tasting
Pooled analysis of seven trials of antibiotic susps.	4-8 (healthy)	Taste acceptance of cefdinir higher than that of comparator
2 flavours of ondansetron syrup	3-12 (chemotherapy)	Preference for strawberry formulation
Activated charcoal with flavouring agents (2 studies)	3-17 (healthy) 5-9 (healthy)	Chocolate milk, Coca-Cola or Cherry syrup improved taste
Lansoprasole delayed release oral susp vs ranitidine effervescent tabs	5-11 (healthy)	More children preferred taste of strawberry flavoured lansoprazole
Ranitidine syrup vs Ranitidine effervescent tablets	4-8 (healthy), and parents	Children preferred taste of effervescent tablets
2 prednisolone preparations	2-10 with acute asthma	Better taste for Orapred than generic prednisolone
Dexamethasone vs Prednisolone oral liquid	5-12 with acute asthma	Taste of Dexamethasone preferred to prednisolone
Powders of Candesartan cilexetil, irbesartan	4-11 (Nephropathic)	Taste of Candesartan cilexetil scored significantly higher

These studies have assessed, in the form of a 'taste panel', the taste and palatability, and rated in a practical setting, children's preferences for one product over another. Whilst the taste panel is a practical approach, it is limited to only being able to assess preference from a defined group of choices, and is limited by what is available rather than asking the questions which will lead to the determination of root cause and actions to prevent recurrence of the medication non-adherence. The solution to the problem might not currently be available, but could be considered as an area for development by the pharmaceutical industry.

Antibiotics are the most frequently studied class of medicines in terms of palatability and taste within the paediatric population. Baguley et al. (2012) reviewed the effect of taste and palatability of antibiotics on medication adherence in children. The review identified studies from Japan, Saudi Arabia and Israel, where taste was a stated barrier by parents in achieving medication adherence with their child. However, the focus of studies published to date has centred on the evaluation of which medicine(s) within a particular therapeutic class of medicines, taste best or are most palatable, or which masking techniques for a particular medicine result in higher taste or palatability ratings amongst children.

Given the potentially significant role of taste in adherence, in depth studies are essential in pharmaceutical product development, balanced with the regulatory requirements for child-resistant packaging which include ensuring children are not unnecessarily attracted to the medicine.

1.7.1.1. Formulation approaches to address taste and palatability

Taste masking of bitter or unpleasant tasting drugs presented as liquid oral formulations may be achieved through the addition of flavours and sweeteners and by way of technologies which coat the active ingredient with hydrophilic agents e.g. microencapsulation. Furthermore, flavour enhancement to not only

mask taste but enhance flavour is an approach which may facilitate the willing participation of the child in medication adherence.

The US company FLAVORx (www.flavorx.com) manufacture, according to their website (accessed in April 2008), flavouring agents, 'bitterness suppressors' and sweetening agents which it is claimed may be added to medicines to improve taste and palatability. The company claim that flavouring medicine increases patient adherence to over 90%, from an average of 50%. It is also claimed that over 500 studies have demonstrated the safety of the products. A literature search failed to reveal published material supporting the claims made, however 2 studies were found (Bunupuradah et al., 2006; Steele, Russo and Thomas, 2006) which used FLAVORx taste flavouring agents. Bunuparadah, Wannachai et al. (2006) studied the use of FLAVORx to taste mask antiretroviral medication and the effects on medication adherence in children. The study found that in 80% of children in the study, FLAVORx helped them to 'take the medication with greater ease' than without, however FLAVORx did not affect adherence as full adherence was reported in all children despite the problem of bitter taste. In the study by Steele, Russo et al. (2006), antimicrobial suspensions to treat staphylococcal infections and oral thrush were studied and ranked in order of preference for taste. The study did not quantify adherence.

The concept of taste masking with sweeteners and flavours and the addition of colouring agents and other excipients to aid formulation may enhance palatability of paediatric medicines, but may cause adverse effects (Ernest et al., 2007) so caution must be observed.

Formulation excipients are substances, which are added to a pharmaceutical preparation, to enhance palatability, appearance and stability. Antioxidants and antimicrobial preservatives in particular are used to extend the shelf life of medicines by respectively retarding the oxidation of active substances and excipients, and reducing microbial proliferation. The properties of these substances result in them being toxic towards living cells and may be toxic when

used in humans. The CPMP note for guidance (CPMP/QWP/419/03), states that where it is not necessary to add these substances they must be avoided.

The ethylene glycol tragedy in 1937 demonstrated the significant adverse effects of what was initially considered a harmless formulation agent, when 107 patients, which included children, died as a result of ethylene glycol poisoning, a constituent of sulphanilamide elixir (Ernest et al., 2007).

Table 1.2 provides some examples of potential risks associated with frequently used pharmaceutical excipients (Ernest et al., 2007).

Table 1.2. Potential risks associated with frequently used pharmaceutical excipients (Lyseng-Williamson, 2003)

Excipient	Function	Potential risk/adverse effect
Alcohol (ethanol)	Solubility enhancement	Idiosyncratic reactions, Disulfiram-like reactions
Aspartame	Sweetener	Hyperactivity
Benzyl alcohol	Antimicrobial preservative	Toxicity
Calcium salts	Non-hygroscopic diluent	May affect bioavailability of active ingredient. Contraindicated in patients with nephrocalcinosis and certain metabolic conditions
Carrageenan	Suspending agent	Induces inflammatory responses
Cellulose	Suspending agent and lubricant	Laxative in large amounts
Citric acid	Effervescent salt	Tooth erosion
Dextrose	Diluent, Sweetner	Hyperglycaemia, dental caries
Diethylene glycol	Vehicle	Poisoning
Docosate sodium	Wetting agent	Diarrhoea
Glycerol	Solvent, Sweetner	40% concentrations may cause mucositis in stomach and diarrhoea and electrolyte disturbance
Lactose	Diluent, Sweetner	Gastrointestinal symptoms in patients with lactate deficiency. Developmental delay, hepatic failure and cataracts with galactosaemia
Propylene glycol	Solvent and antimicrobial agent	CNS adverse events – neurological toxicity
Starch	Binder, Diluent, disintegrant	Moist starch allows microbial growth
Sucrose	Sweetner	Hyperglycaemia, dental caries
Tartrazine	Colorant	Hyperactivity
Thiomersal	Antimicrobial preservative	Toxic (mercurial)

Some safety data on common excipients has since been generated, and new excipients require non-clinical safety testing prior to use in human subjects. There are however limitations with the data and its direct applicability to the paediatric population. The maximum doses of excipients which may be tolerated has mainly been determined for adults and not within the paediatric population. The safety profile of some excipients across the heterogeneous paediatric population may differ somewhat.

The paradigm that oral liquids are the most suitable oral dosage form for children and that medication adherence correlates with improved taste or palatability of medicines appears to exist. The logical conclusion is that the ideal oral dose form, to aid adherence in children, is a nice-tasting oral liquid. However, this lacks scientific rigor and particularly bitter or unpleasant tasting medicines may be difficult to taste-mask in solution. Alternative dose forms for example a tablet or capsule, which enable easier taste masking, may offer a more appropriate delivery system in older children. However, developing an oral age-appropriate formulation for the younger child, in particular babies, remains a challenge, which may not be easily addressed with classical solid dose forms due to the hazard of choking. Additionally the classical tablet or capsule presents limitations with children due to the inability to offer dose flexibility. However, multiple unit dose preparations, such as mini tablets (≤ 3 mm diameter), offer flexibility to vary dosing of a solid dose form. The units are marketed in a multiple-dose container together with a measuring device or as single doses contained within a capsule or tablet (Rose, 2005). Variations in bioavailability are minimised and onset of drug action is accelerated as small-sized units can pass the pylorus in the fasted and full state of the stomach. There are some limitations in use within the paediatric population due to variations in gastrointestinal tract pH and transit times with age (Rose, 2005).

The age children can safely take tablets or capsules, such that inadvertent inhalation and choking are avoided, is of great importance for two key reasons. Firstly, to facilitate patient medication adherence, and secondly the solid oral

dose form is generally cheaper to develop, manufacture, store and transport. There is limited information in the literature, however, feedback from clinical staff at Alder Hey Children's hospital, Liverpool, indicates that traditional tablets may be accepted by children of school age, although this will depend on the size and shape of the tablet and patient factors such as the taste of liquid medicine alternatives. Recent advances in pharmaceutical technology have resulted in the development of many different types of tablets such as melts, chewable and oro-dispersible tablets, mini-tablets and it is technically possible that appropriate tablet formulations could be made available for children of most ages, however it would have a cost implication (Nunn and Williams, 2005).

1.7.2. Assessment of the smell/aroma of a medication and how this affects medication adherence in children

The Collins English Dictionary (1992) defines 'smell': to perceive the scent of (a substance) by means of the olfactory nerves. 'Aroma' is defined as a distinctive and usually pleasant smell.

The taste receptors located in the oral cavity and the olfactory nerves, located high in the nasal chambers, probe the environment and convert the chemicals that are detected into specific patterns of neuronal activity (Birch and Dietz, 2008). Under normal conditions, the consumption of foods or liquids results in the simultaneous perception of smell/aroma and taste which, together with tactile sensations, contribute to the overall flavour of the substance (Noble, 1996). Whilst there are only a small number of primary taste qualities, namely sweet, salty, bitter, sour and savoury/umami (Matsui, 2007), the sensations of smell encompass thousands of diverse perceptions (Birch and Dietz, 2008).

There are two routes by which aroma reaches the olfactory receptors, namely; by inhalation via the orthonasal route and by passing from the oral cavity via the nasal pharynx which is known as the retronasal route. The retronasal route is predominant in the flavour sensations experienced during eating (Birch and

Dietz, 2008). Tastes can increase the apparent intensity of aromas; conversely, the perceived intensity of tastes is increased when flavoured solutions are tasted, especially when there is a logical association between them, such as between sweetness and fruitiness (Noble, 1996).

Therefore, for the purposes of evaluating the impact of the smell or aroma of a medicine and its impact on medication adherence, it is therefore important to consider smell alongside taste and tactile sensations of the mouth, and the affect on flavour.

Studies presented in literature (table 1.1) have considered the overall 'palatability' of the medicine, which incorporates taste, smell and tactile sensations of the mouth. However, as described, it is important that the interaction of each element, which constitutes flavour, is considered.

1.7.3. Assessment of the mouth feel (oral sensation) of a medication and how this affects medication adherence in children

The Collins English Dictionary (1992) defines 'touch' as the sense by which the texture and other qualities of objects can be experienced when they come into contact with a part of the body surface. The tactile sensations brought about by substances within the mouth can have a bearing on flavour and palatability of a food or medicine, combined with the sensations of smell and taste. For example, the palatability of activated charcoal, used as a first-line therapeutic intervention for paediatric poisonings, is problematic (Cheng and Ratnapalan 2007). It forms a thick gritty slurry that must be swallowed or administered enterally via a nasogastric tube. Children often refuse to drink activated charcoal hence the use on occasions of the invasive and aversive nasogastric tube with potential complications. Some success has been achieved with the addition of flavouring agents, however, the palatability remains a problem due to the tactile sensations of the gritty slurry.

There are additional aspects to be considered such as the sensation brought about by the swallowing of a tablet, which may impact the acceptability and adherence of the child to a medication.

1.7.4. Assessment of the appearance of a medication and how this affects medication adherence in children

The Collins English Dictionary (1992) defines appearance as ‘the outward aspect of a person or thing’.

The appearance of the medication, for example the potential association between colour and flavour may play a role although the effect of colour on taste preference has not been particularly well-studied. However, one study which was performed looking at the role of colour cues and people’s beliefs about colour-flavour associations (Levitan et al., 2008) found that people’s expectations concerning colour-flavour associations can modulate their flavour discrimination responses. For people who expected that two products of different colours would taste different to each other, then they were more likely to report a difference in flavour than if they expected the two to taste the same.

1.7.5. Assessment of the sound of a medication and how this affects medication adherence in children

This is an area which, according to the literature search, has not been explored, however, it is possible that predisposition to certain sounds during aversive medication interventions and associations with medicine-taking could influence acceptance of certain medications e.g. the sound of an inhalation device

1.7.6. Children at risk of oral sensory problems

There are a number of medical conditions that place children at risk of oral sensory problems. Whilst the presenting problem may be complex and

multifactorial in aetiology the problem will almost certainly be a mixture of physiological, psychological and experiential factors (Southall and Schwartz, 2007). Southall and Schwartz highlight seven ‘at risk’ subsets of the paediatric population with potential oral sensory problems. These are summarised in table 1.3.

Table 1.3. At risk groups and associated, potential oral sensory problems (Southall and Schwarz, 2007)

Medical Condition	Potential oral sensory problem
Prematurity	At risk following potentially aversive experiences e.g. tube-feeding
Neurological disorders	Oromotor, dysphagia and sensory abnormality e.g cerebral palsy. Other issues seen with Downs syndrome where hypotonicity and hypersensitivity are likely to cause problems
Developmental delay	Delay can result in delayed feeding development
Prolonged and complex medical intervention	Psychological impact of prolonged or invasive medical treatment. Aversive experiences e.g. nasogastric tube, unpleasant medicines, frequent nausea/vomiting, can result in fussy about taste and textures
Metabolic, liver and kidney diseases	Disturbances of taste perception and appetite. Exposed to prolonged medical interventions and periods of feeling unwell
ENT disorders and unusual structure & function	Physical difficulties with feeding and swallowing which can result in disturbances in feeding development

1.8. The pharmaceutical industry perspective

1.8.1. Background

Most drug development has traditionally been focused upon adults with little or no clinical evaluation undertaken in children; hence licences for paediatric use

are not common and therefore present a large unmet medical need and business opportunity. Although many medicines are administered to children, the majority are not licensed for use in children and are not in an age-appropriate format.

As the industry continues to develop, the major companies are focusing greater effort on R&D activities and patent exclusivity. Meanwhile the generic companies are developing a range of strategic options to allow quick market entry of major products, predominately solid dose portfolios for the primary care market once patent protection lapses.

This leaves an area of off-patent, mainly liquid oral pharmaceutical products, which attracts relatively little attention due to the relatively small market size and technical complexity, but, nevertheless, where individual products are capable of yielding returns of between £10m to £30m per annum.

1.8.2. Patient-centred medicines

A patient-centred medicine can be considered as one which the patient will consider acceptable, to the extent that they will willingly participate in taking the medication on a routine basis in chronic treatment and should be 'administration friendly'. This may be defined as one which is easy to measure the dose and administer without modification.

A patient-centred approach should reflect preferences of the child, which, as discussed in section 1.7.1, in terms of taste preferences alone, can differ markedly to those of adults (Baber, 2005). Furthermore, the preferences of individuals are shaped by experiences and exposure to different tastes.

This presents a significant challenge for industry in meeting the needs of the patient's individual preferences and providing medicines which can be practically achieved, rather than numerous variants to meet specific preferences.

1.8.3. Paediatric regulatory framework

The European and US medicines regulatory agencies [EMA (European Medicines Agency) and US FDA (Food and Drug Administration)] have recognised that the costs associated with paediatric product development and the associated research into paediatric medication acceptability and adherence can result in a low return on investment for pharmaceutical companies. They have therefore introduced incentives, which include a period of exclusivity, through data protection or patent extension to stimulate research and development of children’s medicines and increase the availability of licensed medicines (Table 1.4).

Table 1.4. Comparison of EU and US paediatric legislation, adapted from Ernest et al. (2007)

	EU	US PREA	US BPCA
Regulatory Body	EMA	FDA	FDA
Mandatory	Yes	Yes	No
Incentive	6 month extension to supplementary Protection certificate	Paediatric indication approved and amended label	6 month patent extension
Off patent medicines	PUMA – 10 years exclusivity	Not applicable	NIH and FDA can fund if unmet need exists

The EU is following the lead of the USA, who, as part of the FDA modernisation act in 1997 implemented the incentive of exclusivity and a six month patent extension in return for conducting clinical studies in children, followed by the Best Pharmaceuticals for Children Act (BPCA) in 2002 which led to the re-authorisation of the paediatric exclusivity incentive programme under the FDA modernisation act. The BPCA renewed the exclusivity provision and in addition established a route by which the US National Institute of Health (NIH) and FDA could provide public funding for drugs which manufacturers opted not to study i.e. off-patent. The Paediatric Research Equity Act (PREA) in 2003 overturned the

earlier 1997 Paediatric final rule, which required all new drugs be studied in the paediatric population, and instead introduced the requirement for an assessment of the applicability to children, and enabled waivers and deferrals if justified.

On 29th September 2004 the European Commission (EC) adopted a proposal for the regulation and control of medicines for paediatric use. The proposal had the following main objectives: increased availability of medicines specifically adapted and licensed for use in the paediatric population; increased information available to the patient/carer and prescriber about the use of medicines in children, including clinical trial data; increased high quality research into medicines for children.

The European Union (EU) regulation on paediatric medicines (EC No 1901/2006) was adopted on 12th December 2006 and came into force on 26 January 2007, amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation EC No. 726/2004. Regulation EC No. 1902/2006 has also been adopted with minor revisions and published amending the regulation 1901/2006 on medicinal products for paediatric use.

The EU adopted a similar mechanism to the US, incorporating the Paediatric Investigation plan (PIP) which details the process by which the applicant will determine the safety, efficacy and quality of the intended medicinal product. This requires prior approval by EMEA's Paediatric Committee (PDCO). EMEA offer free scientific advice in the process of developing the PIP.

The key incentives are a six month extension of the protection certificate for new drugs.

The Paediatric Regulation established a new type of marketing authorisation: the Paediatric Use Marketing Authorisation (PUMA). A PUMA is available for off-patent products that are already authorised and that are further developed exclusively for use in the paediatric population. Companies that successfully apply for a PUMA will receive ten years of data exclusivity, i.e. no other company will be able to rely on the data collected by the holder of a PUMA until ten years

has elapsed from the date of the marketing authorisation. Other companies will in theory be able to apply for their own PUMA, although in practice it is expected that the PDCO would refuse to sanction further clinical trials in children of the same drug, on ethical grounds. The Paediatric regulations state as a key mission, the elimination of unnecessary trials in children. Thus, in practice, this system is expected to reward the company that is first in the queue with a successful application.

An application for a PUMA should include data on the use of the product in children assembled pursuant to a PIP, approved in advance by the PDCO. It is necessary first to obtain the agreement of the PDCO to a PIP and then to conduct the studies described in that plan before any application for a PUMA can be submitted.

The PUMA will benefit from 10 years protection. This comprises 8 years data protection and 10 years marketing protection running concurrently.

1.9. Conclusions and proposal for research

Despite the reported importance of medication adherence, and the frequently cited role the organoleptic properties of prescribed medication are considered to play in medication adherence in children, there is limited empirical evidence on childrens' medicinal product preferences and how this affects medication adherence.

Studies in the area of medication adherence and organoleptic properties have been conducted, however knowledge gaps exist, within the currently published literature, in the acceptability of medication to the child, as a means of improving medication adherence. Guidance is offered in several forms, however an evidence-based study, evaluating medication organoleptic properties from the child's perspective, was considered useful in providing additional knowledge to focus pharmaceutical product development towards the production of medicines which are acceptable to the child.

1.10 Aims of the study

1.10.1. Rationale for the investigation

The literature review highlighted gaps in the scientific literature on children's medicinal product preferences and how this affects medication adherence.

This places limitations on informed decision-making for paediatric pharmaceutical product developers and prescribers of paediatric medication, which are investigated in this thesis by gathering information on children's preferences in terms of organoleptic properties of their prescribed medication, and how these preferences may affect medication adherence.

1.10.2. Empirical questions to be addressed within this thesis

The research studies were designed to generate evidence, which could be practically applied in the clinical setting, inform the process of paediatric drug development and contribute to the academic debate. The previously limited availability of evidence to underpin clinical and pharmaceutical development decision-making has meant the outcome of the research is much needed and makes a valuable contribution in meeting the aims of the thesis, which were to:

- I. determine children's preference of medication dose form and organoleptic properties
- II. identify medication adherence themes, which indicate whether there is an association with factors such as age, clinical condition, or other factors, including previous medical interventions and life experiences.
- III. evaluate the experiences of the child and that of parents / carers, doctors and nurses in the process of administering medication to children, and the reasons for this, for example, asking whether there are problems experienced with inappropriate presentations/dose forms of the

medication which may require manipulation prior to administering to the child.

- IV. determine whether adherence or non-adherence may be predicted through the use of a prediction tool
- V. determine whether there is a relationship between acceptability of the medicine to the child and their medication adherence
- VI. provide an evidence base to enable dose form selection and help to focus pharmaceutical product development towards the production of medicines which are acceptable to the child

1.10.3. Plan of the empirical work

The scientific methods of investigation are described at the beginning of each chapter. The investigation involved a stepwise approach of: identifying and defining the problem (chapter 1); data gathering (chapter 2); formulation of the hypothesis (chapter 3); hypothesis based scientific evaluation (chapter 4); Critical appraisal, implications and practical application (chapter 5).

This thesis comprises three stages, incorporating two research studies: CHIMP (Childrens' Medication Preferences Study), and MedAPT (Medication Adherence Prediction Tool).

1. Study I - CHIMP

Through the use of qualitative research methodologies, the CHIMP study (presented in chapter 2) examines the child's preference of medication dose form and organoleptic properties together with the behavioural and demographic factors associated with medication adherence in paediatric patients

aged between 3 and 11 years. The research was conducted at The Alder Hey Children's NHS Foundation Trust (AHCNHSFT), Liverpool UK.

2. MedAPT questionnaire development

The CHIMP data were used to develop a medication adherence prediction questionnaire (described in chapter 3).

3. Study II – MedAPT

Study II, MedAPT study involved the evaluation of the prediction tool/questionnaire, in which adherence predictions derived from children and primary caregiver's MedAPT questionnaire response data were statistically evaluated against adherence measurement generated from pharmacy medication refill data (pharmacy repeat prescriptions).

The aims of Study II were to:

- determine whether adherence or non-adherence may be predicted through the use of the prediction tool/questionnaire
- determine whether there is a relationship between acceptability of the medicine to the child and their medication adherence
- provide an evidence base to enable informed decision-making when prescribing medication for children, and help to focus pharmaceutical product development towards the production of medicines which are acceptable to the child.

2. Children’s Medication Preferences study (CHIMP)

2.1. Introduction

The aims of the studies comprising this thesis are described in section 1.10. This chapter describes study I (CHIMP), which investigated children’s preferences of medication dose form and organoleptic properties, and examined the behavioural and demographic factors associated with medication adherence.

2.2. Methods

2.2.1. Ethics

Prior to study initiation, ethics approval was received from The University of Brighton ethics committee, and the Liverpool Children’s ethics committee (NHS Northwest 3 research ethics committee). Appendix 1 contains the letters of authorisation.

2.2.2. Subject recruitment

2.2.2.1. Inclusion criteria

Children who met the following criteria:

- Child aged 3 – 11 years inclusive
- Attending outpatient appointment with a scheduled follow-up visit, or staying in hospital for 24 hours or longer
- Currently being treated with medication for a chronic illness (defined as an illness lasting longer than 3 months)

The age range 3–11 years has been chosen because a main focus of the study seeks to establish whether the preconception that liquid oral medicines are preferred in the early years is substantiated. Additionally, as the development of the child’s organoleptic preferences are most significant from 3 to 11 years it is important to establish whether there is an interrelationship with age or other factors through early development.

Patients should be attending an outpatient appointment, or staying in hospital for 24 hours or longer to allow time for recruitment of the parent/carer and child to the study.

Children with chronic illnesses was an important inclusion criteria, because children with chronic illnesses are more likely to be taking medicines long term, and therefore have an ability to communicate experiences in taking medication.

All doctors, pharmacists, nurses and staff working at the AHCNHSFT were identified as potential participants in the focus groups.

2.2.2.2. Exclusion criteria

Children who did not fall into the inclusion criteria, or surgical and trauma patients, were ineligible for recruitment.

2.2.2.3. Sampling strategy

The qualitative data analysis methodology, chosen for the purposes of the study, was grounded theory (described in section 2.2.4.2.). Grounded theory involves the use of theoretical sampling, which is the process of data collection to generate theory, whereby the analyst jointly collects, codes and analyses the data and decides which data to collect next (Glaser, 1998).

The initial stages of sampling involved the purposeful selection of as diverse a sample as practical, across the clinical groups and age groups within the inclusion criteria (sections 2.2.2.1. and 2.2.2.2.).

As categories emerged from the data during analysis, sampling then moved into a phase of being more focussed and selective. At this point there was selective sampling of new data with the core themes in mind.

2.2.2.4. Parent/carer and child recruitment process

Potential participants were identified from clinic appointment information within the AHCNHSFT electronic patient appointment system. The inclusion and exclusion criteria formed part of the potential participant identification. This initial patient screening process was developed during the study design process as one of the methods of minimising selection bias. In order to assure recruitment was from a diverse range of clinical specialities, clinic appointment lists across all AHCNHSFT departments were reviewed in identifying participants, which further minimised selection bias towards a clinical speciality.

Having been identified, potential participants were approached within the outpatient departments and wards at the AHCNHSFT. The AHCNHSFT nurse specialist or senior nurse in charge and ward manager (for both inpatient and outpatients departments), as appropriate, were consulted prior to approaching potential participants, and advice sought on whether an introduction was the appropriate first step.

Chief investigator Simon Bryson (SB) made an introduction sensitively, at a time that appeared most convenient to the parent/carer and child. The study was explained verbally to the parent/carer by SB, and the information sheet about the research given to them for consideration. (Appendix 2, document entitled "Participant information sheet Parent, Infosheet/Parent/01). The researcher was available to discuss the study and answer any questions.

If convenient, and acceptable to the parent, the child was given a verbal explanation by SB of the study in accordance with the child information sheet (appendices 3 and 4, Infosheet/Child/01 for children aged 3 to 4 years inclusive, or Infosheet/Child/02 for children aged 5 to 11 years inclusive, or as otherwise directed by the parent/carer).

Parents/carers and children were given the opportunity to take the patient information sheets and consent/assent forms home, and were provided with a postage paid, addressed envelope to return the forms to SB, at the hospital. Additionally they were given SB's phone number to make contact should they

wish to confirm their participation and asked whether they would accept SB contacting them by phone to ask whether they wished to participate.

The nature of the research was considered to be 'non-therapeutic research' as described in the UK Department of Health publication, Seeking consent: working with children (Department of Health, 2001). Based on this guidance, for the children within the study who will be aged 3 to 11 years, consent was sought from the individual who has parental responsibility (parent/carer). However, where child objected to their involvement in the study, this was respected and they were not involved in the study. The child's assent was sought in consultation with the parent/carer with due consideration of the child's developmental status and ability to assent.

The parent/carer was 24 hours to decide whether they would like both themselves and their child to participate. If they decided to take part they were asked to complete two copies of the consent/assent forms (appendices 6 and 7, AHCNHSFT Consent and Assent Forms or 'Assent form Child' and 'Assent Form Parent Carer').

One original signed consent/assent form and one participant information sheet was given to the parent/carer to keep. One photocopy was stored with the patient's medical notes.

The researcher's copies of the consent/assent forms were kept in a locked filing cabinet according to the Data Protection Act (1998).

Following receipt of the signed consent/assent form, the participants were assigned a unique participant identification code (PIC), allocated from spreadsheet 'PIC DTB 001 Participant Identification Code'. The PIC was in the format OPM1/000X/Y, where X is a numerical sequence and the Y Suffix represents: C = child, P=Parent/Carer).

The spreadsheet of identifying numbers and names was kept separately on a password-protected database at the AHCNHSFT.

2.2.2.5. Hospital clinical and technical staff

Doctors, pharmacists and nurses working at the AHCNHSFT were contacted via telephone, email and in person for recruitment to the study, for participation in focus groups. SB obtained names and email addresses from the human resources department at Alder Hey.

The participant information sheet 'Participant Information sheet Clinical', Infosheet/Clintech/01 (see Appendix 5) was sent to doctors, pharmacists and nurses working at the AHCNHSFT, for consideration. Where requested, additional information or explanation regarding the study, was provided by SB.

The clinical and technical staff were given time to decide whether they would like to participate. Those who decided to take part were asked to complete two copies of the consent form ("Consent form Clinical/Technical"). One original signed consent form and one participant information sheet was given to the participant to keep. One original signed consent form was kept in a locked filing cabinet in accordance with the Data Protection Act (1998).

Following receipt of the signed consent form, the participants were assigned a unique participant identification code (PIC), allocated from spreadsheet 'PIC DTB 001 Participant Identification Code'. The PIC was in the format OPM1/000X/Y, where X is a numerical sequence and the Y Suffix represents: D=Doctor, Ph=Pharmacist, N=Nurse).

The spreadsheet of identifying numbers and names was kept separately on a password-protected database at the AHCNHSFT.

2.2.3. Data Collection

The study involved the collection of the following data:

- Demographic data of the patient and parent/carer
- Medication and medical history from the child's medical records

- Qualitative data from interviews with children and parents/carers
- Qualitative data from focus groups with hospital staff

2.2.3.1. Demographic data

Demographic data of each child were collected during the medical record review described in section 2.2.3.2. Demographic data were collected from the parent/carer through completion of the final section of the Beliefs and Behaviour Questionnaire (BBQ) described in section 2.2.3.4.

2.2.3.2. Patient medical record review

The Child's medical notes were reviewed within a secure location at the AHCNHSFT to obtain the following information:

- periods of hospital stay over the preceding 12 months and reason for admission
- gender
- date of birth
- height
- weight
- ethnic origin
- current medical conditions
- current prescribed medication and changes over the preceding 12 months
- notes obtained relating to medication adherence/non-adherence.

The data were recorded on spreadsheet 'MHR DTB 001 Medication History Review, Child' (see Appendix 8).

No patient identifiable information was recorded on spreadsheet MHR DTB 001.

The spreadsheet contains the child's PIC generated as described in section 2.2.2.3.

2.2.3.3. Interviews

Following receipt of the signed consent form, each parent/carer was contacted to arrange a convenient date and time to conduct an interview and complete a questionnaire with both the parent/carer and the child.

Each parent/carer and child was interviewed by SB, at the AHCNHSFT. The interview questions were designed to facilitate discussion and expression of the participant's experiences with taking or administering medicines. Additionally, there was an interest in understanding whether the level of knowledge or attitude of the parent/carer and child towards the child's illness and treatment, had a bearing on medication adherence and acceptance.

The semi-structured interview framework was developed as an outcome of the literature review, to meet the aims of the study (section 1.10) with the involvement of the patient research engagement team of nurse specialists, the research and development department and the department of paediatric clinical psychology at AHCNHSFT. This ensured that the questions were appropriately phrased for the age of the child, and the adult parent/carer.

The interviews and focus groups followed a semi-structured design, which had the advantages of standardising the process, ensuring all the key elements are discussed, and the questions phrased in a consistent style with equivalence of meaning across the participants.

2.2.3.3.1. Interviews with Children

The child was interviewed by SB, at the AHCNHSFT, using a semi-structured framework in accordance with document Int/child/01 (see Appendix 9) to examine the child's experiences in taking medicines, and the factors that influence their adherence to their medication regime. This involved investigating the child's likes and dislikes in relation to the medication dose form and organoleptic properties, and investigating the reasons for any difficulties encountered.

Once the child was at ease, the interviewer asked the child the questions listed within Int/Child/01. The questions were adapted further during the interview taking into consideration the age and perceived level of understanding or competence of the child.

Additionally, to facilitate discussion with children regarding their experiences of taking medicines, a series of visual cues (photographs) were used. These are included in Appendix A of Int/Child/01.

For many of the children, in particular the very young, they were interviewed within an area with access to toys when possible, in order that they felt at ease and comfortable with answering questions.

Specific consideration was also be given to the attention span of the child calculated as $3 \text{ minutes} \times \text{age in years} \pm 3 \text{ minutes} = \text{attention span in minutes}$ (Schmitt, 1999). Table 1 within Int/Child/01 was used as a guide, however, this was dependent upon the child's developmental status.

Breaks from the interview questions took place where necessary, using table 1 within Int/Child/01 as a guide.

Throughout the interview process attempts were made to minimise the influence of the parent on the child's responses. Where permissible, to minimise the influence of the parents beliefs on the child's responses, the child interview took place without the parent/carer being immediately present, however, the parent/carer or nursing staff were close by, and able to observe the interview in progress. Where either, or both parent/carer and child were uncomfortable about being separated for the interview, this was respected, and they were interviewed together. To minimise parental influence, over the child's responses to questions, the parent/carer interview preceded that of the child. Additionally, where the child's condition and facilities permitted, the child was interviewed within a location where they could not be overheard. Where the child could not move from the hospital bed, all available measures were sought to minimise the

potential for the interviews being overheard, including the use of bed screening or curtains. However, all children were interviewed in an observable space.

2.2.3.3.2. Parent/carer Interviews

The parent/carer was interviewed using a semi-structured framework in accordance with document Int/parent/01 (see Appendix 10). This examined the parent's/carer's experiences and involvement in the choice of medication, in administering medicines to the child, and the factors responsible for any difficulties encountered. This was evaluated in consideration of the dose form and organoleptic properties of the medication.

Additionally, where the facilities permitted, the parent was interviewed within a location where they could not be overheard. Where the parent was not comfortable with moving away from the hospital bed, all available measures were sought to minimise the potential for the interviews being overheard, including the use of bed screening or curtains.

2.2.3.4. Beliefs and Behaviour Questionnaire (BBQ)

Following completion of the semi-structured interview, the parent/carer was given a copy of BBQ 01 parent/carer questionnaire to complete (see Appendix 11). The questionnaire assessed adherence, experiences with, and beliefs about medicines, and a series of demographic questions. The adaptation of the validated Beliefs and Behaviours Questionnaire (BBQ), developed by George et al. (2006), was used.

The questionnaire was chosen from the published adherence specific questionnaires described in section 1.6.2.5., on the basis that it had been validated to screen for potential non-adherence in patients with chronic ailments, and is not disease specific, which was an important selection criteria for the CHIMP study, where initial sampling (described in section 2.2.4.2.3.) needed to be as diverse as possible across the hospital.

The questionnaire was adapted for the purposes of the study, so that it could be completed by a parent/carer of a child with a chronic illness and hence address the beliefs and behaviours from the parent's/carer's perspective. The adaptation of the BBQ involved rewording each of the questions to a grammatical tense for the parents to be able to respond to the questions in respect of their child's chronic condition and treatment. The adaptation of the BBQ was achieved with the involvement of the patient research engagement team of nurse specialists, the research and development department and the department of paediatric clinical psychology at AHCNHSFT.

The questionnaire responses were scored using a five-point scale, where a score of five points was attributed to the most positive response, down to a score of 1 for the most negative response to each of the 30 questions, for each respondent.

2.2.3.5. Focus groups

Those who agreed to take part in the study were contacted to arrange a date, time and venue for the focus group(s). Focus groups were chosen to gather the data because the doctors, nurses and pharmacists are a group of professionals who can comfortably speak amongst themselves about the topic, with the course of conversation directed by the researcher as facilitator.

The focus groups examined:

- the choice and range of medication variants available to the prescriber
- the extent to which the dose form and organoleptic properties of medicines are considered during medication prescribing at AHCNHSFT
- the involvement of the Pharmacist in medication dose form selection
- the experiences of Nursing staff in consideration of the dose form and organoleptic properties of the medication:
 - in obtaining prescriptions
 - in the choice of medication
- in administering medicines to the child and the factors responsible for any difficulties encountered

Prior information was not provided to the participants regarding how the patients feel about taking medication. This was considered important in terms of research integrity and not biasing the response to questions.

The focus groups all took place at the AHCNHSFT facilitated by the chief investigator, SB in accordance with document FG/Clintech/01 (see Appendix 12).

Each focus group comprised between 6 and 10 participants, and the discussion lasted around 60 minutes. They were audio recorded and transcribed with all participant names changed to the corresponding PIC reference code.

2.2.4. Data analysis

The data collected were analysed using descriptive statistics, grounded theory and statistical analysis of correlation.

2.2.4.1. Descriptive statistics

The main features of the data collected were described quantitatively using a range of descriptive statistics techniques, and are presented in the results.

2.2.4.2. Grounded Theory (qualitative data analysis)

The aim of the CHIMP study (see section 1.10) was to develop hypotheses or theories on children's preferences of medication dose form and organoleptic properties, together with the behavioural and demographic factors, associated with medication adherence.

Grounded theory methodology is a systematic methodology, which was developed within the social sciences discipline. Rather than the deductive research approach, which begins with a hypothesis, which is tested, the initial

phase of grounded theory involves the collection of data, which is analysed. It is through this process that the theory evolves.

There is some debate over the most appropriate approach to Grounded Theory with its two original proponents describing different approaches (Strauss, 1987; Glaser, 1978). This study draws particularly on Glaser's approach, which emphasises an inductive approach to theory development with constant comparison to the data. The purpose of grounded theory is to develop theory about phenomena where the theory needs to be 'grounded' in observation. The methodology seeks to find what theory accounts for the observed research situation. The aim according to Glaser (Glaser, 1998), is to discover the theory implicit in the data.

The transcribed interview and focus group transcripts were reviewed, and the key points were highlighted with a series of 'codes', which were identified within the text as potential themes. The 'codes' were grouped into 'concepts', which were similar so that they could be evaluated easier. Categories were then formed from the 'concepts', which formed the basis for the creation of the theory, or a reverse engineered hypothesis. The approach is the reverse of the traditional research methodology whereby the research is based on the evaluation of a theoretical framework with the application of statistics.

Grounded theory can be described as a set of overlapping stages:

- **Data collection** through interview and observation
- **Note-taking**, capturing the key elements of each data collection immediately afterwards
- **Coding**, in which the researcher writes the "categories" and "properties" contained or implied by each sentence of the notes
- **Memoing**, in which the researcher writes memos on the theoretical hypotheses arising from the coding

These four stages occur simultaneously. The memos progressively build the theory from the categories and properties of the coding, and the links between them. The data are coded as they are collected, or shortly afterwards.

- **Sorting** then begins as soon as further data add little to the emerging theory. The memos are sorted to an order which allows the theory to be communicated clearly
- **Writing** the report is guided by the sorting

2.2.4.2.1. Coding

Having transcribed the interview and focus group sound records, and memos taken, the information was stored within the 'Sources' folder structure of NVivo 8 (QSR International).

The initial level of coding, referred to as 'open coding' involved taking each transcript and examining one sentence at a time.

In the beginning of the project everything was coded which yielded many concepts. As coding progressed through more data, the concepts were compared and merged into new concepts, and eventually renamed and modified. The review involved the constant comparison of data, constantly modifying, and focussing the developing theory.

In summary, constant comparison involved initially comparing dataset to dataset and later comparing dataset to theory. For the first interview or focus group the categories or codes were broad. The second interview or focus group was coded with the first in mind. Subsequent interviews or focus groups (or data from other sources) were coded with the emerging theory in mind.

Within NVivo8, the open codes were captured as 'free nodes' within the folder structure and subsequently sorted and connected (both existing and new codes) into a branching system of 'tree nodes' that reflects the structure of the data.

Over time some categories emerged with higher frequency, and were connected to many of the other categories, which were emerging.

After identifying the data, the core variable, the data were selectively coded ('Selective coding') with the core directing or guiding the coding, excluding concepts with little importance to the core and sub-cores. Finally, 'Theoretical codes' reflecting high order concepts running through the data by integrating the individual concepts into hypotheses that work together, and from which the theory emerged.

2.2.4.2.2. Saturation

In the process of data collection and interpretation the point was reached whereby the interviews and focus groups did not add new data to what has already been discovered about a category, its properties, and its relationship to the core category. When this occurred, coding for that category ceased.

2.2.4.2.3. Sampling

The initial sampling chosen was as described in the inclusion and exclusion criteria, described in sections 2.2.2.1. and 2.2.2.2. This initial sample was purposefully as diverse a sample as practical, across the clinical groups and age groups within the inclusion criteria.

As categories emerged from the data, sampling then moved into a phase of being more focussed and selective. Glaser and Strauss refer to this as theoretical sampling. The sample was emergent, as is the theory and the method generally. At this point there was selective sampling of new data with the core in mind. This is known as 'theoretical sampling'. Selective coding enabled the generation of concepts to progress at pace, and is a key part of grounded theory (Glaser, 1998). Selective coding was achieved by the further review of previously coded transcripts and data from an earlier stage and by coding newly gathered data.

2.2.4.2.4. Theoretical memoing

Theoretical memoing is, as described by Glaser (1998), "the core stage of grounded theory methodology". Memos are where the theory develops and are

written-up from ideas about substantive codes and their theoretically coded relationships as they emerge during memoing, and in addition during the process of coding, data collection and analysis (Glaser, 1998).

During the early phase of the process the incidents were conceptualised, and memoing helped to facilitate this process. Memos were important in tracking ideas that developed during comparison of incidents and then concepts to concepts in the evolving theory. In memos, ideas developed about naming concepts and relating them to each other. Memoing is the creative element “without rules of writing, grammar or style” (Glaser 1998). When writing memos, the ideas were converted from thoughts in the researchers mind to words.

2.2.4.2.5. Sorting

In the next step memos were sorted, which was the key to formulate the theory to be explained or presented. Sorting puts pieces of data back together. During sorting, new ideas emerged, which in turn generated new memos giving the “memo-on-memos” phenomenon. Sorting memos generated theory that explained the main action in the research. A theory written from unsorted memos was rich in ideas but the connection between concepts was weak.

2.2.4.2.6. Writing up

Writing up the sorted memos proceeds sorting in the grounded theory process. The different categories identified at this stage were related to each other and the core variable.

Selective coding was achieved by the further review of previously coded transcripts and data from an earlier stage and by coding newly gathered data.

The qualitative data obtained following each interview, completed questionnaire and medication history review from patient records were analysed for emerging themes. Grounded theory was used to analyse interview data and children and parents/carers interviewed until no new themes emerged.

2.2.5. Statistical Analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) for windows PC PASW (Predictive Analysis Software) version 18. A database was created within SPSS to input the study data for analysis. The statistical tests used are described within the results section 2.3.

2.2.6. Medication adherence classification

Evaluation of the emerging themes identified the high frequency themes, which were connected to the other categories, which were emerging. In order to determine which were relevant attributes, which may affect adherence, the children were categorised into adherence categories.

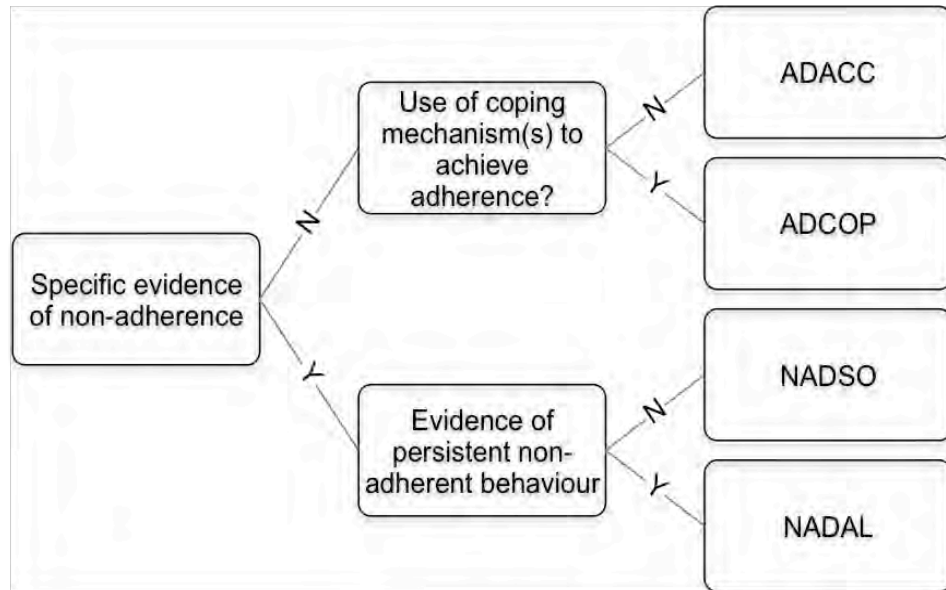
Qualitative data and information relating to medication adherence of each child were gathered through medical note review (provider report) and the child and parent interviews (self- report).

The interview transcripts and medical notes for each child were reviewed for evidence of medication adherence or non-adherence. The interview transcripts were also reviewed for evidence of whether the child considered their medications acceptable to take, and whether coping mechanisms were used to achieve acceptability or facilitate administration.

For the purpose of classification, adherent was specified as having no evidence of non-adherence, therefore, no evidence that a single dose was missed. Non-adherent was specified as there being evidence of a missed dose.

The classification data are tabulated in Appendix 13. This information was used to assign each child participant into one of the four adherence categories in accordance with figure 2.1.

Figure 2.1. Medication classification process



i) Adherent acceptable (Adacc)

Children categorised as Adacc were identified as adherent to all their medication(s), and reported that the medication is acceptable in terms of the organoleptic properties.

ii) Adherent with coping mechanisms (Adcop)

Children categorised as Adcop were identified as adherent to their medication(s), and reported that the medication is not acceptable in terms of the organoleptic properties. As a result, coping mechanisms were used by the child or parent/carer.

iii) Non-adherent sometimes (Nadso)

Children categorised as Nadso were identified as being non-adherent to their medication(s) sometimes.

A distinction has not been made between intentional and non-intentional non-adherence, because the data were not available to accurately make this distinction in all cases.

iv) Non-adherent always (Nadal)

Children categorised as Nadal were identified as being non-adherent to their medication(s) always.

2.3. Results

The aim of this study was to determine the child's preferences in terms of the organoleptic properties of medicines, and to identify factors, which influence these preferences and medication adherence.

2.3.1. Demographic data

The study sample comprised a total of 97 people from the AHCNHSFT: 32 children, 30 parents, 1 grandparent carer, 1 nurse carer, 33 clinical and technical staff (15 Medical Doctors, 6 Nurses, 5 Pharmacists and 7 Technical staff).

A total of 42 children with their parent/carer were approached, and given informed consent. Of these, 33 returned the completed consent and assent forms and were allocated a PIC number (recruitment rate of 78.6%), and 32 were subsequently available for interview and recruited into the study (participation rate of 76.2%).

All of the clinical and technical staff who were contacted, participated in the focus groups, giving 100% recruitment and participation rates.

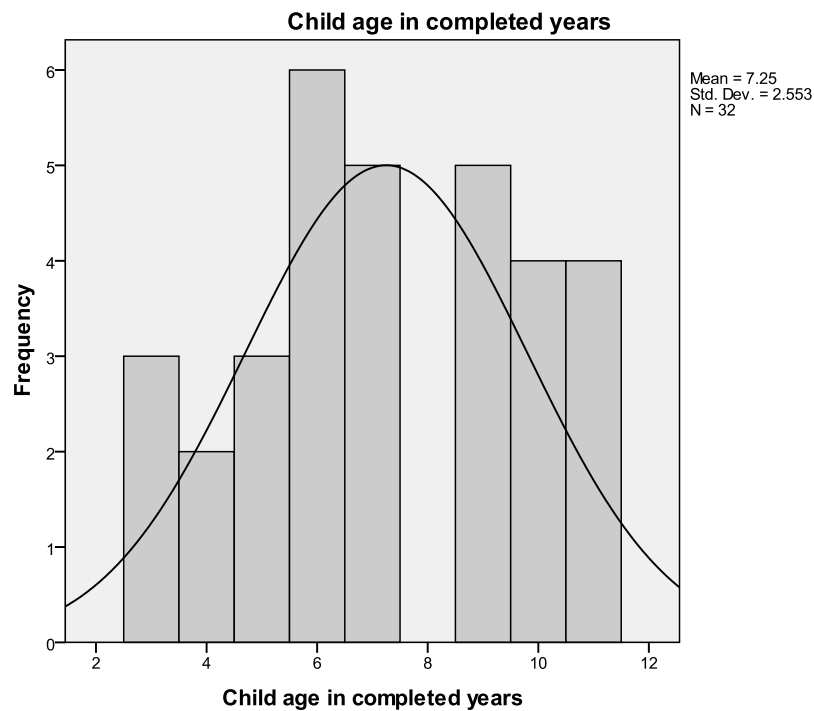
2.3.1.1. Children

Of the 32 children recruited into the study 14 (43.8%) were female, and 18 (56.3%) male. There were 7 in-patients (21.9%), 3 were male and 4 female.

The ages of the children (represented graphically in figure 2.2) were distributed across the inclusion criteria age range of 3 to 11 years.

The 3 to 5 year old group proportionately slightly under-represented (25%). The 6 to 8 year group represented 34% of the study cohort, with the remaining 41% represented by the 9 to 11 year olds.

Figure 2.2. Histogram of the frequency of childrens' age in completed years

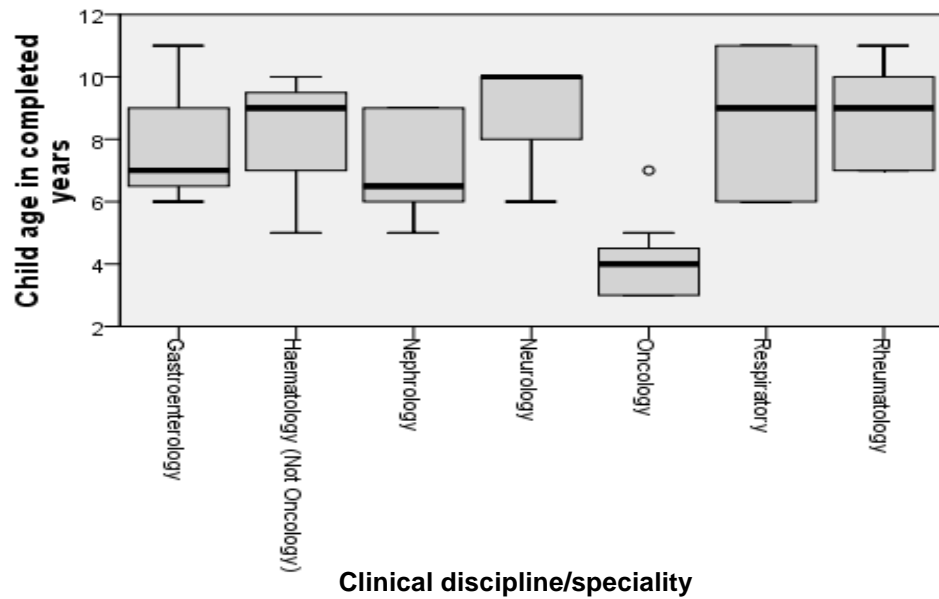


In accordance with the study inclusion criteria, each child was undergoing treatment for a chronic illness at AHCNHSFT. Each child was under treatment within one or more of the clinical speciality areas of gastroenterology, haematology (not oncology related), nephrology, neurology, oncology, respiratory and rheumatology. Where a child was under the treatment of multiple clinical specialities, the lead clinical speciality was assigned for the purpose of evaluation, although the specifics of the cross-speciality treatment have been documented within the study documentation, and evaluated. Figure 2.3 summarises the age distribution by clinical speciality.

The age distributions across the clinical disciplines are mostly within the range of 5-6 years up to 10-11 years, with the exception of the oncology patients whose ages range from 3 to 7 years.

Figure 2.3. Box plot of child age within each clinical discipline/speciality

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the line in the middle represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values. There is one outlier represented by the circle beyond the whisker in the oncology group.



2.3.1.2. Parents/carers

Of the 32 parents in the study sample, 29, just over 90%, were female and 3, just over 9%, were male. The percentages are a typical representation of the high proportion of females, mostly mothers, who are the primary carers and thus attend the hospital with the child.

The majority of the parents were aged between 31 and 50 years (figure 2.4)

Over 90% of the study population (30 of the 32 parents) were from the white ethnic group (Table 2.1). In each case, the ethnicity of the child was the same as the parent.

Figure 2.4. Age of parent/carer frequency distribution

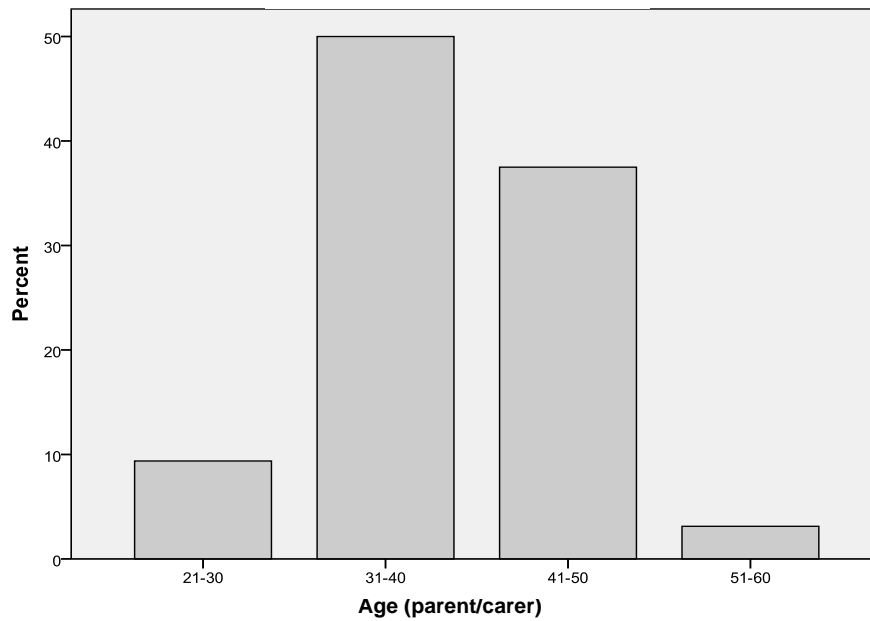


Table 2.1. Ethnic group of parent

Ethnic group	Frequency	%
Mixed race	1	3.1
Other	1	3.1
White	30	93.8
Total	32	100.0

Most of the parents (75%) were either married or living with a partner, with just under 19% single parents.

The education level, which the parents'/carers' attained, is presented in table 2.2. Each of the attainment levels are represented within the study, although not uniformly.

Table 2.2. Parent/carer highest level of education attained

Highest level of educational qualification achieved	Frequency	%	Cumulative %
No qualifications	2	6.3	6.3
GCSE/O level	12	37.5	43.8
A Level	6	18.8	62.5
Diploma	1	3.1	65.6
Degree	8	25.0	90.6
Postgraduate	3	9.4	100.0
Total	32	100.0	

One third of parents (a total of 11) declared having a chronic illness (Table 2.3), 4 of whom were within the same clinical speciality as the child (36.4%), which represents 12.5 % of the total parent population in the study.

Table 2.3. Medical conditions of parent/carer

Medical condition	Frequency	%
Not applicable (Nurse carer)	1	3.1
Asthma	3	9.4
Asthma and thyroid	1	3.1
Asthma, High Hypertension, Kidney disease	1	3.1
Asthma, Hypertension	1	3.1
Depression	1	3.1
HIV	2	6.3
Thyroid problem	2	6.3
None	20	62.5
Total	32	100.0

Just under one fifth of parents stated they did have a medical or healthcare background e.g. nurse, doctor, physiotherapist.

2.3.1.3. Clinical and Technical participants

The 33 clinical and technical participants involved in focus groups comprised 15 Medical Doctors, 6 Nurses, 5 Pharmacists and 7 Technical staff (1 Dietician and 6 pharmacy technicians), with doctors comprising nearly half of the participants.

The focus groups were held within the clinical specialities summarised in Table 2.4.

Table 2.4. Clinical speciality of clinical and technical staff

Clinical speciality	Frequency	%
Gastroenterology	8	24.2
Haematology (not Oncology)	6	18.2
Nephrology	5	15.2
Oncology	4	12.1
Pharmacy	10	30.3
Total	33	100.0

2.3.2. Analysis of child adherence category and demographic data

The adherence history of children in the study is tabulated in Appendix 13. The table summarises the allocation of each child participant within the study to one of the four adherence categories. The Adacc group comprised 25% of the children, Adcop 62%, Nadso 13% and Nadal 0%. The table includes the evidence, collated through transcript and medical note review, which informed the category allocation for each child (see section 2.2.6).

The Fisher's exact test was used to investigate whether the distributions of the demographic categorical variables and the adherence categories differ from one another. The Fisher's exact test is the method of choice for analysis when the cells in the contingency table are small (less than 5), rendering the chi-squared analysis unreliable. Table 2.5 summarises the results.

Table 2.5. p values for adherence category by demographic category

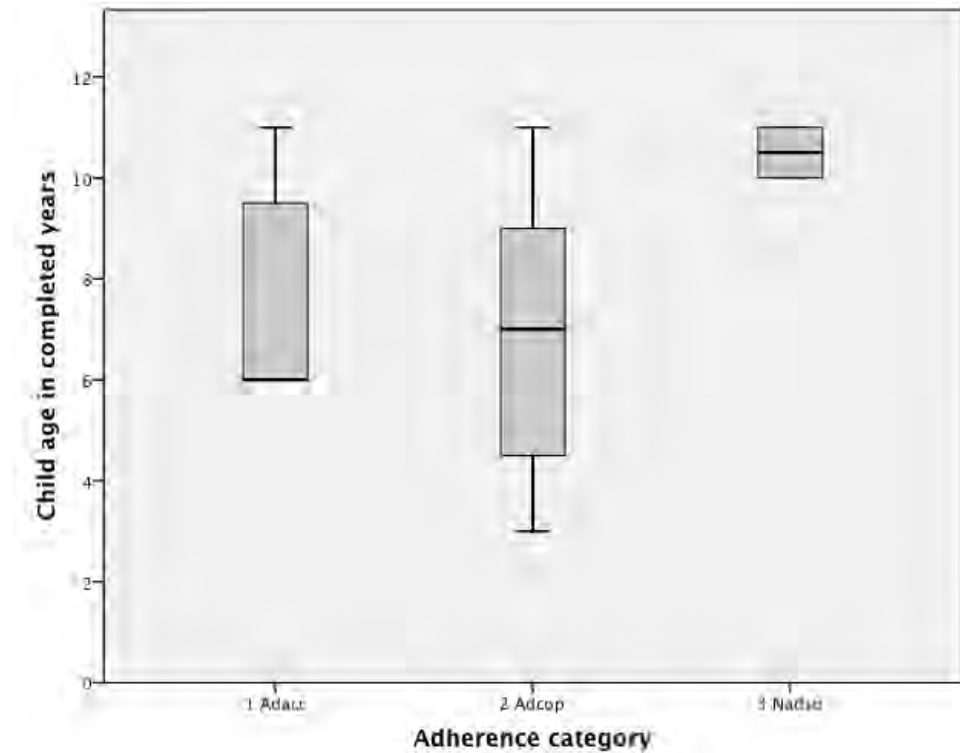
Demographic variable	p value
Medical condition (child)	0.019
Age (parent/carer)	0.792
Child age	0.006
Clinical discipline	0.041
Education (parent/carer)	0.705
Ethnic group (parent/carer)	0.310
Gender (child)	0.268
Gender (parent/carer)	0.494
Marital status (parent/carer)	0.347
Medical background (parent/carer)	1.0
Parent/carer medical speciality same as child?	0.757
Has a chronic condition (parent/carer)	0.245
Number of children	0.395
Relationship of parent to child	0.838

The results indicate that the distributions of the child's medical condition, the child's age and clinical discipline are statistically different between the allocated adherence categories.

As shown in figure 2.5 the 50th percentile for the Adacc group is age 6 years, for the Adcop it is age 7 years, and for the Nadso group it is age 10.5 years. The age range is largest with the Adcop group.

Figure 2.5. Box plot of child age within each adherence category

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the thicker dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values.



2.3.3. Children and parents/carers - data coding and emerging themes

Child and parent/carer interview transcripts and child medication review documentation, were analysed using grounded theory methodology described in section 2.2.4.2, with emerging themes evolving through the course of the research process. The common themes emerged throughout the interviewing process, and were documented as research notes and memos. Furthermore the themes were identified from a combination of text search queries and detailed review of the qualitative research data transcripts within NVivo8.

The emerging themes identified within the data are summarised in table 2.6.

Table 2.6. Emerging themes identified from the CHIMP study qualitative data

Emerging themes (Nodes within NVivo8)		
<ul style="list-style-type: none"> • Appearance • Bad experiences and aversive responses • Dose form (Capsules, Oral Liquids, Tablets) • Choice 	<ul style="list-style-type: none"> • Coping mechanisms • Family and child impact • Mouth feel (oral sensation) • Parental influence • Dislikes/Preferences 	<ul style="list-style-type: none"> • Routine/ Frequency of medicine taking • School • Taste/Smell

The themes summarised in table 2.6 were recurrently discussed within the interviews, with the references within the transcripts being coded to the theme to enable evaluation of the theme across the research participants.

Evaluation of the emerging themes identified that a number of the themes had a high frequency, and were connected to many of the other categories, which were emerging. In order to determine which of the themes were relevant attributes, which may affect adherence, the child research participants were categorised into adherence categories as described in section 2.2.6, and the statistical significance of the emerging themes analysed by adherence category.

2.3.3.1. Appearance

Adacc children did not provide strong negative comments on the appearance of their current medication, and there is some evidence of colour preference, for example, a 9 year haematology patient “She’s quite happy [with her capsule medication] because it has purple writing on”.

There was also some evidence of medication colour dislike, for medication that they had previously taken, but were no longer taking, and hence no longer presented a problem. A 6-year-old neurology Adacc patient displayed a positive preference for pain relief medication, which was white in colour, and an aversion to medicines which are coloured. The white medication was available for the child to take, and there is evidence that she made the positive choice and found the medication acceptable.

Some of the Adacc children, when asked directly about the appearance of their medication did not make negative statements regarding colour, rather statements of fact:

- “..I don’t take ones like that, they are the same shape but different colours, like greeny, but more dark” 6-year-old respiratory patient.
- “...the ones that are half coloured they taste really the same but don’t have any taste ..” 7-year-old respiratory patient.

Where the child has a learned colour-taste association, good or bad, the appearance of the medicine can have an impact on the child’s acceptance of the medication, e.g. one patient did not like orange flavour, so she expressed an aversion to orange tablets (6-year-old neurology Adacc patient).

Adcop and Nadso patients and parent/carers made statements of dislike to some, although not all, of their current medications:

- “He does always comment on the appearance of it. It has an almost luminescence look to it. It looks horrendous. So there's this visual recognition, then stress, and then the taste hits” parent of a 7-year-old oncology Adcop patient.
- “he dislikes methotrexate. It’s got a colour all of it’s own” parent of 7-year-old rheumatology, Nadso patient.
- “with the whole trauma of medicine, and me being concerned he still remembers and says, not that pink one. I think that might be why he doesn’t like calpol [pink], despite us telling him it’s different” parent of 7-year-old Adcop oncology patient.

- “I like clear ones [medicines] and any other colour, but I don't like yellow ones, there's something about the frothy yellow medicine you just don't want to take it” 7-year-old rheumatology Nadso patient.
- “she likes coloured medicine, yes particularly if it is pink” parent of neurology Nadso patient.
- “He knows all the colours well and which medicine is which colour...for example the yellow methotrexate he doesn't like so has to have that first” parent of 3-year-old oncology Adcop patient.

2.3.3.2. Bad experiences and aversive responses

A number of parents expressed the challenging early days and weeks proceeding diagnosis, as an intense period of change where the child and parent/carer were coming to terms with the diagnosis. This period often involves trying to establish the child on a regime of medical treatment, which usually includes medication to treat the condition. In some cases, additional medication was required to manage the side effects, including anti-emetics to control drug-induced nausea and gastrointestinal medicines to manage reflux. There was evidence, from the interviews, of bad experiences with medication, resulting in continued aversive behaviour within the Adcop and Nadso groups. Within the Adacc group, some previous bad experiences had shaped the child's preferences but changes in the medications they were prescribed, had addressed the problem. An example is the neurology patient, described in section 2.3.3.1, who made a choice based on previous experiences and colour-taste association, and found the current medication acceptable.

Oncology parents, the children of whom are all categorised as Adcop, describe the early period following diagnosis as a traumatic time where they felt concerned at the number of medicines their newly diagnosed child is required to take. Some also expressed concern that their child was receiving numerous medicines for the first time, whilst feeling unwell and not eating well. This is expressed well in the words of the parent of a 7-year-old oncology patient: “He was diagnosed when he was 4. It was horrendous. We had a torrid time. In the first year it was nigh on every day he was on iv and chemotherapy medication....

most of these were iv and made him very sick and he's scared of needles now. Also, the thing is, when he was sick it was a grey gruel which came out, and we knew he hadn't eaten much, so it was clear it was a direct result of the chemotherapy drugs he was on".

There is evidence that, as a result of the traumatic experience post-diagnosis, in all cases of oncology patients studied, and all the Adcop sub-group, this has left the child with some aversive behaviours with oral medications. Only through the use of coping mechanisms (discussed in section 2.3.3.5.) was adherence achieved.

There was evidence of side effects from medicines linked to aversive behaviour. One oncology patient, diagnosed with acute lymphoblastic leukaemia (ALL) at age 21 months was said to have been established on his medication until he was administered a medicine to improve his depleted potassium, which made him vomit and resulted in him disliking all medicines, and subsequently requiring a nasogastric tube to facilitate administration of all oral medicines.

The rheumatology sub-group comprised of 5 children, 4 Adcop and 1 Nadso, all of whom were prescribed the anti-metabolite and anti-folate drug methotrexate, which is yellow in colour, and is administered in both oral and injectable form, was referred to by a number of the participants as eliciting drug-induced nausea and inducing a resultant aversive behaviour towards the product and additionally the colour yellow. Examples of aversive conditioning with methotrexate included nausea induced on the journey to hospital or arrival at the GPs surgery, smell of the alcohol swab used to prepare the site of injection, and nausea induced at the sight of the colour yellow, including the site of the yellow sharps bin.

The aversive conditioned response could also be observed out of the immediate healthcare environment e.g. one 7-year-old Adcop rheumatology patient, prescribed methotrexate for Juvenile Idiopathic Arthritis (JIA) described his nausea at the site of a yellow tennis ball: " Things that are yellow make me feel sick. The yellow tennis ball reminded me of my tablets and made me sick".

The nausea and associated aversive response with oral methotrexate was stated by the children and parents, as being more of a problem than the injection, which has resulted in some patients choosing to transfer to the injection format, despite the inconvenience of weekly hospital visits to receive the injection. A 7-year-old Adcop rheumatology patient is a typical example, as described by their parent: “she used to get so sick alter she took the solution and the tablets, so that is why we changed to the injection”.

Aversive conditioning has been observed with other medication where colour was associated with the poor palatability of the medicine resulting in the child disliking medicines of a particular colour e.g. a 7-year-old Adcop oncology patient had a bad experience with taste of a pink oral liquid antibiotic (Acyclovir) and as a result demonstrates an aversion of pink medicines. A similar conditioned behaviour has been observed with one Adcop HIV patient having an aversion to her bubble bath as it had a smell similar to one of her medicines.

Needle phobia was reported by a number of the patients. This was prevalent with the oncology participants whose initial medical treatment following diagnosis included a period of intravenous chemotherapy. As a result, 4 out of the 7 oncology children have developed a severe needle phobia. It was common for children to state a dislike of needles with severe needle phobia being the result of either a bad experience with needles or recurrent exposure to needles through injectable medications or blood sampling. Observations of children undergoing blood sampling within haematology and nephrology highlighted more than 50% of children having a phobia of needles to varying degrees, including some patients who were physically restrained by their parents to achieve compliance.

2.3.3.3. Dose form

The dose forms taken by the participants, tabulated with the adherence category is summarised in table 2.7.

The Adacc group comprised eight children aged 6 to 11 years. Two of the children (6-years-old and 10-years-old) were routinely taking an oral liquid. Six children

(One aged 11-years-old, one aged 9-years-old and four aged 6-years-old) were routinely taking tablets.

Table 2.7. Dose forms prescribed to children within each adherence category

Dose form	Adherence category			Total
	Adacc	Adcop	Nadso	
Injectable	0	3	0	3
Oral Liquids	2	14	2	18
Solid Oral	6	3	2	11
Total	8	20	4	32

The two children who found their oral liquid medication acceptable found the taste and frequency of medication acceptable. Additionally, the children were on a simple, single product treatment regime. Of the 20 children in the Adcop group, 14 (3 to 9 years old) routinely took their medication as oral liquids. These children expressed a dislike of the taste of their medicines. There were 3 children (7 to 11 years old) who routinely took their medication by injection. Each of these children were having subcutaneous methotrexate injections, having previously taken oral forms (liquid and/or tablet) and found the taste and associated nausea unacceptable. They stated that the nausea remained with the injection form, however, the taste problem was eliminated. There were 3 of the children (5 to 10 years old) were routinely taking their medication as tablets. The 5-year-old child found the tablet got stuck in his throat, which his mother explained was most probably due to the size of the tablet. The 7 year old experienced drug-induced nausea with the tablet, however he stated that the palatability was improved from the oral liquid. The 10-year-old found that the taste issue partially remained with the tablet.

The Nadso group comprised 4 children aged 10 to 11-years-old. Two of who routinely took their medication as oral liquids. These children expressed a dislike of the taste of their medicines. In addition, one of the children queried the

effectiveness of the medication and discarded medicines, which she felt, were ineffective. Two of the children were routinely taking their medication as tablets. One of these children expressed a dislike to the taste and texture of tablets but found some coated tablets acceptable. The other child found the tablets acceptable in terms of organoleptic properties, however, she made the irrational decision on occasions not to take the medicine for a reason she could not herself explain.

2.3.3.4. Choice

This section incorporates the emerging themes of preferences and dislikes.

The study examined the child and parents'/carers' involvement in the choice of their medication, the choice and range of medication variants available to the prescriber and the extent to which the dose form and organoleptic properties of medicines are considered during medication prescribing. This also included an evaluation of the involvement of the pharmacist in medication dose form selection.

To determine whether choice had a bearing on adherence, the child and parent/carer interview transcripts were reviewed for evidence of (i) whether the prescribed product(s) is/are available in a range of formats to enable a choice to be offered (ii) whether choice is being offered to the child or parent/carer, (iii) whether there is evidence of a choice being made (iv) whether there are limiting factors other than organoleptic factors which may affect the ability of choice to improve adherence

In the Adacc group of 8 children, the prescribed product was available to enable a choice to be offered to 7 of them (87.5%), and each of the 7 (100%), were offered a choice of dose form, and for each of those offered a choice, there is evidence of a positive choice having been made.

In the Adcop group of 20 children, a choice could have been offered to 50% of them. In 90% of the cases the choice was offered to the child where it was

available, however in just 25% of children overall there is evidence of a choice being made, despite a dislike of their existing medication. Additionally, 20% of the Adcop children who were offered a choice and made a choice there remained a side effect with drug-induced nausea, which could not be addressed by improvement to the organoleptic properties of the drug

In the Nadso group of 4 children a choice was available in all cases, however only 50% of the children were offered a choice, but all of them made the choice where it was offered.

2.3.3.5. Coping mechanisms

A series of coping mechanisms were identified through the interviews. These were developed by parents/carers to address the challenges getting their children to take medicines. The study identified ten key mechanisms employed in order to achieve medication adherence:

- a. Taste masking of the medicine
 - i. Mixed with masking agent
 - ii. Taste mask by eating/drinking before or after medicine to mask e.g. packet of crisps or drink of juice before or after taking the medicine
- b. Physical force
- c. Bribery e.g. offer of money
- d. Persuasion and reasoning
- e. Surgical procedure to bypass the process of ingesting the medicine
 - i. Gastrostomy
 - ii. Nasogastric tube
- f. Self-coping where the child takes medicine despite aversion, due to level of understanding of the need to take the medicine(s)
- g. Move to an alternative dose form or unlicensed name patient special product
- h. Other medication given to manage side effects e.g. anti-nausea medication

Within the Adacc group, coping mechanisms were not required. The medicine, in its prescribed formulation, frequency and dose was considered acceptable. Five of the 8 Adacc children who had previously been within the Adcop category were within the Adacc category at the time of the study, having addressed the problems with their medication.

Each of the children and/or their parent/carer in the Adcop group admitted achieving adherence with the assistance of one or more of the coping mechanisms listed above:

- 7 used masking (ai)
- 1 parent used physical force (b)
- 1 used bribery with money (c)
- 20 (all Adcop) used some form of persuasion or reasoning (d)
- 7 had enteral feeding tubes (5 gastrostomy, 2 nasogastric tube), (e)
- 4 used anti-nausea medication to manage drug-induced nausea. (h)

2.3.3.6. Impact on the child and their family

The key factors stated by the parents and children as having an impact on the child and their family, were, the inconvenience of frequent hospital visits, frequency of having to take medication, the stress of coming to terms with severe, potentially life-threatening illness, coping with the severity of symptoms, and the stage of treatment (time elapsed since diagnosis).

The early stages, post diagnosis, when the parent, child and their family are coming to terms with the child's diagnosis, treatment and prognosis, were stated as the most challenging time. The early phase was said to place a strain on the family, with the time commitment for frequent hospital visits and overnight hospital stays for child and parent(s). For example:

The mother of one 7 year Adcop ALL patient "... found it very difficult to come to terms with, and still can't come to terms with him being ill..".

The mother of a 10 year old Nadso patient stated "Oh it's a big impact. You don't realise just how big an impact it is".

The impact of trying to meet the demands of the treatment regime during the early weeks post diagnosis was expressed by the mother of a 5 year old, Adcop, oncology patient with Downs syndrome: "It hasn't been easy, especially as the [nursing] sister at the time said it was a matter of life and death, but you know, there's no point in being alive if you've got post traumatic stress disorder and you're that damaged that you can't function..".

As the focus was placed on the ill child, the siblings were said, by the parents/carers, to be adversely affected by lack of attention on them. Example "My older daughter and younger son have missed out on quite a bit. And I missed out on quite a bit. School plays and things like that, because all my time is taken up with visits to clinic appointments", Mother of 10 year old Nadso patient. Some siblings were said to crave attention by wishing to be ill themselves. For example, the mother of a 5 year old Adcop oncology patient said " She [sibling] craves to be sick herself for the attention".

The intensity of the stresses placed on the families reduced with time elapsed post diagnosis in most of the cases studied, as the chronic condition was stabilised with treatment. However, the parents stated that stresses still remained within the family due to the effect of living with a chronically ill child.

Parents reported problems with being restricted by the child's treatment and dietary routine, and in some cases, for example ALL (Acute Lymphoblastic Leukaemia) children, who were not able to play contact sports or go swimming throughout the course of treatment. This was also said to adversely impact their siblings in addition to the child themselves, some of whom had developed resentment for their disease.

Other adverse impacts reported were the restriction on overnight visits with friends or school trips, as the parent needed to be available to administer or support treatment in many cases.

2.3.3.7. Mouth feel (oral sensation)

The texture of the medication in the oral cavity was not routinely considered to be a problem with the research participants with only three stating particular problems with specific medicines including erythromycin 'sticky and bitter', one child stating that omeprazole granules in their mouth were 'grainy' and one child who disliked the uncoated tablets in their mouth and throat.

The texture of solid oral medication (tablets and capsules) did contribute to the reason why some of the children expressed a problem with taking tablets as some of the children stated that they get stuck in their throat.

2.3.3.8. Parental influence

The children within the study were aged between 3 and 11 years, and therefore subject to the influence of their parents. There are examples of negative parental reinforcement with 8 of the 20 Adcop children not having tried tablets, despite taste issues with oral liquids, due to the parents' view that their child would be unsuited to tablets. In two of the cases the parent stated that, as they are not good with tablets, they consider it unlikely that their child would be. During observations of parents receiving medication from pharmacy and discussing the dose form given, a number of them stated, with the child by their side, that their child cannot take tablets, whilst in many cases the child hadn't previously tried tablets.

In contrast, there are examples of positive parental influence, with HIV positive parents stating support for the switch from oral liquid anti-retrovirals (ARVs) to tablets, which they stated was due to their own positive experiences with tablets. The switch to solid dose was said to be an effective means of gaining acceptance from age 3 years in this population.

2.3.3.9. Routine

Children expressed a view that medication schedules and treatment was an interruption which limited their ability to play (see section 2.3.3.6.) In addition to the intentional non-adherence of not wanting to take their medication, children sometimes unintentionally non-adherent due to forgetfulness, in particular when they were out of routine, however parents did not readily admit this.

The Beliefs and Behaviours questionnaire explored whether a routine was in place (section 2.3.5), Question 24, which was found to be statistically significantly to the adherence category.

2.3.3.10. Schools

Most of the children in the study were able to take most of their medicines outside school hours, however, for 10 of the children this was not possible. For 3 of these children the parent was required to go to the school to administer the medicine, and in 7 cases the child was required to take the medicine in school by attending the school office.

2.3.3.11. Taste/Smell/Palatability

Palatability and taste were frequently cited in the literature as an influencing factor in medication adherence. To explore this statement the child and parent/carer interview transcripts were reviewed to determine which of the patients stated a dislike for the taste or palatability of their medication, the results of which are shown in table 2.8.

The results indicate that the presence of a stated taste or palatability problem differs across the adherence categories. Within the Adacc sub-group, there is a stated taste/palatability issue with just 1 of the 8 children (12.5%), whereas 95% of the Adcop and 100% of the Nadso children stated a palatability issue with their medication.

Table 2.8. Adherence category vs Taste/Palatability Cross-tabulation

Adherence category	Taste/Palatability issue?		Total
	N	Y	
1 Adacc	7	1	8
2 Adcop	1	19	20
3 Nadso	0	4	4
Total	8	24	32

Fisher’s exact analysis of the data indicate that, the existence of a stated taste/palatability issue, is statistically different between the allocated adherence categories (p value of <0.001).

2.3.4. Clinical and technical participants - Data coding and emerging themes

Transcripts from the focus groups held with clinical and technical staff were analysed using grounded theory methodology described in section 2.2.4.2, with emerging themes evolving through the course of the research process.

The emerging themes identified within the data are summarised in table 2.9.

Table 2.9. Emerging themes identified from the CHIMP study focus groups

Emerging themes (Nodes within NVivo8)	
<ul style="list-style-type: none"> • Medication adherence perspectives and management • Appearance • Influence of experiences • Dose form 	<ul style="list-style-type: none"> • Choice • Complexity of medication regimen • Parental influence • Palatability

The common themes emerged throughout the interviewing process, and were documented as research notes and memos. Furthermore the themes were identified from a combination of text search queries and detailed review of the qualitative research data transcripts within NVivo8. The themes summarised in table 2.9 were recurrently discussed within the interviews, with the references within the transcripts being coded to the theme to enable evaluation of the theme across the research participants.

Evaluation of the emerging themes identified that a number of the themes had a high frequency, and were connected to many of the other categories, which were emerging.

2.3.4.1. Medication adherence perspectives and management

The term adherence was considered, by a number of the focus group participants, to be a term with variable meaning. An example given by one nephrology consultant; 70% adherence by one patient may be considered by one healthcare professional to be sufficient to categorise the patient as 'adherent' whereas 99% adherence by another patient may be considered by a different healthcare professional to be 'non-adherence'.

The accuracy of patient/carer self report was questioned by the participants with a view that parents don't like to admit failure of adherence of their child and some examples of self report being less accurate if the patient/carer understands that the clinical team will be reviewing the data. There were examples of this within nephrology where self-reporting of dialysis adherence was significantly different to the electronic recording captured directly by the dialysis machine.

There were differences between clinical disciplines and consultants with regards to the level of detail of follow-up questions asked with regards to patient medication adherence. Most of the questioning involved general questions asking how the patient is 'getting on' with their medicines and whether they were managing to take them. Most clinical disciplines consider progression of symptoms to be an indicator of adherence problems e.g. gastroenterology

consultant: “On follow-up we always ask them whether they are taking their medication. If they are having poor control of their symptoms then obviously compliance may be a problem and it’s time to ask questions”.

Whether the patient’s symptoms are symptomatic or asymptomatic was considered to have a bearing on adherence. E.g. gastroenterology nurse stated, “they are not keen on it [taking medicines] and it’s difficult for them to do it. When they feel better they will stop. Even when you tell them they must carry on, they stop”.

There was an observed difference in the way adherence was considered within each clinical discipline. Within the haematology HIV patient population there was a focussed programme, involving a multi-disciplinary team (MDT), with patient adherence management including blood monitoring and management of dose form to optimise adherence. The patients were trained to move onto tablets as young as possible to facilitate adherence as a means of addressing the significant palatability/taste issues of the liquid antiretroviral products. In addition to the HIV MDT, MDTs were in place in some other clinical disciplines, with a focus on disease management, and there were examples of good practice focussed on achieving medication adherence. Examples of good management practice included discussions between the child and the consultant around the general topic of chronic disease management, with the consultant asking questions to determine the child’s understanding of the disease, reason for taking medicines and what the medicines are for (medication indication). Questions including ‘are they difficult to take?’ were aimed at making admission of non-adherence easier for the child. Some consultants said that they would be alerted by progression of symptoms as a possible indicator of non-adherence.

2.3.4.2. Appearance

The appearance of the medication was a recurrent discussion point within the focus groups. It was considered possible that the child could have a learned colour-taste association, good or bad, the appearance of the medicine could have

an impact on the child's acceptance of the medication. An example given within the rheumatology focus group was the aversion to the colour yellow associated with the yellow colour and poor taste of oral methotrexate experienced by a number of the group's patients. One of the consultants reported that some children experience nausea at the sight of the yellow sharps bin within the hospital environment, which she believed to be as a direct effect of the drug induced nausea of yellow-coloured methotrexate.

2.3.4.3. Influence of experiences

There was evidence, from the focus groups, of bad experiences with medication resulting in aversive behaviour. Pharmacy technical focus group participants expressed the view that once a child has had a bad experience with a particular medicine it will present a challenge in achieving adherence with the medicine in the future. A similar view was expressed across the clinical disciplines.

The participants stated that they were aware of cases where known success with a given treatment regimen or medication had a positive influence on adherence. In an extreme circumstance there was also a view from one chronically ill and non-adherent rheumatology patient (teenager referenced in focus group but not one of the study participants) that if he didn't take his medication then he didn't have the disease.

Healthcare professionals were mostly aware of the series of coping mechanisms developed by parents/carers to address the challenges of achieving paediatric medication adherence. These included taste masking and incentives, and surgical solutions used by doctors. These are discussed in section 2.3.3.5.

Needle phobia was observed in a number of the patients as discussed in section 2.3.3.2.

The intervention of play specialists within some severely needle phobic nephrology patients was said to have delivered positive results. The play specialists engaged with children who had reached a point where their needle

phobia was inhibiting their treatment. Through intervention over a period of weeks, the play specialists had successfully managed to reach a point where the child would accept needles. With the success achieved with children who have reached the point of needle phobia, it remains to be understood whether prospective intervention would prevent the needle phobia.

2.3.4.4. Dose form and Choice

Within the focus groups, the clinical and technical participants expressed the view that younger children aged less than six years tended to be more suited to liquid preparations, and children from seven years old more suited to tablets. However it was found that in some cases older children had a preference for liquid preparations. One consultant stated: "I used to think liquids would be most suitable for kids. But it's not necessarily the case. Some kids have a problem with liquids and prefer tablets, and visa versa "

Previous exposure to medicines with poor palatability was considered by the participants to be factor, which shaped preference towards dose form, with the solid dose forms an easier formulation to mask taste the unpleasant taste of the active drug.

The number of different medicines, and the frequency with which medicines need to be taken by the child was stated as influencing the dose form prescribed, and in some cases due to the licensed status of the drug in a particular dose form, the prescriber would steer the child towards the licensed dose form.

Where possible, offering a choice of dose form was seen as valuable by most prescribers due to the individual preferences. However, situations where it was considered in the child's best interests to direct them towards a particular medication were described e.g. one pharmacist stated, "There are some medicines which we know taste absolutely foul. And so we will guide them and see if for example they can take capsules." The pharmacists were seen to play a key role in dose form selection. One pharmacist stated "on the whole they

[prescriber] would prescribe a dose and then it's up to me and the patient, carer and nurse to decide what dose form they receive". This represented the view of the group.

The study examined the child and parent/carer involvement in the choice of their medication, the choice and range of medication variants available to the prescriber and the extent to which the dose form and organoleptic properties of medicines are considered during medication prescribing. This also included an evaluation of the involvement of the pharmacist in medication dose form selection.

Choice was also considered, by the contributors of the focus groups, to be an important factor in the acceptability and a contributing factor in medication adherence. Within the nephrology discipline they approached the difficulty in adherence to calcium carbonate by providing new patients with a calcium carbonate starter pack, which included different dose forms of the product. The prescribed medication was based on the patients preferred dose form. Within each of the clinical disciplines the importance of choice was seen as important to aiding adherence, however the choice was not always available for certain products. Within pharmacy, choice was considered to be a key element of the dispensing process, which involved engagement with the patient and/or parent/carer.

Within the clinical teams there was, universally, a good knowledge of the dose form variants available to them to prescribe, however the options were said to be limited. Not all medicines were available in multiple dose forms or flavours, as licensed medicines. The prescribers in the study also highlighted the additional practical challenge of variable dosing by weight, which is practical with a liquid, and not possible with a standard tablet or capsule, however newer technologies including mini tablets were said to be making variable dosing a possibility in solid dose format.

There were specific examples of medicines given e.g. mycophenolate mofetil, which was available as a manufactured liquid, capsule and a tablet, and which

presented a good range of choice to meet individual needs. There were others however where the only available liquid form may be an unlicensed, named patient special, which had to be purchased from a hospital pharmacy or specials manufacturing company. And there were others where the parent/carer or child may require training on how to crush a tablet and re-suspend it.

In routine practice choice was not always offered, rather it was based on the judgement of the prescriber whether to offer choice and whether to guide the child to a particular medicine. The decision on which medicine to prescribe and in which dose format was based on the interplay of the child's medical condition, age, dose requirement, history and preferences, together with the prescribers perspective regarding the evidence base for each drug, drug licence status, preconceptions on the dose form appropriate for the child, and relevant prescribing guidelines.

In the Adacc group of 8 children, the prescribed product was available to enable a choice to be offered to 7 of them (87.5%), and each of the 7 (100%) were offered a choice of dose form by the prescriber or pharmacist.

In the Adcop group of 20 children, a choice could have been offered to 50% of them. In 90% of the cases the choice was offered to the child where it was available,

In the Nadso group of 4 children a choice was available in all cases, however only 50% of the children were offered a choice.

2.3.4.5. Complexity of medication regimen

The number of different medicines, and the frequency with which medicines need to be taken by the child was considered by be an influencing factor in adherence. One gastroenterology consultant stated that he believed this to be an important factor to consider: "The frequency. Whether they have to take it once a day or three times a day". He explained that this has been shown to be an important factor with adult inflammatory bowel disease and he'd expect this to be similar with children. Furthermore, a gastroenterology nurse stated "I think if

you try and give something three times a day they just forget. Given you've addressed the taste, size and all that, it's just remembering to take it"

2.3.4.6. Parental influence

Teenagers were viewed, by the clinical and technical focus group participants, as having a higher degree of non-adherence than the younger age group, who have parental influence to drive adherence, however little quantitative evidence exists, and the recognition that parents do not appear to readily admit to non-adherence through fear of appearing to have failed their child.

The extent of influence on a child's beliefs and adherence behaviour was, according to the clinical consultants considered to be greater in the early years, diminishing as the child reaches adolescence, however this was considered to be largely dependent upon the parent-child relationship developed to that point.

2.3.4.7. Palatability

The clinical and technical participants considered the organoleptic properties of medicines to have an influence on patient adherence, with taste and smell viewed as the predominant influencing factor.

The texture of the medicine were also reported as a potential influencing factor within some of the clinical disciplines e.g. omeprazole granules were described by one nurse: "sometimes the tablets [capsules] taste horrible when they disperse and you end up with these little beads all round your mouth, so we tend to use a lot more granules now rather than actual tablets [capsules]. You can put the granules onto a spoon with yoghurt or something and most of the children find that easier to take"

Pharmacists were also aware of the challenges of medication with, what they described as, a grainy texture. They explained that most children disliked this, and could not recall any example of a child having this as a preference.

2.3.5. Beliefs and Behaviours Questionnaire (BBQ)

The BBQ is an adaptation of a validated questionnaire (George et al.,2006) which was developed and validated to screen for potential non-adherence in patients with chronic ailments. The questionnaire was adapted, for the purposes of this research, so that it could be completed by a parent/carer of a child with a chronic illness (see Appendix 11 - BBQ/Parent/01) to gather information on the beliefs and behaviours from the parent/carers perspective. The questions were also adapted and added to the child semi-structured interview outline, Int/Child/01 (see Appendix 9).

The 30 questions are listed below. The questions were answered using a tick box on a 5-point Likert scale within the questionnaire BBQ/Parent/01.

1. I have sufficient understanding about my child's illness
2. I know what to expect from my child's illness management
3. My child's current illness management will keep my child's illness at bay
4. My child is receiving the best possible management
5. The management of my child's illness is a mystery for me
6. It is helpful to know the experiences of others with similar illness as my child
7. Natural remedies are safer than medicines
8. My doctors have limited management options to offer my child
9. My child's medications are working
10. Using any medication involves some risk
11. My child is on too many medications
12. I have sufficient understanding about the options for managing my child's illness
13. I have a say in the way my child's illness is managed
14. My doctors are very knowledgeable
15. I am concerned about the side effects from my child's medications

16. It is unpleasant (e.g. taste and smell) for my child to use some of their medications
17. It is physically difficult to handle some of my child's medications
18. I am satisfied with the information my child's doctors share with me
19. My doctors are compassionate
20. Financial difficulties limit access to the best healthcare for my child
21. My doctors spend adequate time with my child
22. The management of my child's illness disrupts my child's life
23. We get confused about my child's medications
24. We have strict routines for my child in using regular medications
25. I keep my child's medications close to where they need to use them
26. I ensure I have enough medications so that my child does not run out
27. I push my child to follow the instructions of the doctors
28. I make changes in the recommended management to suit lifestyle
29. We vary the recommended management based on how my child is feeling
30. I put up with medical problems before taking any action

2.3.5.1. Evaluation of BBQ responses by adherence category

Questions 23 to 30 in the original BBQ developed and validated by George et al. (2006), were known as the 'behaviour' questions and separately entitled the 'Tool for Adherence Behaviour Screening (TABS)'. The tool has a two-factor solution—'adherence' and 'non-adherence', with internal consistencies of 0.80 and 0.59, respectively.

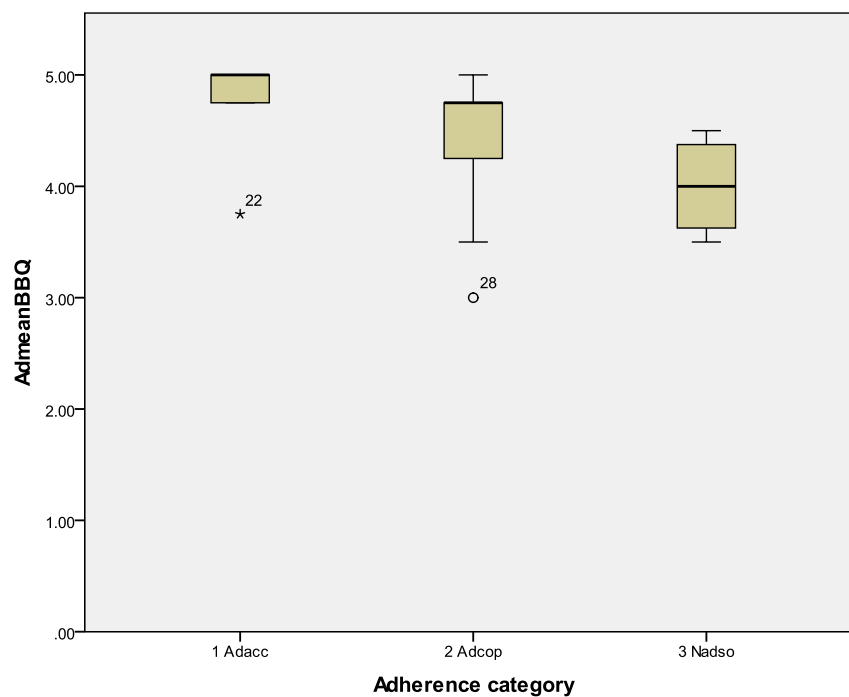
The participants' responses to the TABS questions (23 to 30 inclusive), within the CHIMP study, in addition to the questions within BBQ1 which focussed on the medication specifically (questions 7, 9, 10, 11, 15 and 16), were analysed to determine whether the question responses differed across the adherence categories into which children had been placed.

Figure 2.6 represents the patient population by adherence category, by the mean of the scores given in response to questions 23 to 26 (AdmeanBBQ).

The figure illustrates a clustering of the Nadso assigned children with consistently lower mean scores (≤ 4.5) compared with the cluster of Adacc assigned children whose mean scores were, in all but one case, ≥ 4.75 .

Figure 2.6. Questions 23-26 mean score (AdmeanBBQ) by adherence category

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values. There are two outliers represented by the star (Adacc group) and circle (Adcop group) beyond the whiskers.



The Adcop assigned children were distributed across a range of mean scores. The alignment of the higher mean scores with the adherent group are consistent with

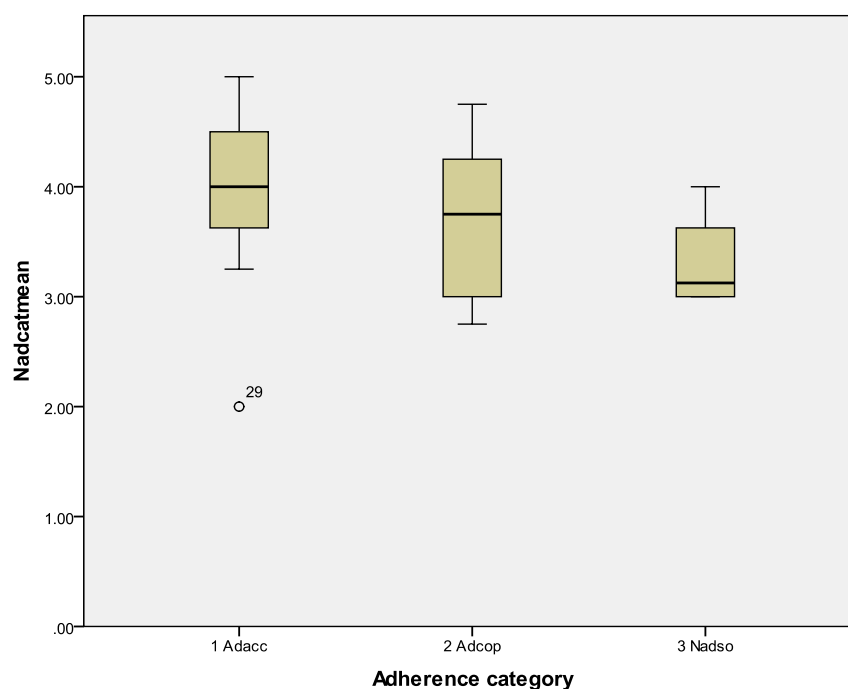
the findings of George et al. (2006), who found the internal consistency (Cronbach's alpha) of questions 23 to 26 to be 0.80, indicating a good degree of alignment.

Spearman's correlation, which is a suitable statistic for the evaluation of non-parametric and ordinal data, was used to calculate the correlation between adherence category and the mean score for BBQ questions 23 to 26. A Spearman's rho correlation coefficient of -0.56 was derived, with $p=0.01$. The critical value of the Spearman correlation (Zar, 1972) with an N (number of subjects) of 31 total respondents, is 0.459 at $p=0.01$. The value of -0.56 indicates a strong negative correlation at the 99% confidence level.

Figure 2.7 represents the patient population by adherence category, by the mean of the scores given in response to questions 27 to 30 (Nadcatmean). These series of questions are termed the 'non-adherence' section of the TABS.

Figure 2.7. Questions 27 to 30 mean score (Nadcatmean) by adherence category

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values. There is one outlier represented by the circle (Adacc group) beyond the whiskers.

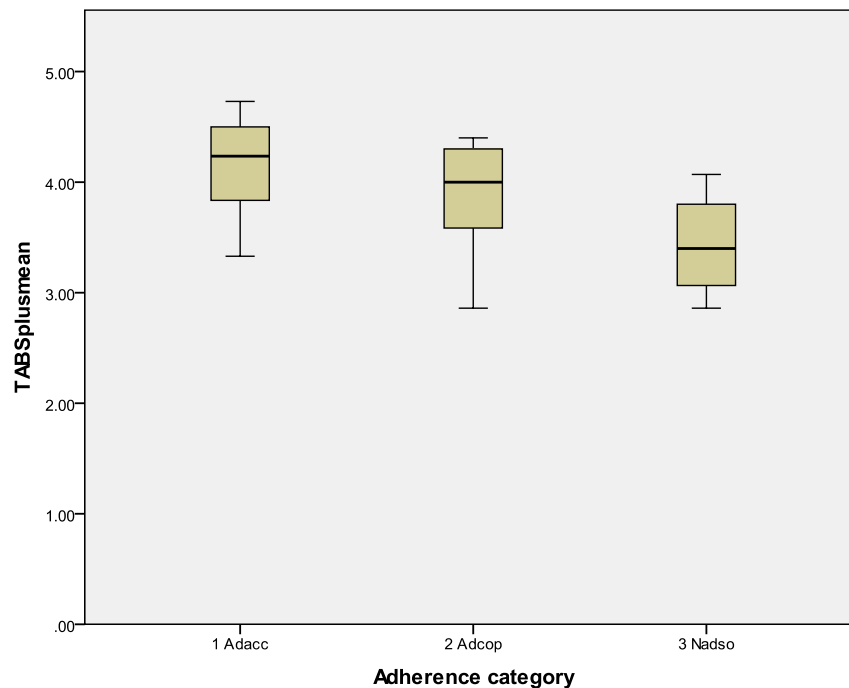


The data illustrates there is a weak association between adherence category and mean score. The weak alignment is consistent with the findings of George et al. (2006), who found the internal consistency (Cronbach's alpha) of questions 27 to 30 to be 0.59, indicating a poor degree of alignment. The critical value of the Spearman correlation with an N (number of subjects) of 32 total respondents, is 0.350 at $p=0.05$. A Spearman's rho correlation coefficient of -0.246 was derived, indicating a weak association with a p value = 0.183. This indicates a weak negative correlation.

Figure 2.8 represents the patient population by adherence category, by the mean of the scores given in response to the medication related questions 7, 9, 10, 11, 15, 16, 23 to 30 inclusive (TABSpplusmean).

Figure 2.8. TABS score plus medication specific questions mean score (TABSpplusmean) by adherence category

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values.

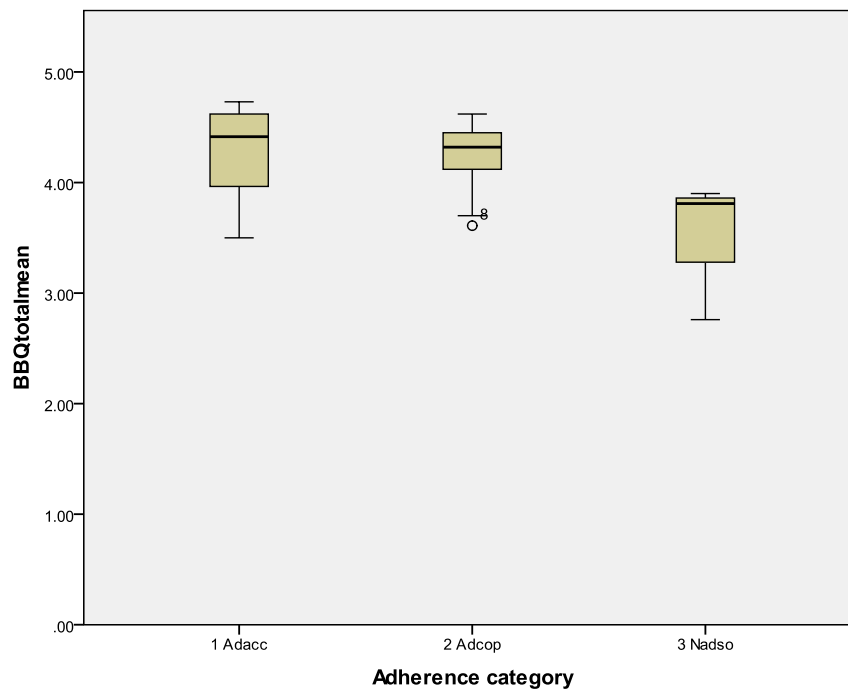


The data support an association between adherence category and mean score. A Spearman's rho correlation coefficient of -0.449 was derived, which is significant at the $p=0.05$. The critical value of the Spearman correlation with an N (number of subjects) of 32 total respondents, is 0.350 at $p=0.05$. This indicates a strong negative correlation.

Figure 2.9 represents the patient population by adherence category, ordered by the mean of the scores given in response to all questions in the BBQ (BBQtotalmean).

Figure 2.9. All BBQ questions mean score (AllBBQ) by adherence category

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values. There is one outlier represented by the circle (Adcop group) beyond the whiskers



The data illustrate a clustering of the Nadso assigned children within consistently lower mean scores (≤ 3.90) compared with the Adacc assigned children who's mean scores in 78% of cases, ≥ 4.30 . The Adcop and Adacc assigned children

were distributed across the range of mean scores. A Spearman's rho correlation coefficient of -0.419 was derived, which is significant at the $p=0.05$. The critical value of the Spearman correlation with an N (number of subjects) of 32 total respondents, is 0.350 at $p=0.05$. This indicates a strong negative correlation.

The correlation of the individual responses (BBQ score) to the BBQ vs adherence category was calculated. Those results which were calculated as being significant are summarised in table 2.10.

Table 2.10. Adherence category vs BBQ score cross-tabulation

	Spearman's Correlation Coefficient	Sig. (2-tailed)	N
BBQ 14	-.436	.014	31
BBQ 16	-.492	.006	30
BBQ 24	-.449	.013	30

The response to questions 14, 'My doctors are very knowledgeable' (p value 0.05); 16, 'It is unpleasant (e.g. taste and smell) for my child to use some of their medications' (p value of 0.01); and 24, 'We have strict routines for my child in using regular medications (p value 0.05), have significant correlation with the adherence category.

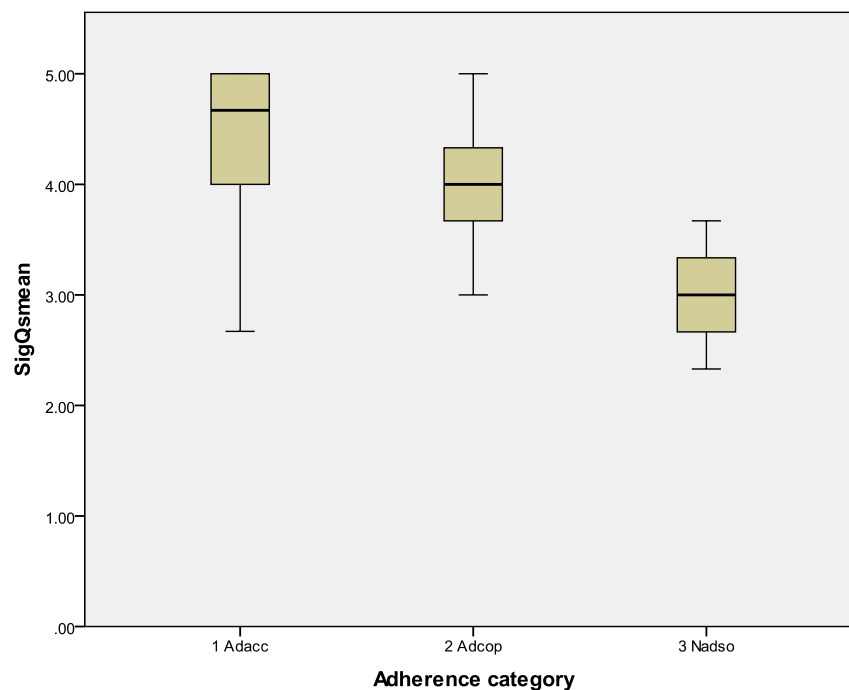
Figure 2.10 represents the patient population by adherence category, ordered by the mean of the scores given in response to questions 14, 16 and 24 in the BBQ (SigQsmean).

The data illustrate a clustering of the Nadso assigned children with generally lower mean scores compared with the Adacc assigned children. The Adcop assigned children were distributed across the range of mean scores. A Spearman's rho correlation coefficient of -0.550 was derived, which is significant, whereby $p=0.01$. The critical value of the Spearman correlation with an N (number of

subjects) of 32 total respondents, is 0.452 at $p=0.01$. This indicates a strong negative correlation.

Figure 2.10. Questions 14, 16 & 24 mean score (SigQsmean) by adherence category

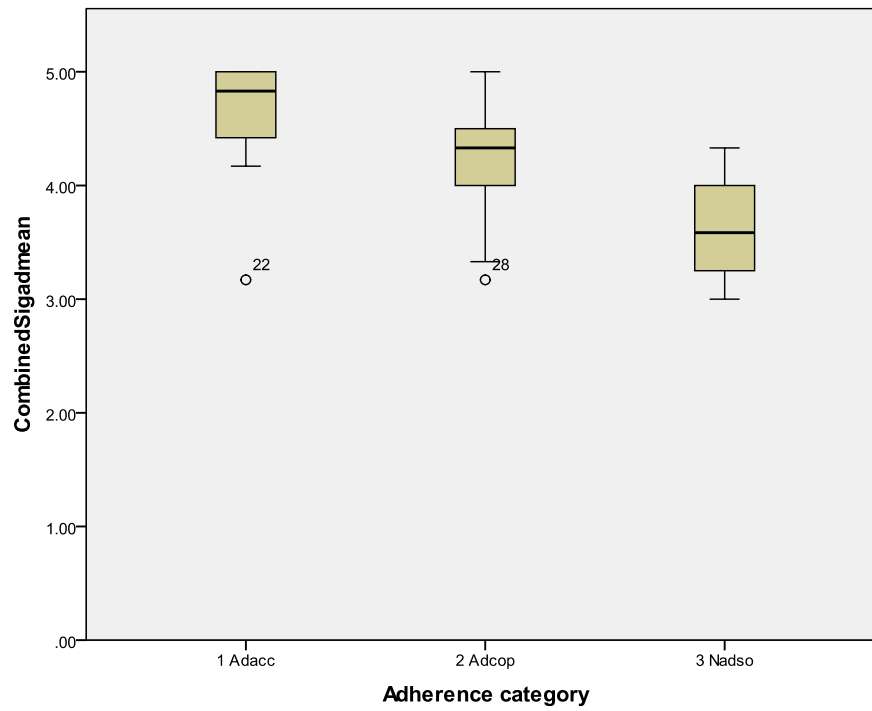
The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values.



Combining the Adherence mean questions (AdherenceBBQ) and the significant individual questions which demonstrated correlation (14, 16 and 24), SigQsmean, gave a Spearmans rho correlation coefficient of -0.573 which is significant with $p=0.01$. This indicates a strong negative correlation. This combined set of questions, termed CombinedSigadmean, is represented in figure 2.11.

Figure 2.11. CombinedSigadmean by adherence category

The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and dark line within the box represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values. There are two outliers represented by the circles, within the Adacc and Adcop groups, beyond the whiskers.



2.4. Discussion and Conclusion

2.4.1. Study sample

The recruitment and participation rates for the study were quite high (child and parent/carer, 76.2%, and clinical/technical, 100%). Whilst experts differ in their view of what constitutes an acceptable recruitment or response rate in qualitative research, figures as low as 60% can be considered acceptable (Badger and Werrett, 2005), and 75% considered good (Badger and Werrett, 2005).

The reasons why 23.8% of children and parent/carers, who were approached and taken through the informed consent process, did not participate, may be due to intentional or non-intentional factors.

Non-intentionally failing to return the signed consent forms due to forgetfulness was quoted in discussion with R&D staff at AHCNHSFT as a common barrier to recruitment. The informed consent process required the participants must be given 24 hours to consider whether to participate. In a number of cases, parents wished to participate in the interview, and complete of the BBQ questionnaire immediately following informed consent, rather than rearrange an appointment at their subsequent visit, or on an alternative day for in-patients. However, due to the ethics stipulation of 24 hours, this was not permitted, and placed an additional barrier to participation.

Intentionally deciding not to return the signed consent forms results from the parent/carer or child deciding on reflection that they do not wish to participate. This can be the result of a number of different reasons including, having read and considered the information provided they did not believe there was value in participation, they did not wish to be inconvenienced, they did not wish to discuss their medication with the researcher, or were concerned with lack of confidentiality of the information they would provide. Concern regarding confidentiality, and use of the information, was specifically cited by two different parents, who were concerned about discussing their child's condition outside of the immediate healthcare team.

The final sample size was determined by the qualitative research methodology used. The sampling strategy used theoretical sampling as part of grounded theory, which ensured that sampling progressed until saturation was reached, and no new theories emerged. The sample size is therefore considered acceptable to meet the aims of the CHIMP study.

2.4.2. Demographics

Both boys and girls were well represented, across the clinical specialities, within the child study population, which comprised children across the age range of 3 to 11-years-old. There was a slightly lower proportion of younger children (3-5 years-old) in the study. This is expected, reflecting the Public Health England (2008) statistics on chronic disease prevalence, which shows that chronic disease prevalence is lower in children less than 4-years-old, compared to older children in the CHIMP study age range.

The parents/carers were predominantly female (90.6%). This aligns with the proportion of mothers who are primary caregivers for their children (Aviva, 2010), and therefore accompany their child to hospital appointments.

The age the parents was as expected, when compared with the Office of National Statistics (2012) statistical bulletin on live births in England and Wales.

A high proportion of the children and parents/carers (93.8%), were from the white ethnic group. The population statistics published by the Office of National Statistics (2009) estimates that 92% of the north-west England population were from the white ethnic, and 89.5% of the population were 0 to 15-year-olds were from the white ethnic group. This suggests a slight under-representation of the ethnic minority groups when the north-west population is considered as a whole.

However, there are two paediatric specialist hospitals in north-west England, the AHCNHSFT and the Royal Manchester Children's Hospital (RMCH). The RMCH serves Manchester and surrounding areas and AHCNHSFT mainly serves the Liverpool region. Sub-classification of the estimates by region within north-west England highlights the significantly higher relative proportion of ethnic minority

groups within Manchester and surrounding boroughs, when compared with Liverpool and surrounding areas: Manchester (29%); Blackburn and Darwen (32.4%); Trafford (16.2%); Bury (12.5%); Bolton (18.1%). Liverpool and surrounding boroughs: Halton and St Helens (3.65%); Knowsley (4.3%); Liverpool (9.9%); Sefton (4.3%); Wirral (4.58%). In conclusion, the proportion of ethnic minority groups within the study population may be considered representative of the population attending AHCNHSFT.

Of the parents in the study, 19% stated they had a healthcare background, which aligns favourably with the Office for National Statistics (2014) labour market data for the north-west region, where 16.7% of the population of working age work within the human health and social work industry.

Comparing the highest educational level achieved by parents/carers in the study, with the Department for Education (2006) data for “The Level of Highest Qualifications held by Adults” within the north-west of England, parents/carers with degrees or postgraduate qualifications (34.4%), were over-represented compared to the 2006 statistical estimates (25.5%). The parents/carers without any qualifications were also under-represented at 6.3% compared with the Department for Education figure of 14.1%. Explanations for the differences were sought from R&D and clinical psychology experts within the AHCNHSFT, who commented that this is an expected outcome in qualitative research recruitment, where parents with higher educational status may be over-represented within study samples, due to being more confident in undertaking interviews and completing questionnaires.

2.4.3. Children’s medication preferences and adherence behaviour

As discussed in chapter 1, children’s organoleptic preferences can, and have been shown to, differ from those of adults. The study aimed to understand children’s organoleptic preferences of their medicines.

Whether some of the children’s medicines are unpleasant to take was shown to be a significant contributing factor in medication adherence. The results indicated

that the presence of a stated taste or palatability problem increased the barrier to adherence. The findings align with the published literature (Squires et al., 2013; Ernest et al., 2007; Matsui, 2007; Costello, Wong and Nunn, 2004).

There is a commonly held preconception, amongst healthcare and medical professionals, that liquid oral medicines are preferred by younger children. The preconception is substantiated within the study by comments from medical doctors, during the focus groups, who routinely prescribed liquid oral medication as the first choice for young children. It is known that bitter or unpleasant-tasting active substances may be difficult to taste mask in solution, and a number of the children within the study expressed a dislike for their oral liquid medication. Tablets or capsules, which enable easier taste masking, may offer a more appropriate delivery system for children 3 to 11 years. Within the study, the youngest child taking tablets was aged 5 years, however, through the focus groups, children as young as 3 years were said to be routinely taking solid oral medication.

There is some evidence within the CHIMP study that taking tablets is associated with improved adherence although there is a need to determine whether the child has an aversion, or whether drug induced nausea could present a barrier to adherence. Previous exposure to medicines with poor palatability was observed as a factor, which was considered to shape preference towards dose form, with the solid dose forms providing an alternative formulation to mask the unpleasant taste of the active drug. The children within the Nadso group displayed some negative behaviour towards medication, which presented potential medication adherence barriers. There is however some evidence, in two of the children, of some success with moving to tablets, which could present a positive means of addressing the potential non-adherence.

Whether the medication makes the child feel nauseous or unwell has been shown to result in aversive reactions including anxiety and sickness, and therefore should be considered as a potential contributing factor in medication acceptance and adherence. Where the child had a learned colour association,

good or bad, the appearance of the medicine was found to have an impact on the child's acceptance of the medication.

Finding one medicinal product to meet the needs of all children appears unlikely, therefore offering a choice may provide the opportunity for the child to select the preferred medication dose form, removing one potential barrier to achieving adherence. Data collected through the CHIMP study demonstrated the value of offering choice, and a positive choice being made, in achieving acceptance by the child. The ability to offer the child a choice is limited by: the availability of alternative dose formats and formulations; whether the prescriber or pharmacist offers a choice; preconceptions of the parent/carer. Whilst choice being offered, taken and the alternative found to be acceptable appears to be a contributing factor in achieving medication adherence, there still remains within the group who have been offered a choice, the requirement for the use of coping mechanisms.

With Children of pre-school age, parents supervise and are responsible for drug administration. Supervised administration is an accepted practice to improve medication adherence (Gardiner and Dvorkin, 2006; Costello, Wong and Nunn, 2004; Carter, Taylor and Levenson, 2003). The study data supports the conclusion that younger children, with supervised administration, are more adherent than the older children in the age range. As the maximum age of children in the study was 11 years, parental influence was expected to play an influential role in the child's beliefs and behaviour towards their medication and treatment. Bush and Iannotti's (1990) children's health belief model (section 1.4.1.) emphasises the influential role of the parent/carer on the child's health related behaviour. The negative effect of a parent's/carer's preconceptions, and personal preferences was observed in relation to tablet-taking (section 2.3.3.8.). In contrast, HIV-positive parents, with HIV-positive children successfully supported their child in switching to tablets due to their own good experiences.

The child is exposed to numerous influences and life experiences, which shape their health-related beliefs and behaviours. As described by Wallston et al. (1976) in the Health Locus of Control (HLC) theory of health related behaviour (section

1.4.3.), the parent/carer and medical professional role exemplifies the influential role played in an external locus of control, whereby the child believes that 'powerful others' are responsible for health outcome. What has been shown within the CHIMP study, and supported by the work of Fotheringham and Sawyer (1995) is that children with internal HLC orientations show better adherence than those with external HLC orientations. There was evidence found within the CHIMP demonstrating the successful work of play specialists (section 2.3.4.3.), who's work with needle phobic children seeks to place the locus of control with the child (internal HLC).

2.4.4. The role of parents/carers in children's medication preferences and adherence behaviour

The parents/carers were knowledgeable and involved in the child's healthcare. As previously discussed, the parent/carer can play a key influential role in the health related behaviour of the child in their care. Through supervised administration parents/carers can have a positive influence on achieving medication adherence, and conversely the barriers presented by negative parental influence has been observed. MDT engagement with the parent in the early stages post-diagnosis, with a focus on educating the parent on their important and influential role as part of the wider MDT, could be beneficial.

During the interview process, it was common for parents/carers to initially present a positive image of medication administration with their child. They typically stated that everything was fine, and that they did not have any particular issues with getting their child to take their medication. However, on further discussion issues did emerge, including the range of coping mechanisms employed to achieve adherence, when faced with a child who didn't wish to take their medication, due to a dislike of one or a number of the medicine's organoleptic properties. Issues also emerged in relation to the adverse impact on family life in having to care for a child with a chronic illness. Particular emphasis was placed upon the early days, post diagnosis, which was said to be a particularly challenging time for the whole family. Examples of bad experiences

during the early stages of investigation and treatment have remained as aversive responses, including needle phobia.

The BBQ questionnaire, completed by the parent/carer, identified six questions which correlated with the child's adherence category: My doctors are very knowledgeable; It is unpleasant (e.g. taste and smell) for my child to use some of their medications; We get confused about my child's medications; We have strict routines for my child in using regular medications; I keep my child's medications close to where they need to use them; I ensure I have enough medications so that my child does not run out. This indicates that belief in the medical professional, palatability of the medication and the administrative or practical aspects of medication in the home play an important role.

A number of behavioural and organoleptic factors may affect the child's willingness to take their medication. The use of coping mechanisms was found to be a key factor in achieving acceptance of the child's prescribed medication. The coping mechanisms identified in section 2.3.3.5. have been developed by parents/carers as a means of addressing the problems they encounter in achieving adherence. The use of coping mechanisms has become commonplace, and are known to the child's medical teams.

2.4.5. The role of clinical and technical specialists in children's medication preferences and adherence behaviour

Medication adherence was shown to be affected by the medical speciality or department, within which the child was being treated. There were more children within the oncology, rheumatology, pain and nephrology clinical disciplines within the Adcop and Nadso categories, than children within other clinical disciplines, including HIV and cystic fibrosis. The reasons for the differences may be explained by the differences in approach, which were identified across the different medical specialities, in relation to medication adherence. Those teams following the best practice of a defined, patient-focussed strategy with the aim of medication adherence had some success with their approach. The foundation of

the MDT and healthcare professional's best practice described in 2.3.4.1, places a focus on individualised medication management and child engagement and participation. This is aligned to Gardiner and Dvorkin's (2006) improvement strategies in medication adherence with children.

This focussed medication management approach by the clinical speciality teams and the medication prescribers is important in evaluating available alternative, or preferred dose forms or formulations, whilst avoiding the commonplace preconceptions that liquid medications are favoured by young children.

Engagement with the parent/carer and child was also considered to be important in defining the child's medication treatment plan, where the frequency of medicine taking, and the complexity of the routine was indicated by both the medical team, as a factor in adherence, and by children and parents who expressed the impact the routine of adhering to the strict and complex routines places on family life.

2.4.6. Limitations

The main limitations are summarised below.

Grounded theory methodology has limitations like any other research methodology. It is both complex and time-consuming due to the detailed coding process. In an attempt to speed up the lengthy coding process, the CHIMP study used NVivo 8 software. Another limitation of grounded theory is the skill of the researcher to objectively assess the qualitative data during coding. This was addressed by ensuring that SB received specific training in grounded theory and NVivo 8.

Whilst efforts were made to prevent researcher-induced bias in subject selection and responses during the interview and focus groups, this can be difficult to detect or to prevent. In order to minimise bias, the selection of study subjects was facilitated by healthcare professionals, who are experienced in approaching potential subjects and are not biased in selection.

Consistency in the data collection process was achieved through the use of semi-structured interview and focus group scripts, with questions phrased in a non-threatening style with data gathered confidentially.

There was a reliance on patient self-report during interview and questionnaire response. It has been established that patients have a tendency to over report adherence (Soliday and Hoeksel 2000), and may adapt their answers to meet expectations of the researcher. The approach described above was used to minimise bias from SB.

The study was limited to a single centre in north-west England, which raises questions regarding the applicability of the research findings in other hospital trusts, where practices and the demographics may be different.

Being based in north-west England, the representation ethnic minority participants is limited (see section 2.4.2.). Some ethnic groups have different religious beliefs regarding medical treatment, and different dietary requirements and preferences. These aspects could not be evaluated within the study cohort.

2.4.7. Conclusion

The study addressed aims I, II and III (section 1.10), which were to:

- I. determine children's preference of medication dose form and organoleptic properties
- II. identify medication adherence themes, which indicate whether there is an association with factors such as age, clinical condition, or other factors, including previous medical interventions and life experiences.
- III. evaluate the experiences of the child and that of parents / carers, doctors and nurses in the process of administering medication to children, and the reasons for this, for example, asking whether there are problems experienced with inappropriate presentations/dose forms of the

medication which may require manipulation prior to administering to the child.

The conclusions from the CHIMP provided the data for the development of the Medication Adherence Prediction Tool (MedAPT), described in chapter 3.

3. Development of the Medication Adherence Prediction Tool (MedAPT)

3.1. Introduction

The aims of the studies comprising this thesis are described in section 1.10.

This chapter describes the development of the Medication Adherence Prediction Tool (MedAPT), in the form of a questionnaire, derived from the CHIMP study data presented in chapter 2.

3.2. Methods

The methods described in chapter 2 were used for data collection and analysis of the CHIMP study data. These data have been further analysed as described in this chapter, to construct the Medication Adherence Prediction Tool (MedAPT).

3.2.1. MedAPT questionnaire development approach

The initial step in constructing the MedAPT questionnaire involved an examination of the aims of the proposed research within which the MedAPT questionnaire was to be used. The primary aims of the study were to:

- Determine whether adherence or non-adherence may be predicted through the use of the MedAPT questionnaire
- Determine whether there was a relationship between acceptability of the medicine to the child and their medication adherence
- Provide an evidence base to enable dose form selection and help to focus pharmaceutical product development towards the production of medicines which are acceptable to the child

The questions were designed to gather this information directly from the participants, therefore only information which the child and parent/carer, could be reasonably expected to provide, was sought.

In constructing the questionnaire it was important to consider the audience (children and their parents/carers), their background, especially their education and readability levels, and the process used to select the participants.

To ensure the research would be a non-discriminatory, fully inclusive process, the language used in the questions was non-technical and the questions designed to enable minimal writing in the responses if required. Support with reading, and completing the questionnaire, was offered by the chief investigator (SB), who performed the informed consent.

3.2.2. Questionnaire format and content

During this stage, the data and information collected and analysed in the CHIMP study, were transformed into questions, following the question development approach described in 3.2.1.

The questions were designed to provide information in two parts. In part 1, questions were designed to collect demographic data, data on the types and number of medications taken by the child, methods of administering medication, medication preferences and direct likes and dislikes of medicines. In part 2, the questions sought to gather information on the child and parent's beliefs and behaviours towards medicines and treatment.

The questions, which formed part of the MedAPT questionnaire, were derived from the conclusions of the CHIMP study and guided by the MedAPT study aims. The factors which were shown, within the CHIMP study, to have a significant difference between the medication adherence categories, defined in section 2.2.6, were included within the questionnaire.

In part 1, the questions were written in non-technical, unambiguous language, with multiple-choice responses. Where the child and parent/carer was able to, or wished to provide additional information, space was available for a more detailed response, however this was not mandatory, and was explained to the

participants during informed consent. This ensured that those participants who were unable to remember or incapable of providing technical information in written form, could still be included within the study. In part 2, the questions were taken directly from BBQ1 (Beliefs and Behaviours Questionnaire 1) used in the CHIMP study. The same five-point Likert scales were used.

At the time of developing the questionnaire, it was anticipated that the data would be analysed by Chi-squared or Fisher exact test of categorical data. The response variables were therefore assigned binary categorical values of '0' or '1' to enable analysis. A score of '0' corresponding with a positive question response, or response aligned with a factor which has been shown to be an indicator of adherence, and '1' assigned to a negative response, or response aligned with a factor which has been shown to be an indicator of non-adherence.

3.2.3. Questionnaire validation

Having developed the draft questionnaire, the next stage involved establishing validity of the questionnaire. Validity is defined as, the amount of systematic or built-in error in measurement, and is established by confirming face validity, construct validity and content validity.

3.2.3.1. Face validity

Face validity is defined as the extent to which a test is subjectively viewed as covering the concept it purports to measure (Holden 2010). It refers to the transparency or relevance of a question as it appears to question participants. A questionnaire can be said to have face validity if it looks like, from the perspective of people who are not experts in testing methodologies, it is going to measure what it is supposed to measure, as apposed to having been shown to work.

This was determined by discussing the questionnaire with the patient research engagement group based at Alder Hey Children's NHS Foundation Trust (AHCNHSFT). The group represent patient interests in research, and provided feedback on the questionnaire.

3.2.3.2. Construct validity

Construct validity examines whether the questions and questionnaire behave like the theory says a measure of that construct should behave.

It refers to whether inferences derived from the questions actually represent or measure the construct being investigated.

As there is no gold standard measure for the questions being asked, construct validity cannot be determined at this stage. The validity of the questionnaire's construct to measure or predict adherence will be determined through the use of the questionnaire in the Medication Adherence Prediction Tool Study (MedAPT), described in chapter 4.

3.2.3.3. Content validity

Content validity (also known as logical validity) is the extent to which a measure, in this case question, represents all facets of a given construct.

Content validity evidence involves the degree to which the content of the test matches a content domain associated with the construct.

Content evidence was generated through review by subject matter experts, who evaluated the questionnaire in relation to the specifications of what was being measured in the MedAPT study. Through the use of experts in reviewing the MedAPT study specification and the selection of items, the content validity of the test was improved. The experts were able to review the items and comment on whether the questions provided sufficient content to meet the study specification.

The questionnaire was reviewed and accepted as fit for purpose by: Research and Development committee at the AHCNHSFT; Subject matter experts at the

University of Brighton (Dr Angela Macadam and Dr Paul Gard); Clinical consultants within each of the clinical speciality groups at AHCNHSFT.

3.2.3.4. Questionnaire scoring and evaluation

The questionnaire scoring mechanism was evaluated to determine whether the scores generated by completion of the questionnaire could be used to predict the adherence category of the child.

3.2.3.4.1. Questionnaire part 1

For part 1 of the questionnaire, the scoring mechanism devised was a simple binary score, where a score of 0 corresponds to a factor, which has been shown to be an indicator of adherence, and a score of 1 corresponding to a non-adherence factor.

Questionnaire part 1 was completed for each of the child participants using the data collected from their interviews and medical note review. The total score for part 1 was calculated. The maximum theoretical score was 14 and the minimum theoretical score 0.

The scores were then analysed to determine correlation with adherence category.

3.2.3.4.2. Questionnaire part 2

For part 2 of the questionnaire (BBQ questions), the same rating scales used in the CHIMP study were used.

No further analysis was performed on these data as the correlation of the responses to the questions by adherence category has previously been determined in section 2.3.5. of the CHIMP results, and forms the basis of questionnaire part 2.

3.3. Results

The CHIMP study results are presented in section 2.3, and describe medication treatment of children with chronic medical conditions, within AHCNHSFT.

The factors which were shown to correlate with adherence category were:

- Medical condition
- Whether some of medicines are unpleasant to take.
- Age of child
- Appearance (colour)
- Whether child takes solid oral or liquid oral dose forms
- Whether medication choice is offered and taken
- Whether coping strategies are required to achieve compliance
- The frequency of medicine taking and complexity of the routine
- BBQ Questions (14, 16, 23, 24, 25 and 26 inclusive) shown to correlate with adherence category:
 - My doctors are very knowledgeable
 - It is unpleasant (e.g. taste and smell) for my child to use some of their medications
 - We get confused about my child's medications
 - We have strict routines for my child in using regular medications
 - I keep my child's medications close to where they need to use them
 - I ensure I have enough medications so that my child does not run out

3.3.1. Questionnaire Part 1

Part 1 of the questionnaire incorporated each of the factors shown to be differentiated by adherence category, and potentially predict medication adherence, other than the BBQ questions, which are within part 2 of the questionnaire.

Table 3.1 contains the final part 1 questions.

Table 3.1. Adherence prediction questionnaire part 1

Question	Response
1. Child age	
2. Medical condition	
3. Do your medicines taste ok?	Y/N
4. Are any of your medicines unpleasant or not nice to take?	Y/N, which one(s)
5. Are there any colours of medicines you like?	Y/N, which one(s)
6. Are there any colours of medicines you do not like?	Y/N, which one(s)
7. Do you take any tablets?	Y/N, which one(s)
8. Do you take any oral liquids?	Y/N, which one(s)
9. Do any of your medicines make you feel unwell?	Y/N, which one(s)
10. Do you use any of the following to help you/your child take their medicines? (please tick each that apply): <ul style="list-style-type: none"> • Mix the medicine with food or drink • Child takes something before or after the medicine as reward or to mask taste? 	<ul style="list-style-type: none"> • Physical force or restraint • Offer money • Persuasion or reasoning
11. Does your child have a Gastrostomy Nasogastric tube	Y/N Y/N
12. How frequent does your child need to take their medicines?	< once a week 3 times/week every day >2 times each day
13. How many different medicines do you regularly (total each week) take?	
14. Have you ever been offered a choice of type of medicines (tablets or liquids) for your child?	Y/N

3.3.2. Questionnaire Part 2

In part 2, the questions were taken directly from BBQ1 (Beliefs and Behaviours Questionnaire 1) used in the CHIMP study. The same rating scales were used.

Table 3.2. Adherence prediction questionnaire page 2 of 2

	Definitely False	Mostly False	Don't know	Mostly True	True
My doctors are very knowledgeable					
	Not at all	Slightly	Moderately	Quite a bit	Extremely
It is unpleasant (e.g. taste and smell) for my child to use some of their medications					
	Never	Rarely	Sometimes	Often	Always
We get confused about my child's medications					
We have strict routines for my child in using regular medications					
I keep my child's medications close to where they need to use them					
I ensure I have enough medications so that my child does not run out					

3.3.3. Adherence prediction questionnaire scoring

Tables 3.3 and 3.4 contain the scores assigned for each response.

For part 1 of the questionnaire the scoring mechanism devised was a binary 0 or 1 score, where a score of 0 corresponds to a factor, which has been shown to be an indicator of adherence, and a score of 1 corresponding to a non-adherence factor.

Table 3.3. Adherence prediction model score sheet Part 1

Question	Response	Score
1. Child age	3-9	0
	10-11	1
2. Medical condition	ALL/Oncology, JIA. Pain or Nephrotic synd	1
	HIV or CF	0
3. Do your medicines taste ok?	Y	0
	N	1
4. Are any of your medicines unpleasant or not nice to take?	Y	1
	N	0
5. Are there any colours of medicines you like?	Answer aligns with med prescribed? Y	0
	N	1
6. Are there any colours of medicines you do not like?	Answer aligns with med prescribed? Y	1
	N	0
7. Do you take any tablets?	Y	0
	N	1
8. Do you take any oral liquids?	Y	1
	N	0
9. Do any of your medicines make you feel unwell?	Y	1
	N	0
10. Do you use any of the following to help you/your child take their medicines?	Y (to 1 or more)	1
	N	0
11. Does your child have a Gastrostomy ?	Y	1
	N	0
Nasogastric tube?	Y	1
	N	0
12. How frequently does your child need to take their medicines?	< once a week	0
	1- 3 times/week	0
	every day	1
	>2 times each day	1
13. How many different medicines do you regularly take each week?	1-2	0
	3 or more	1
14. Have you ever been offered a choice of type of medicines (tablets or liquids) for your child?	Y	0
	N	1

For part 2 of the questionnaire the response scales are the same as BBQ1. The scoring between part 1 and 2 is opposite, whereby a high score in part 1 equates to non-adherence whereas a high score in part 2 equates to adherence.

Table 3.4. Adherence prediction model score sheet part 2

	Definitely False	Mostly False	Don't know	Mostly True	True
My doctors are very knowledgeable	1	2	3	4	5
It is unpleasant (e.g. taste and smell) for my child to use some of their medications	Not at all 5	Slightly 4	Moderately 3	Quite a bit 2	Extremely 1
	Never	Rarely	Sometimes	Often	Always
We get confused about my child's medications	5	4	3	2	1
We have strict routines for my child in using regular medications	1	2	3	4	5
I keep my child's medications close to where they need to use them	1	2	3	4	5
I ensure I have enough medications so that my child does not run out	1	2	3	4	5

3.3.4. Questionnaire evaluation with study data

Table 3.5. contains the questionnaire scores for each of the children in the CHIMP study. The scores for part 1 and part 2 of the questionnaire were calculated as described in section 3.2.4.4.

Table 3.5. Study participants sorted by questionnaire part 1 total score

Patient Identification Code (PIC)	Adherence category	Questionnaire Part 1 score (Total score)	Questionnaire Part 2 score (Mean score)
OPM1 0005 P & C	2 Adcop	1	4.33
OPM1 0011 P & C	1 Adacc	1	4.83
OPM1 0020 P & C	1 Adacc	1	5.00
OPM1 0023 P & C	1 Adacc	1	3.17
OPM1 0025 P & C	1 Adacc	1	4.83
OPM1 0030 C & P	1 Adacc	2	5.00
OPM1 0010 P & C	1 Adacc	3	4.67
OPM1 0024 C & P	1 Adacc	3	4.17
OPM1 0032 P & C	3 Nadso	3	4.33
OPM1 0009 P & C	1 Adacc	4	5.00
OPM1 0018 C & P	2 Adcop	5	4.67
OPM1 0021 P & C	3 Nadso	5	3.50
OPM1 0017 P & C	2 Adcop	6	4.00
OPM1 0019 P & C	1 Adacc	6	5.00
OPM1 0022 P & C	2 Adcop	6	4.17
OPM1 0013 P & C	2 Adcop	7	4.00
OPM1 0016 P & C	3 Nadso	7	3.00
OPM1 0026 P & C	2 Adcop	7	4.33
OPM1 0029 P & C	2 Adcop	7	3.17
OPM1 0027 P&C	2 Adcop	8	4.50
OPM1 0001 P & C	2 Adcop	9	4.50
OPM1 0003 P & C	2 Adcop	9	3.67
OPM1 0006 P & C	3 Nadso	9	3.67
OPM1 0028 C & P	2 Adcop	9	4.33
OPM1 0031 C & P	2 Adcop	9	4.20
OPM1 0033 P & C	2 Adcop	9	4.83
OPM1 0002 P & C	2 Adcop	10	4.50
OPM1 0004 P & C	2 Adcop	10	3.33
OPM1 0007 P&C	2 Adcop	10	4.17
OPM1 0008 P & C	2 Adcop	10	4.00
OPM1 0012 N	2 Adcop	11	n/a *
OPM1 0015 C & P	2 Adcop	11	4.50

* BBQ questionnaire not completed by carer

The Fisher's exact test was used to investigate whether the distributions of the Questionnaire part 1 total scores differ by adherence category. The Fisher exact test is the method of choice for analysis when the cells in the contingency table are small (less than 5), rendering the chi-squared analysis unreliable. The calculation produced a p value of 0.013 indicating that the child's Questionnaire part 1 scores are statistically different between the allocated adherence categories.

The results indicate that a prediction score of 6 or less is indicative of a child who is highly likely to be adherent to their medication regime, and a score of 6 or more indicative of children who are likely to have an issue with adherence or acceptability of their medication.

A Questionnaire part 2 mean score of 4.5 or less is indicative of a potential adherence issue (Adcop grouping) and a mean score of <4.0 indicative of a more significant issue (Nadso grouping).

3.4. Discussion

3.4.1. Study sample

The MedAPT questionnaire has been developed from the input of all participants of the CHIMP study (section 2.3.1, chapter 2). The questionnaire part 1 scores (section 3.3.4.) were calculated for each of the 32 children in the study. The questionnaire part 2 scores (section 3.3.4) were calculated for 31 of the children, as one of the BBQ questionnaires was not returned by the parent/carer in the CHIMP study, therefore the score could not be calculated. The CHIMP BBQ01 response of 96.9% (31 out of 32) is however considered acceptable.

3.4.2. Limitations

There were several limitations involved in the construction of the MedAPT questionnaire, which are based on the main limitations of the CHIMP study, described in section 2.4.6 of chapter 2.

Additionally, whilst the MedAPT questionnaire has been constructed in a methodological process, based on data, the nature and extent of any limitations were unknown prior to the evaluation of the questionnaire with patients in the MedAPT study (chapter 4). These limitations are discussed in the discussion section of chapter 4.

3.4.3. The MedAPT questionnaire

Results from the CHIMP study have provided data on children's organoleptic preferences and experiences with medication, which has enabled the construction of the MedAPT questionnaire. The CHIMP study identified a number of significant factors, which comprise the questionnaire.

Evaluation of MedAPT as a medication adherence prediction tool, by evaluating whether adherence predictions derived from questionnaire responses, aligned with reported adherence, is described in chapter 4.

4. Medication Adherence Prediction Tool (MedAPT)

4.1. Introduction

The aims of the studies comprising this thesis are described in section 1.10. This chapter describes study II (MedAPT), which evaluated the MedAPT questionnaire as a medication adherence prediction tool, in which adherence predictions, derived from children and primary caregiver's MedAPT questionnaire response data, were statistically evaluated against adherence measurement generated from pharmacy medication refill data (pharmacy repeat dispensing).

4.2. Methods

4.2.1. Ethics

Prior to study initiation, ethics approval was received from the NRES Committee North West - Greater Manchester East (ref 12/NW/0687, 03 September 2012) by proportionate review, AHCNHSFT R&D site approval (authorisation received 04 September 2012), and The University of Brighton ethics committee (Favourable opinion received 11 September 2012). The letters of authorisation can be found in appendix 14.

4.2.2. Subject recruitment

4.2.2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria for this study were the same as for the CHIMP study described in section 2.2.2.1. and 2.2.2.2., with one additional inclusion criteria. A fundamental requirement of the MedAPT study was the ability to measure pharmacy refill as a proxy for medication adherence. Therefore, it was a requirement for patients approached for recruitment into the study, to receive the medication being measured for adherence, from AHCNHSFT pharmacy only.

Pharmacy medication refill, or repeat dispensing, was chosen in an attempt to enable recruitment from all clinical specialities at AHCNHSFT without relying on

provider or patient self reporting, use of invasive blood monitoring, or the use of expensive and impractical medicine container technologies.

4.2.2.2. Sampling strategy

The sampling involved the purposeful selection of as diverse a sample as practical, across the clinical groups and age groups within the inclusion criteria (section 4.2.2.1.). The participant identification and recruitment process is described in section 4.2.2.3.

4.2.2.3. Recruitment process

Identification of potential participants was achieved by initially meeting with the pharmacy team and each of the clinical teams within AHCNHSFT. Groups of patients who received at least some of their medication consistently through AHCNHSFT pharmacy were identified.

As part of an initiative within the trust (AHCNHSFT) to transfer repeat prescribing into the community, there were a number of patient groups who were unsuitable for inclusion within the study. Recruitment was therefore directed towards the identified clinical groups of endocrinology and metabolic disorders, rheumatology, oncology, nephrology and dermatology, as repeat prescribing for these groups remained within AHCNHSFT.

Individual patients were identified within the department of pharmacy from their medication records, through outpatient appointment lists via the AHCNHSFT electronic patient system, Medisec, and by the child's clinical care team. The inclusion and exclusion criteria formed part of the potential participant identification. This initial patient screening process was developed during the study design process as one of the methods of minimising selection bias. In order to assure recruitment was from a diverse range of clinical specialities, clinic appointment lists across all AHCNHSFT departments were reviewed in identifying participants, which further minimised selection bias towards a clinical speciality.

The parent or carer of patients within the identified patient population, attending AHCNHSFT, aged 3 to 11 years, taking medication to treat a chronic illness (defined as an illness lasting longer than 3 months), staying in hospital for over 24 hours, or attending an outpatients appointment, were approached for recruitment of both the child and the parent/carer to the study.

The AHCNHSFT nurse specialist or senior nurse in charge and ward manager (for both inpatient and outpatients departments), as appropriate, were consulted prior to approaching potential participants, and advice sought on whether an introduction would be the appropriate first step. This ensured that only parents/carers and children who were, in the opinion of the medical team, considered comfortable with discussing their medication were approached at a time, which was considered convenient and appropriate.

Chief investigator Simon Bryson (SB) made an introduction, sensitively, at a time, which appeared most convenient to them. The study was explained verbally to the parent/carer by SB, and the information sheet about the research (Infosheet/Parent/02, Appendix 15), given to them for consideration. SB was then available to discuss the study and answer any questions.

If it was convenient, and acceptable to the parent, the child was given a verbal explanation of the study, by SB, in accordance with the child information sheet. See Appendix 16 for Infosheet/Child/03 for children aged 3 to 4 years inclusive, or Infosheet/Child/04 for children aged 5 to 11 years inclusive (Appendix 17), or as otherwise directed by the parent/carer.

The parent/carer was given time to decide whether they would like both themselves and their child to participate. The parent was offered two options:

- i. Take the information sheets and a copy of the questionnaire away to give them at least 24 hours before making a decision on whether to participate. Where they subsequently decided to participate, they returned the completed questionnaire and consent/assent forms to SB at AHCNHSFT.

- ii. Where the parent/carer and child chose to, they were permitted to complete the consent form and questionnaire within the 24 hour period. If they later decided they do not wish to participate, SB destroyed their completed consent/assent forms and completed questionnaire and they were removed from the study.

The nature of the research was considered to be 'non-therapeutic research' as described in The UK Department of Health publication, Seeking consent: working with children, 2001. Based on this guidance, for the children within the study who were aged 3 to 11 years, consent was sought from the individual with parental responsibility (parent/carer). However, the child's assent was sought in consultation with the parent/carer with due consideration of the child's developmental status and ability to assent.

Where child and parent/carer decided to take part they were asked to complete the consent (CF/Parent/002) and assent forms (AF/Child/002), see appendices 18 and 19. A photocopy of the original signed consent/assent form and the participant information sheet was given to the parent/carer to keep. A photocopy of the original signed consent/assent form was stored with the patient's medical notes. The original signed consent/assent form was stored within a locked filing cabinet with the R&D department at AHCNHSFT.

Following receipt of the signed consent/assent form, the participants were assigned a unique participant identification code (PIC), allocated from spreadsheet 'PIC DTB 002 Participant Identification Code'. The PIC was in the format MEDAPT/000X/Y, where X is a numerical sequence and the Y Suffix represents: C = child, P=Parent/Carer).

The spreadsheet of identifying numbers and names was kept separately on a password-protected database at the AHCNHSFT.

4.2.3. Data Collection

The main sources of data collected during the MedAPT study were:

- Participant responses from the completed MedAPT (Medication Adherence Prediction Tool) questionnaire
- Demographic data from the MedAPT questionnaire and patient records (AHCNHSFT electronic patient system, Medisec)
- Medication refill and prescription data from the children's pharmacy records

4.2.3.1. MedAPT Questionnaire

Following completion of the consent procedure and consent and assent forms, each parent/carer was asked to complete the MedAPT questionnaire together with their child (see Appendix 20).

The questionnaire was designed (see chapter 3) to collect data, which have been shown, in the CHIMP study (see chapter 2), to be indicative of the acceptability of medicines to children and medication adherence.

The respondent's answers to each question in the MedAPT questionnaire were assigned a score, as described in chapter 3 section 3.3.3.

The data and information from the completed questionnaire, together with the questionnaire scores, were entered into a spreadsheet and transferred to the IBM statistical package SPSS v 20 to enable data analysis.

4.2.3.2. Demographic data

The age and gender of the child were collected from the completed MedAPT questionnaire. The child's age in months at the time of completing the MedAPT questionnaire was calculated from their date of birth, taken from the Medisec patient information system.

4.2.3.3. Prescribing data

The details of all prescribed medication dispensed through AHCNHSFT pharmacy, for each participant, was collected retrospectively for a 3 to 6 month period, where data were available. The data were retrieved from the pharmacy electronic medication database.

The following data were collected:

- Patient's hospital number
- Patient's name
- Medicinal product description (Active ingredients, dose form and strength)
- Date of refill (Date and time the medication was dispensed to patient)
- Quantity of refill / Day's supply obtained
- Prescription dosage instructions (Prescription label text)

The data were recorded on a spreadsheet without any patient identifiable information within the spreadsheet. The spreadsheet contained the child's PIC, generated from the spreadsheet PIC DTB 002.

4.2.4. Calculation of medication refill

From the data obtained through AHCNHSFT Pharmacy, the medication refill measures were calculated as follows:

i. Number of Days supply obtained

$$\text{Number of days supply obtained} = \frac{\text{Quantity (units)}}{\text{Total Daily Dose (units)}}$$

Number of days supply obtained was calculated for each medicine prescription and subsequent medication refill.

ii. Number of days to next interval

Number of days elapsed between the prescription refill and the next refill of the same medication.

iii. Single interval adherence (SIA)

$$\text{SIA} = \frac{\text{Number of days supply obtained}}{\text{Number of days to next interval}}$$

A value ≥ 1.0 indicates adherence for the interval. The days elapsed until the subsequent refill being \leq the days supply obtained. A value <1.0 indicates non adherence for the interval. The days elapsed until the next refill being greater than the day's supply obtained.

SIA was calculated initially for each medication prescribed to each patient in the study, however SIA was not subsequently used as the measure of adherence as described in section 4.2.4.1.

iv. Cumulative days supply obtained

The total number of days supply was obtained from the initiation of the refill measurement period to the current refill event.

v. Cumulative Measure of adherence (CMA)

$$\text{CMA} = \frac{\text{Cumulative days supply obtained}}{\text{Total number of days from first prescription to the next refill event}}$$

As with single interval adherence, values for cumulative measure of adherence ≥ 1.0 indicate adherence. The cumulative number of days elapsed until the subsequent refill being \leq the total number of days supply obtained. A value <1.0 indicates non adherence for the period. The total number of days elapsed until the next refill being greater than the cumulative days supply obtained.

vi. Dose CMA (DCMA), where applicable

Where a patient was prescribed the same medication (active pharmaceutical ingredient, dose form and strength) over a period of time with different dosing requirements on the prescription, it was difficult to calculate CMA with this additional variable. A DCMA was calculated to evaluate the data in these cases. The calculation is similar to CMA, but calculated for each prescribed dose as discrete medications.

Values for dose specific cumulative measure of adherence ≥ 1.0 indicate adherence. The cumulative number of days elapsed until the subsequent refill being \leq the total number of days supply obtained. A value <1.0 is indicative of non-adherence for the period. The total number of days elapsed until the next refill being greater than the cumulative days supply obtained.

4.2.4.1. Interpretation of refill data calculations

Three measures of medication adherence were calculated for each medication taken by each child, namely, SIA, CMA and DCMA. The principle of pharmacy refill as a measure of medication adherence relies upon the assumption that if a medicine is available in the correct quantity, the patient takes it in accordance with the prescription. Conversely, non-adherence is indicated by a lack of availability of the medicine, which is therefore unavailable for the child to take.

Refill practices at AHCNHSFT differ between clinical specialities, with some groups for example oncology consistently dispensing an overage, to minimise supply shortage for the patient, should an outpatient visit be delayed. Across the other clinical specialities dispensing quantities vary by patient and by prescriber.

SIA provides information on the pattern of pharmacy medication refill, however, over the short term measurement interval in this study of 3 to 6 months, the value of the data are limited given that a missed single interval refill may not be indicative of non-adherence where the patient has sufficient supplies of the medication received as part of an earlier prescription, provided as an overage. On this basis, only the CMA data has been used to determine medication adherence. Where the

dose has been altered throughout the period measured, the DCMA has been measured, as a means of analysing the data in more specific detail to determine whether the medication is available for the patient to take, or not.

4.2.5. Data analysis

4.2.5.1. Descriptive statistics

The main features of the data collected were described quantitatively using a range of descriptive statistical techniques using IBM SPSS Statistics version 20 (SPSS 20) and are presented in section 4.3.

4.2.5.2. MedAPT Data analysis

Following data collection, the measures of medication refill were calculated as described in section 4.2.4., for each medicine prescribed through AHCNHSFT pharmacy, to each patient recruited.

To enable further analysis within SPSS 20, to determine whether the MedAPT questionnaire input variables may explain differences in medication adherence, the patients were categorized by adherence to their prescribed medication. The medication refill calculations provided the data for the basis of determining whether the patient was:

- Adherent to all prescribed medication?
- Non-adherent to at least one of their prescribed medications?
- Adherent to all prescribed solid oral medication?
- Non-adherent to at least one of their prescribed solid oral medication?
- Adherent to all prescribed liquid oral medication?
- Non-adherent to at least one of their prescribed liquid oral medication?

Each question had three possible answers for each patient, yes, no or insufficient data (refill data insufficient to determine). In addition, the dose form specific adherence questions had a further possible answer, not applicable (patient not

prescribed particular dose form).

To enable the MedAPT part 2 (Beliefs and Behaviours – BBQ) questions to be statistically analysed, the patients' responses to each question was assigned a score of 1 to 5 in accordance with the MedAPT score sheet (section 3.3.3). The scores were assigned with a 1 representing the most negative response to the question, and 5 representing a positive response.

Fisher's exact test was used to analyse the categorical variables within the data. The Fisher's exact test was the method of choice for analysis as the cells in the contingency table were small (less than 5), rendering the standard chi-squared analysis unreliable. Fisher's exact test was used to investigate whether distributions of categorical variables differ from one another. The Fisher's exact test compares the counts of categorical responses between two (or more) independent groups.

The distributions of MedAPT questionnaire response data, demographic data and medication adherence data were compared to determine whether a difference exists between the distributions of the sets of variables, to look for correlations between the child's medication, their beliefs and behaviours towards their medication, beliefs and behaviours of the parent/carer towards their child's medication, and reported adherence.

4.3. Results

The MedAPT questionnaire response data, demographic data of the patient population and the medication adherence of each child was tabulated within SPSS 20. The table contains the data gathered from the completed MedAPT questionnaires, and the summary of medication adherence taken from an analysis of medication refill.

The following sections describe the patient population, their responses to the MedAPT questionnaire, their medication adherence and non-adherence and the data analysis performed to investigate possible relationships within the data.

4.3.1. The patient population

The child and parent study sample comprised a total of 76 people from the AHCNHSFT (Alder Hey Children's National Health Service Foundation Trust): 38 children and 38 parents.

A total of 361 potential participants were identified from pharmacy records and the electronic appointment system at AHCNHSFT as potentially meeting the study inclusion criteria. Of the 361 identified, only 71 children were identified as receiving some of their medication consistently from AHCNHSFT pharmacy. Of the 71 children identified, 53 attended their outpatient appointments within the study timeframe and were approached for recruitment. Of those approached, 38 agreed to participate, which resulted in a recruitment rate of 71.6%.

Of the 38 children recruited into the study, 14 (36.8%) were female, and 24 (63.2%) male.

The ages of the children (figure 4.1) were distributed across the inclusion criteria age range of 3 to 11 years.

Figure 4.1. Age of patient population histogram

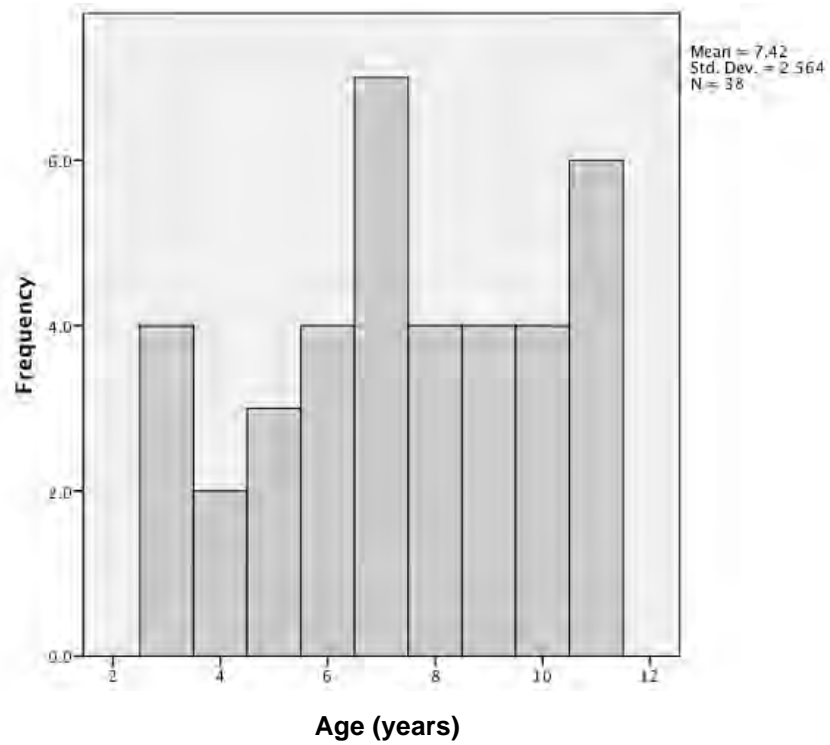
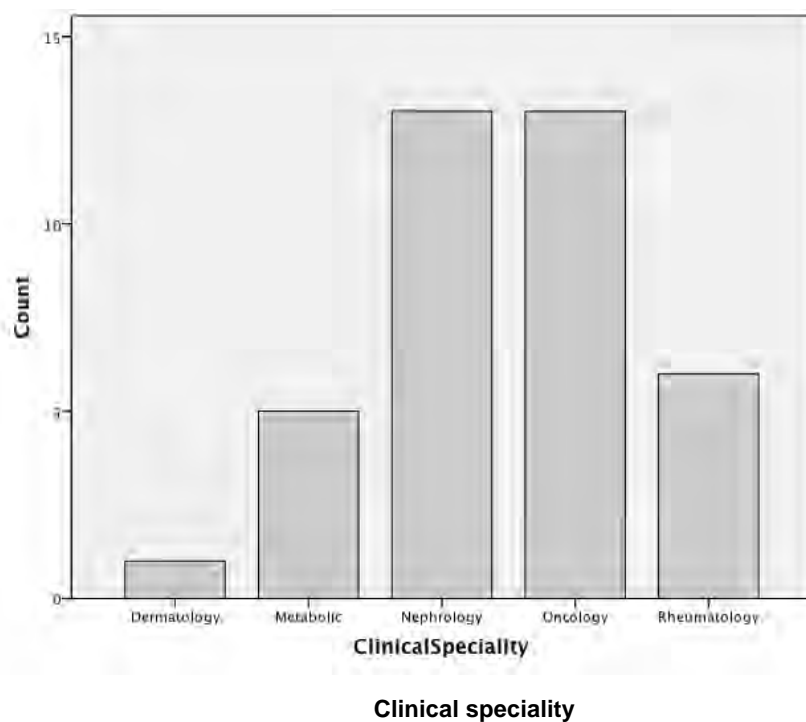


Figure 4.2 summarises distribution by clinical speciality. Children undergoing treatment for oncology and nephrology conditions are the main areas, accounting for 68.4% (34.2% per group) of the study cohort.

Figure 4.2. Histogram showing number of children by clinical speciality

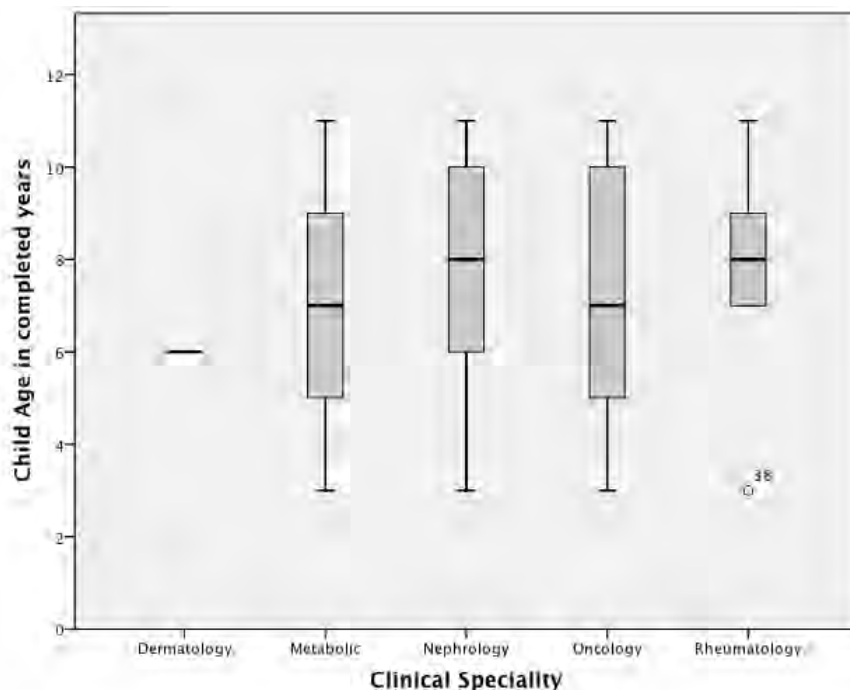


In accordance with the study inclusion criteria, each child was undergoing treatment for a chronic illness at AHCNHSFT. Each child was under treatment within one or more of the clinical speciality areas of nephrology, oncology, rheumatology, dermatology and metabolic disorders. Where a child was under the treatment of multiple clinical specialities, the lead clinical speciality was assigned for the purpose of evaluation, although the specifics of the cross-speciality treatment has been documented within the study documentation, and evaluated.

Figure 4.3 shows the age distribution across the clinical specialities.

Figure 4.3. Box plot of child age by clinical speciality

Top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the line in the middle represents the 50th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values. Outliers (values that are between 1.5 and 3 times the interquartile range) and extreme values (values that are more than 3 times the interquartile range) are represented by circles beyond the whiskers.



The age distributions across the clinical disciplines cover the selection criteria age range, with most children falling within the range of 5 years up to 10 years. Data are limited within dermatology, with only one patient represented (age 6 years). There

is one outlier, patient number 38 within the rheumatology group, who at 3 years of age is more than 1.5 times the interquartile age range of the rheumatology group, who are aged 7, 9, 11, 9 and 7 years

Numeric refill data for each patient recruited were obtained from the electronic pharmacy records at AHCNHSFT, and measures of adherence for each patient for each of their prescribed medications were calculated in accordance with the methods described in section 4.2.4, where there were sufficient data available.

The study cohort comprises an approximately even division between those children found to be adherent to all their prescribed medication, and those found to be non-adherent to at least one of their prescribed medications (table 4.1).

Table 4.1. Summary of participants categorized by adherence to their medication, inclusive of all dose forms prescribed.

	Count, % in brackets		
	Non-adherent	Adherent	Insufficient data
Children (n=38)	18 (47.4)	16 (42.1)	4 (10.5)

Analysis of the children’s adherence data by dose form is summarised in table 4.2.

Table 4.2. Summary of children categorized by adherence to their medication (tablets and oral liquids)

	Count, % in brackets		
	Non-adherent	Adherent	Insufficient Data
Children taking tablets (n=24, 63.2%)	11 (45.8)	8 (33.3)	5 (20.8)
Children taking oral liquids (n=31, 81.6%)	11 (35.5)	15 (48.4)	5 (16.1)

Of the study participants, 24 children (63.2%) had at least one tablet as part of their medication regimen. Within the sub-group who took tablets, 45.8% were found to be non-adherent and 33.3% adherent.

Within the study cohort 31 children (81.6%) have at least one oral liquid as part of their medication regimen. Within the sub-group who take oral liquids 35.5% were found to be non-adherent and 48.4% adherent.

The medication adherence summary data have been further evaluated within sections 4.3.3., to identify statistical significant relationships with MedAPT response variables and demographic factors of the patient population.

4.3.2. Medication Adherence prediction using the MedAPT

The MedAPT questionnaire scores for each participant were calculated in accordance with the scoring sheet, table 3.3 in section 3.3.3. Each participant's score for part 1 and part 2 of the MedAPT questionnaire, together with the predicted adherence, and adherence determined by medication refill, are tabulated in table 4.3.

Table 4.3. MedAPT scores for study participants

Table sorted by Part 1 score and predicted adherence. The grey shaded cells highlight the predictions that were correct, based on adherence to all medication.

PIC	Part 1 score	Predicted adherence (based on part 1 score)	Part 1 Prediction correct? (All meds.)	Part 2 score	Predicted adherence (based on part 2 score)	Part 2 prediction correct? (All meds.)	Medication adherence		
							All meds.	Solid oral	Oral liquids
29	3	Y	Correct	NA	ND	ND	Y	Y	Y
30	3	Y	Incorrect	5	Y	Incorrect	N	N	NA
3	4	Y	Incorrect	4.67	Y	Incorrect	N	N	NA
34	4	Y	Correct	4.5	N	Incorrect	Y	Y	NA
1	5	Y	Correct	5	Y	Correct	Y	Y	Y
10	5	Y	Correct	5	Y	Correct	Y	Y	NA
22	5	Y	Incorrect	4.83	Y	Incorrect	N	N	N
37	5	Y	Correct	5	Y	Correct	Y	NA	Y
6	6	N	Incorrect	4.33	Y	Correct	Y	NA	Y

PIC	Part 1 score	Predicted adherence (based on part 1 score)	Part 1 Prediction correct? (All meds.)	Part 2 score	Predicted adherence (based on part 2 score)	Part 2 prediction correct? (All meds.)	Medication adherence		
							All meds.	Solid oral	Oral liquids
13	6	N	Correct	5	Y	Incorrect	N	Y	N
21	6	N	Correct	5	Y	Incorrect	N	N	NA
26	6	N	Correct	4.5	N	Correct	N	NA	N
33	6	N	Incorrect	4.83	Y	Correct	Y	Y	NA
35	6	N	ND	4.5	N	ND	ND	ND	ND
15	7	N	Incorrect	4.5	N	Incorrect	Y	NA	Y
16	7	N	Incorrect	4.67	Y	Correct	Y	Y	ND
23	7	N	Incorrect	3.5	N	Incorrect	Y	NA	Y
27	7	N	Correct	4.67	Y	Incorrect	N	N	NA
31	7	N	Incorrect	5	Y	Correct	Y	Y	Y
32	7	N	Incorrect	5	Y	Correct	Y	NA	Y
8	8	N	Incorrect	4.5	N	Incorrect	Y	NA	Y
9	8	N	Incorrect	4.67	Y	Correct	Y	NA	Y
17	8	N	ND	4.17	N	ND	ND	ND	ND
18	8	N	Correct	4.33	N	Correct	N	N	N
20	8	N	Correct	5	Y	Incorrect	N	N	N
25	8	N	Correct	5	Y	Incorrect	N	NA	N
38	8	N	Incorrect	4.33	N	Incorrect	Y	NA	Y
4	9	N	Correct	4.5	N	Correct	N	N	Y
7	9	N	Correct	3.33	N	Correct	N	ND	N
14	9	N	Correct	4.67	Y	Incorrect	N	N	N
24	9	N	Incorrect	4.33	N	Incorrect	Y	NA	Y
28	9	N	Correct	4.33	N	Correct	N	N	Y
36	9	N	Correct	4.5	N	Correct	N	N	Y
2	10	N	ND	4.33	N	ND	ND	ND	ND
11	10	N	Correct	4.5	N	Correct	N	NA	N
12	10	N	Correct	4	N	Correct	N	NA	N
19	10	N	Correct	4.17	N	Correct	N	NA	N
5	11	N	ND	4.83	Y	ND	ND	NA	ND

Based on part 1 score, prediction of adherence was correct in 62.5% of cases for all medication, 57.1% for solid oral medication and 75% for oral liquid medication.

Prediction of non-adherence was correct in 57.7% of cases for all medication, 66.7% of cases with solid oral, and 45.5% for oral liquid medication.

Based on part 2 score, prediction of adherence was correct in 50.0% of cases for all medication, 46.2% for solid oral medication and 54.5% for oral liquid medication.

Prediction of non-adherence based on part 2 score was correct in 60.0% of cases for all medication, 75.0% of cases with solid oral, and 42.9% for oral liquid medication. Hence, the ability of the tool to predict adherence and non-adherence was not reliable.

Fisher’s exact analysis of the distributions of predicted adherence based on part 1 and part2 scores and the measured medication adherence for all medication, solid oral medication and oral liquid medication, were performed. The results are shown in table 4.4.

Table 4.4. Fisher’s analysis of Part 1 and part 2 prediction and adherence outcome

Medication adherence prediction		Medication adherence					
		All medication		Solid oral medication		Liquid oral medication	
		Subset	P value	Subset	P value	Subset	P value
Part 1 adherence prediction	Yes, n=8	Y, n=5 N n=3	0.276	Y, n=4 N n=3	0.297	Y, n=3 N n=1	0.426
	No, n= 26	Y, n=11 N n=15		Y, n=4 N n=8		Y, n=12 N n=10	
Part 2 adherence prediction	Yes, n=18	Y, n=9 N n=9	0.412	Y, n=6 N n=7	0.324	Y, n=6 N n=5	0.607
	No, n=15	Y, n=6 N n=9		Y, n=1 N n=4		Y, n=8 N n=6	

Based on the scoring mechanism assigned in chapter 3, no significant relationships were identified between the MedAPT part 1 or part 2 scores and any of the medication adherence measures (Adherent, Adherent to solid oral, Adherent to liquid oral).

Further analysis of the study data was performed (sections 4.3.3 to 4.3.5) prior to refining the questionnaire (section 4.3.6).

4.3.3. Demographic data analysis

The MedAPT questionnaire response data and medication adherence of each child were tabulated within SPSS to enable statistical analysis. The SPSS 20 table

contained the data gathered from the completed MedAPT questionnaires, and the summary of medication adherence taken from an analysis of medication refill.

Fisher’s exact test was used to investigate the patient population demographic data from two perspectives. Firstly, to explore whether there was a relationship between patients’ demographic data and patients’ responses to the MedAPT questions, by determining whether the distributions of the patients’ demographic data of gender, age and clinical speciality differed from the MedAPT response variables (section 4.3.3.1). Secondly, to explore whether there was a relationship between patients’ demographic data and refill adherence, by determining whether the distributions of the patients’ demographic data of gender, age and clinical speciality differ from the medication adherence data (section 4.3.3.2).

4.3.3.1. Analysis of demographic data and MedAPT Part 1 response variables

To explore whether there is a relationship between the patient’s demographic data and MedAPT response variables, the distributions of the demographic factors of gender, age and clinical speciality were compared with the distributions of the MedAPT response variables, by using the Fisher’s exact test. The results are tabulated in table 4.5.

Table 4.5. Fisher’s exact test data for patients’ demographic data by MedAPT response variable

	MedAPT Question response		Demographic data					
			Gender		Age		Clinical Speciality	
			Subset	P value	Subset	P value	Subset	P value
TASTE	MedAPT 3 (Medicines taste OK?)	Yes, n=14	M, n=8 F, n=6	0.403	3-9, n=6 10-11, n=8	0.002	n=14	0.974
		No, n= 24	M, n=16 F, n=8		3-9, n=22 10-11, n=2		n=24	
	MedAPT 4 (Medicines unpleasant to take?)	Yes, n=26	M, n=17 F, n=9	0.472	3-9, n=23 10-11, n=3	0.005	n=26	0.758
		No, n=13	M, n=7 F, n=5		3-9, n=5 10-11, n=7		n=12	

Table 4.5. Continued								
	MedAPT Question response		Demographic data					
			Gender		Age		Clinical Speciality	
			Subset	P value	Subset	P value	Subset	P value
COLOUR	MedAPT 5 (Colours like?)	Yes, n=18	M, n=11 F, n=7	0.583	3-9, n=13 10-11, n=5	0.462	n=19	0.316
		No, n=19	M, n=12 F, n=7		3-9, n=15 10-11, n=4		n=19	
	MedAPT 6 (Colours dislike?)	Yes, n=11	M, n=8 F, n=3	0.316	3-9, n=10 10-11, n=1	0.163	n=11	0.734
		No, n=26	M, n=15 F, n=11		3-9, n=18 10-11, n=8		n=26	
DOSE FORM	MedAPT 7 (Take tablets?)	Yes, n=22	M, n=16 F, n=6	0.137	3-9, n=14 10-11, n=8	0.099	n=22	0.013
		No, n=16	M, n=8 F, n=8		3-9, n=14 10-11, n=2		n=16	
	MedAPT 8 (Take oral liquids?)	Yes, n=30	M, n=19 F, n=11	0.635	3-9, n=24 10-11, n=6	0.106	n=30	0.064
		No, n=8	M, n=5 F, n=3		3-9, n=4 10-11, n=4		n=8	
SIDE EFFECT	MedAPT 9 (Medicines make you feel unwell?)	Yes, n=9	M, n=6 F, n=3	0.536	3-9, n=9 10-11, n=0	0.056	n=9	0.052
		No, n=28	M, n=17 F, n=11		3-9, n=19 10-11, n=9		n=28	
COPING MECH.	MedAPT 10 (Coping mechanism used)	Yes (≥ 1), n=20	M, n=10 F, n=10	0.094	3-9, n=19 10-11, n=1	0.004	n=20	0.929
		No, n=17	M, n=13 F, n=4		3-9, n=9 10-11, n=8		n=17	
	MedAPT 11 (gastrostomy or nasogastric tube?)	Yes, n=3	M, n=2 F, n=1	0.684	3-9, n=1 10-11, n=2	0.141	n=3	0.290
		No, n=34	M, n=21 F, n=13		3-9, n=27 10-11, n=7		n=34	
COMPLEXITY OF MEDICATION REGIME	MedAPT 12 (Med. frequency)	≤ 3 /wk, n=5	M, n=3 F, n=2	0.638	3-9, n=5 10-11, n=0	0.225	n=5	<0.001
		≥ 3 /wk, n=32	M, n=20 F, n=12		3-9, n=23 10-11, n=9		n=32	
	MedAPT 13 (Diff. meds each week)	≤ 2 , n=12	M, n=7 F, n=5	0.507	3-9, n=9 10-11, n=3	0.624	n=12	0.011
		≥ 3 , n=25	M, n=16 F, n=9		3-9, n=19 10-11, n=6		n=25	
CHOICE	MedAPT 14 (Choice offered?)	Yes, n=21	M, n=14 F, n=7	0.321	3-9, n=16 10-11, n=5	0.573	n=21	0.217
		No, n=15	M, n=8 F, n=7		3-9, n=11 10-11, n=4		n=15	

4.3.3.1.1. Gender

Within the patient population, girls more commonly used coping mechanisms than boys did, with 71.4% of the girls using at least one coping mechanism, compared to 43.5% of boys. However, there was no statistically significant difference in the use of coping mechanisms (MedAPT question 10 'Do you use any of the following to help your child take their medicines?') between boys and girls ($p = 0.094$).

4.3.3.1.2. Age

A significant difference in the acceptability of taste (MedAPT question 3, 'Do your medicines taste OK?') between different ages of the children was observed, with a p value of 0.002. Additionally, a significant difference in how pleasant the child's medicines are to take (MedAPT question 4, 'Are any of your medicines unpleasant or not nice to take?') between different age groups was also observed, with a p value of 0.005.

Of the children aged between 3 and 9 years, 22 of the 28 (78.6%) stated that their medicines did not taste OK (MedAPT question 3), compared to 20% (2 out of 10) of the children aged 10 to 11 years. 82% of the 3 to 9 year old children also stated that their medicines were unpleasant or not nice to take (MedAPT question 4), compared to 30% of the 10 to 11 year old children.

Half (50%) of the younger children (3 to 9 years) took at least one tablet medication, whilst 80% of the older children 10 to 11 years took tablets. However, no significant difference in whether the child took tablets (MedAPT question 7) was observed between different ages of the children ($p=0.099$).

No significant difference was observed between the age groups and whether the child took oral liquids (MedAPT question 8). Most children were prescribed an oral liquid, with a higher proportion, 85.7%, of the younger children (3 to 9 years) taking at least one oral liquid medication, whilst 60% of the older children 10 to 11 years took at least one oral liquid.

None of the older, 10 to 11 year old children said their medicines made them feel unwell, compared to 32.1% of the younger, 3 to 9 year olds. However, there was no significant difference in whether the child’s medication makes them feel unwell (MedAPT question 9) between age groups (p= 0.056).

The extent to which coping mechanisms were used differed between age groups. A significant difference in the use of coping mechanisms was observed between the age groups (p=0.004). 67.9% of the younger age group use coping mechanisms, compared with 11.1% of the older children.

Within the older age group (10 to 11-years-old), 22.2% (2 out of 9 children) had an enteral feeding line inserted, through which their medicines were administered, compared with 3.6% (1 child out of 28) of the 3 to 9-years-old age group. There was no significant difference between the age groups and whether enteral feeding tubes were in place (nasogastric or gastrostomy lines, MedAPT question 11), p=0.075.

4.3.3.1.3. Clinical Speciality

A significant difference between clinical specialities with four of the MedAPT responses was observed, as shown in table 4.5.

A significant difference in whether the child took tablets or not (MedAPT question 7 responses), was observed between clinical specialities, with p value of 0.013. Table 4.6 shows the patients prescribed tablets by clinical speciality.

Table 4.6. Number of patients prescribed tablets by clinical speciality

Clinical Speciality	Prescribed tablets	Not prescribed tablets	Total
Dermatology	0	1	1
Metabolic	1	4	5
Nephrology	11	2	13
Oncology	5	8	13
Rheumatology	5	1	6
Total	22	16	38

The nephrology group were the largest sub-group, accounting for 50% of the children who took tablets.

No significant difference in whether the child took oral liquids (MedAPT question 8 responses) was observed between clinical specialities ($p=0.064$).

Table 4.7 shows the patients prescribed oral liquids by clinical speciality.

Table 4.7. Number of patients prescribed oral liquids by clinical speciality

Clinical Speciality	Prescribed oral Liquids	Not prescribed oral Liquids	Total
Dermatology	1	0	1
Metabolic	5	0	5
Nephrology	11	2	13
Oncology	11	2	13
Rheumatology	2	4	6
Total	30	8	38

Oral liquids are the predominant dose form prescribed across the clinical specialities, with 79% of all children prescribed at least one oral liquid.

A significant difference in whether the medicines make the child feel unwell (MedAPT question 9 responses), was observed between clinical specialities, with p value of 0.052. A total of 66.7% of the rheumatology patients, 30.8% of oncology patients and 8.3% of nephrology patients stated that their medicines made them feel unwell, whilst none of the children within the dermatology and metabolic clinical specialities stating their medicines had this effect on them.

A significant difference in the frequency of medicine taking (MedAPT question 12) was observed between clinical specialities, with a p value of <0.001 . Within the dermatology, metabolic, nephrology and oncology groups all patients take medicines at least 3 times each week, whereas 83.3% of the rheumatology patients take their medicines less than 3 times each week.

A significant difference in the number of different weekly medicines taken by the child (MedAPT question 13 responses) was observed between clinical specialities, with a p value of 0.011. The nephrology and oncology groups contained the highest proportion of children regularly taking at least three different medicines weekly, accounting for 55.3% of the total and 83.3% of nephrology patients and 84.6% of oncology patients. Conversely, only 16.7% of rheumatology patients took 3 or more different medicines each week.

4.3.3.2. Analysis of demographic data and medication adherence

To explore whether there was a relationship between the patients' demographic data and Medication adherence, the distributions of the demographic factors of gender, age and clinical speciality were compared with the distributions of the medication adherence variables by Fisher's exact analysis. The results are tabulated in table 4.8.

Table 4.8. Fisher's exact analysis for patient factors by medication adherence data

Independent Variable		Adherence (Dependent variable)					
		Adherent		Adherent to Tablet		Adherent to Liquid	
		Subset	P value	Subset	P value	Subset	P value
Gender	Male n=24	Yes, n=9 No, n=15	0.088	Yes, n=5 No, n=10	0.177	Yes, n=9 No, n=9	0.226
	Female n=14	Yes, n=7 No, n=3		Yes, n=3 No, n=1		Yes, n=6 No, n=2	
MedAPT 1 (Age of child)	3-9 yrs, n= 28	Yes, n=11 No, n= 14	0.417	Yes,n=4 No, n=8	0.297	Yes, n=12 No, n=9	0.654
	10-11 yrs, n= 10	Yes, n=5 No, n=4		Yes, n=4 No, n=3		Yes, n=3 No, n=2	
Clinical Speciality	Dermatology	Yes, n=0 No, n=0	0.196	Yes, n=0 No, n=0	0.607	Yes, n=0 No, n=0	0.509
	Metabolic	Yes, n=4 No, n=1		Yes, n=1 No, n=0		Yes, n=3 No, n=1	
	Nephrology	Yes, n=3 No, n=9		Yes, n=3 No, n=7		Yes, n=4 No, n=6	
	Oncology	Yes, n=6 No, n=6		Yes, n=2 No, n=2		Yes, n=6 No, n=4	
	Rheumatology	Yes, n=3 No, n=2		Yes, n=2 No, n=2		Yes, n=2 No, n=0	

No significant difference in adherence to all medication (Adherent) between boys and girls was observed ($p=0.088$). No significant difference was observed between girls and boys in their adherence to oral tablet medication (Adherent to tablet) or oral liquid medication. The findings showed 70% of girls were adherent when the outcome measure was adherence to all their medication, 75% were adherent to their tablet medication, and 75% to their oral liquid medication. This compares with values for boys of 43% (Adherent to all medication), 33% (adherent to tablets) and 50% (adherent to oral liquids).

The children in the metabolic group were more adherent with values of 80% (Adherent to all medication), 100% (adherent to tablets) and 75% (adherent to oral liquids), with the nephrology group indicating the lowest level of adherence with values of 25% (Adherent to all medication), 30% (adherent to tablets) and 40% (adherent to oral liquids). However, there was no significant difference in adherence to all medication (Adherent) between clinical speciality groups observed.

4.3.4. MedAPT part 1 responses and Adherence outcome

This section evaluates the relationship between the independent variables of MedAPT question 1 to 14 responses (Part 1) and the dependent variables of adherent to all medication (Adherent), adherent to tablets and adherent to liquid (Oral liquid adherence).

Fisher's exact test was then used to investigate whether there is a relationship between the MedAPT responses and medication adherence, by determining whether the distributions of the MedAPT responses differ from the summary of medication adherence data. Table 4.9 summarises the results.

Table 4.9. Fisher's exact data for medication factors by medication adherence data

	MedAPT Question response (Independent variable)		Medication adherence (Dependent Variable)					
			Adherent		Adherent to Tablet		Adherent to Liquid	
			Subset	P value	Subset	P value	Subset	P Value
AGE	MedAPT 1 (Age of child)	3-9 yrs, n= 28	Yes, n=11 No, n= 14	0.417	Yes, n=4 No, n=8	0.297	Yes, n=12 No, n=9	0.654
		10-11 yrs, n= 10	Yes, n=5 No, n=4		Yes, n=4 No, n=3		Yes, n=3 No, n=2	
CLINICAL SPECIALITY	MedAPT 2 (Medical condition)	Sub-group 1: ALL/Onc., JIA, Neph., n=33	Yes, n=12 No, n=18	0.039	Yes, n=7 No, n=11	0.421	Yes, n=12 No, n=11	0.175
		Sub-group 2: Dermat., Metab., n=5	Yes, n=4 No, n=0		Yes, n=1 No, n=0		Yes, n=3 No, n=0	
TASTE	MedAPT 3 (Medicines taste OK?)	Yes, n=14	Yes, n=8 No, n=6	0.262	Yes, n=6 No, n=4	0.115	Yes, n=6 No, n=4	0.588
		No, n=24	Yes, n=8 No, n=12		Yes, n=2 No, n=7		Yes, n=9 No, n=7	
	MedAPT 4 (Medicines unpleasant to take?)	Yes, n=26	Yes, n=9 No, n=13	0.270	Yes, n=3 No, n=8	0.144	Yes, n=10 No, n=8	0.543
		No, n=12	Yes, n=7 No, n=5		Yes, n=5 No, n=3		Yes, n=5 No, n=3	
COLOUR	MedAPT 5 (Colours like?)	Yes, n=18	Yes, n=8 No, n=9	0.563	Yes, n=2 No, n=5	0.417	Yes, n=8 No, n=6	0.607
		No, n=19	Yes, n=7 No, n=9		Yes, n=5 No, n=6		Yes, n=6 No, n=5	
	MedAPT 6 (Colours dislike?)	Yes, n=11	Yes, n=4 No, n=7	0.357	Yes, n=1 No, n=4	0.324	Yes, n=7 No, n=4	0.393
		No, n=26	Yes, n=11 No, n=15		Yes, n=6 No, n=7		Yes, n=7 No, n=7	
DOSE FORM	MedAPT 7 (Take tablets?)	Yes, n=22	Yes, n=7 No, n=13	0.091	n/a	n/a	Yes, n=6 No, n=6	0.368
		No, n=16	Yes, n=9 No, n=5		n/a		Yes, n=9 No, n=5	
	MedAPT 8 (Take oral liquids?)	Yes, n=30	Yes, n=13 No, n=14	0.571	Yes, n=5 No, n=7	0.663	n/a	n/a
		No, n=8	Yes, n=3 No, n=4		Yes, n=3 No, n=4		n/a	

Table 4.9. Continued								
	MedAPT Question response (Independent variable)		Medication adherence (Dependent Variable)					
			Adherent		Adherent to Tablet		Adherent to Liquid	
			Subset	P value	Subset	P value	Subset	P value
SIDE EFFECTS	MedAPT 9 (Medicines make you feel unwell?)	Yes, n=9	Yes, n=2 No, n=5	0.283	Yes, n=1 No, n=3	0.485	Yes, n=3 No, n=3	0.548
		No, n=28	Yes, n=13 No, n=13		Yes, n=6 No, n=8		Yes, n=11 No, n=8	
COPING MECH.	MedAPT 10 (Coping mechs. used)	Yes (≥1), n=20	Yes, n=6 No, n=10	0.295	Yes, n=2 No, n=6	0.278	Yes, n=8 No, n=5	0.430
		No, n=17	Yes, n=9 No, n=8		Yes, n=5 No, n=5		Yes, n=6 No, n=6	
	MedAPT 11 (gast or ng. tube?)	Yes, n=3	Yes, n=1 No, n=2	0.570	Yes, n=0 No, n=1	0.611	Yes, n=1 No, n=2	0.407
		No, n=34	Yes, n=14 No, n=16		Yes, n=7 No, n=10		Yes, n=13 No, n=9	
MEDICATION COMPLEXITY	MedAPT 12 (Med. frequency)	≤3/wk, n=5	Yes, n=2 No, n=2	0.626	Yes, n=1 No, n=2	0.674	Yes, n=2 No, n=0	0.303
		≥3/wk, n=32	Yes, n=13 No, n=16		Yes, n=6 No, n=9		Yes, n=12 No, n=11	
	MedAPT 13 (Diff.meds each week)	≤2, n=12	Yes, n=9 No, n=2	0.004	Yes, n=4 No, n=2	0.117	Yes, n=8 No, n=0	0.003
		≥3, n=25	Yes, n=6 No, n=16		Yes, n=3 No, n=9		Yes, n=6 No, n=11	
CHOICE	MedAPT 14 (Choice offered?)	Yes, n=21	Yes, n=8 No, n=12	0.261	Yes, n=3 No, n=8	0.220	Yes, n=8 No, n=6	0.611
		No, n=15	Yes, n=7 No, n=5		Yes, n=4 No, n=3		Yes, n=6 No, n=4	

A significant difference in adherence to all medication (Adherent) between the two medical condition groups (MedAPT question 2) was observed (p=0.039). Within the study, only children within sub-group 1 [ALL/oncology, juvenile idiopathic arthritis (JIA), pain or nephrology] showed evidence of non-adherence to their medication. Conversely, all the children within sub-group 2 (Dermatology and Metabolic) were adherent to their medication.

Sufficient refill data were not available to determine adherence in all cases, however, where data was available 77.8% of children who responded 'No' to MedAPT 3 (Medicines do not taste OK) were found to be tablet non-adherent, and

60% of children who responded 'Yes' (medicines taste OK) were found to be tablet adherent.

Of the study participants, 72.7% of children who responded 'Yes to MedAPT 4 (Medicines are unpleasant to take) were found to be tablet non-adherent, and 62.5% of children who responded 'No' (medicines are not unpleasant to take) were found to be tablet adherent.

The responses to MedAPT 3 and 4 have been analysed in section 4.3.4.2. and further, in terms of the use of coping mechanisms, within section 4.3.4.6.

No significant difference in observed outcome of medication adherence to all medications (Adherent) between responses to the question 'Do you take any tablets?' (MedAPT question 7) was observed ($p=0.091$).

A significant difference in observed outcome of medication adherence to all medication (Adherent), and adherence to [oral] liquids, with how many different medicines the child takes each week (MedAPT question 13) was observed. Adherence to all medication (Adherent) produced a p value of 0.004, and adherence to oral liquids ($p=0.003$).

No significant difference in adherence to tablets was observed between the two medication frequency groups, however within the group who take up to 2 different medicines each week, 66% were adherent to tablets. Of children who take more than 2 different tablets each week, 75% were non-adherent to tablets.

This indicator of the complexity of the medication regime is further explored in section 4.3.4.4.

4.3.4.1. Analysis of MedAPT Part 1 responses to colour preferences

Two questions within the MedAPT questionnaire sought to gather information on the patients' colour preferences: question 5, Are there any colours of medicines you like?, and question 6, Are there any colours of medicines you do not like?

A total of 48.6% of children stated that they liked a particular colour of medicine (question 5), and 29.7% stated a dislike for a particular colour of medicine (question 6), with 81.8% of the children who stated a dislike for a given colour (question 6) also having stated a colour preference (question 5).

Fisher's exact analysis of the distributions of MedAPT question 5 response and the measures of refill adherence are detailed in table 4.9. Refill adherence (all medication) produces a p value of 0.563, adherent to tablet $p=0.417$ and adherent to liquid $p=0.607$ indicating that there is not a significant relationship between the child's positive colour preference and whether they are adherent to their medication.

No significant difference in adherence was observed between children who stated a colour dislike and those who did not. Of children who expressed a colour dislike, 36.4% were non-adherent to at least one of their liquid medicines, and 80% non-adherent to oral solid medicines. Of children who expressed a medication colour dislike, 63.6% were found to have some evidence of non-adherence to at least one of their medicines.

4.3.4.2. Analysis of MedAPT Part 1 responses to taste preferences

Two questions within the MedAPT questionnaire sought to gather information on the patients' taste preferences, namely: question 3, Do your medicines taste OK? And question 4, Are any of your medicines unpleasant or not nice to take? 63.2% of children stated that their medicines did not taste OK (question 3), and 68.4% stated that at least one of their medicines was unpleasant or not nice to take (question 4),

There was highly significant agreement between the responses to questions 3 and 4, with a Fisher's exact p value of 0.0001, demonstrating that the child responded consistently to the two questions relating to taste.

Fisher's exact analysis of the distributions of MedAPT questions 3 and 4 response and the measures of refill adherence are detailed in table 4.9. Refill adherence (all

medication) produces p values of 0.262 (question 3) and 0.270 (question 4), adherent to tablet $p=0.115$ (question 3), 0.144 (question 4) and adherent to liquid $p=0.588$ (question 3), 0.543 (question 4).

There is no significant relationship between the distributions of Question 3 ‘Do your medicines taste OK?’ and adherence to tablets, however, there was evidence of a relationship between the child’s taste preference and whether they are adherent to their tablet medication. The cross tabulation data reveals that a negative response to question 3 is associated with the response variable of tablet non-adherence, with 60% of children who stated that their medicines taste OK being adherent to tablets and conversely 78% who stated their medicines did not taste OK were non-adherent to tablets. Whilst not statistically significant, the data indicate that a negative response to medicine taste was associated with non-adherence and conversely a positive response was associated with adherence. This has been discussed further in chapter 5, general discussion.

4.3.4.3. Analysis of MedAPT part 1 responses to dose form preferences

The child and parent study sample comprised a total of 76 people from the AHCNHSFT: 38 children and 38 parents. The 38 children were prescribed 182 different medicines, containing 110 different active ingredients through AHCNHSFT Pharmacy. The count and percentage of each dose form variant prescribed is detailed in table 4.10.

Table 4.10 Dose forms prescribed to study participants (number of variants)

	Dose form					
	Tablet	Oral Liquid	Capsule	Oral Melt	Injection	Topical (Cream/Ointment)
Count	41	64	16	2	46	13
%	22.5	35.2	8.8	1.1	25.3	7.1

There were more oral liquid medicine variants prescribed, representing over a third of all prescribed medicine variants, followed by injections and tablets representing approximately one quarter each. A large number, 78.9% of the children in the study, were prescribed at least one oral liquid as part of their treatment protocol, and 60.5% were prescribed tablets.

Insufficient data were available to enable evaluation of topical treatment adherence due to imprecise dosing of creams and ointments to enable meaningful refill data analysis. Injection medication was predominantly administered by healthcare professionals within the trust, therefore refill data were not considered to provide an indicator of patient medication adherence.

Data were only available on two oral melt products for two patients. Due to the limited quantity of data, the data were not analysed further to explore trends. Capsule data were combined with tablet data to give the solid oral medication group.

Table 4.11 details the percentage of each age group prescribed tablets and liquids.

Table 4.11. Dose form of prescribed medication by age

	Age (Years)								
	3	4	5	6	7	8	9	10	11
Tablets (%)	0	0	67	50	57	75	67	75	83
Oral liquids (%)	100	100	100	100	86	76	50	67	50

Tablets were prescribed to children from 5 years up to 11 years only. The older age groups representing the higher percentage prescribed tablets. Oral liquids were prescribed across the age range from 3 to 11 years, with the lower age range 3 to 7 years representing the higher percentage prescribed oral liquids

Oral liquid prescribing is predominant in the younger children, with an associated reduction with age. Oral liquids were prescribed across the age range from 3 to 11 years, with the lower age range 3 to 7 years representing the higher percentage prescribed oral liquids.

Two questions within the MedAPT questionnaire gathered information on whether children took tablet and oral liquid medications: Question 7, Do you take any tablets? ; question 8, Do you take any oral liquids?

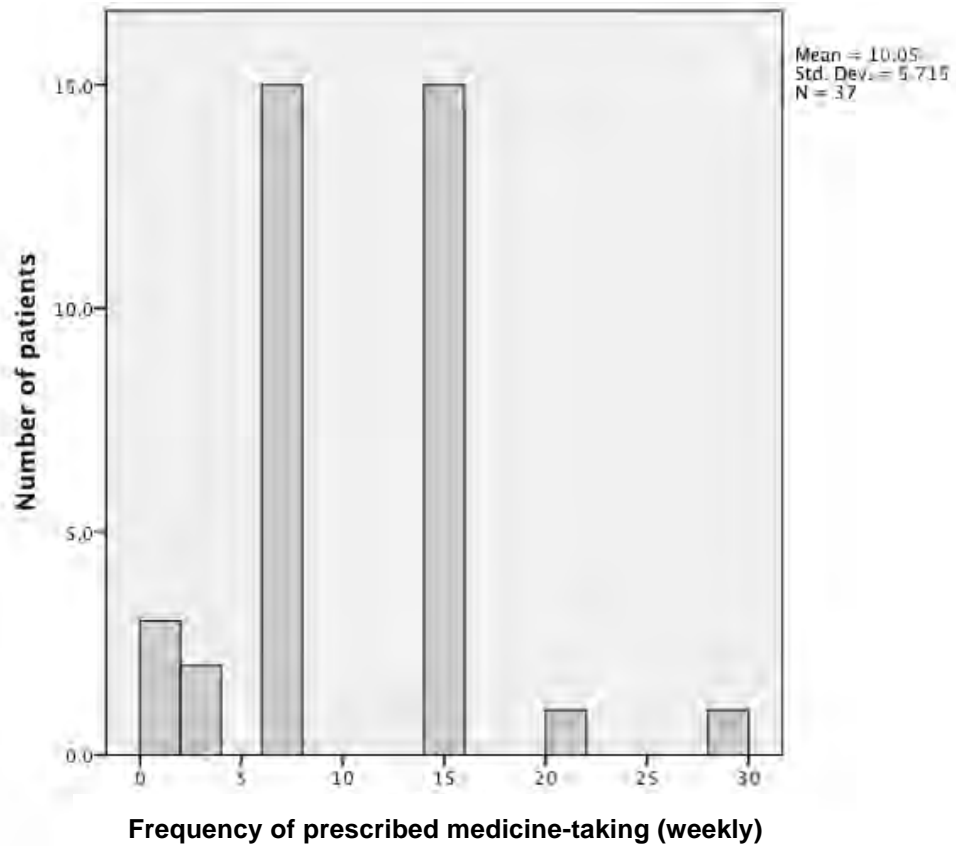
Fisher's exact analysis of the distributions of MedAPT questions 7 and 8 responses and the measures of refill adherence identified no significant difference in observed outcome of medication adherence. Evaluation of the cross-tabulation of the data shows that 58% of children who take tablets are non-adherent to at least one of their tablet medications with 65% of children who take tablets being non-adherent to at least one of their medicines, when all forms of medication are considered. This compared with 36% of children who do not take tablets being non-adherent to at least one of their medicines.

4.3.4.4. Analysis of complexity of medication protocol

The frequency with which a given medication must be taken, and the number of different medicines within the child's medication protocol, are measures of the complexity of the medication protocol.

Figure 4.4 shows the number of times patients are required to take medication each week. The study participants had a weekly medication frequency of between once a week and 28 times each week, the most common frequency being 7 or 14 times per week. 86.5% of children took medicines at least 3 times a week.

Figure 4.4. Histogram of number of times patients are required to take medication each week



The frequency of medication taking and adherence outcome is presented in tables 4.12 to 4.14. Fisher's exact analysis of the distributions of medication frequency and adherence outcome did not indicate statistical significance, with p values of 0.142 (Adherent, all medication), 0.103 (Adherent to oral solid medication), 0.518 (Adherent to oral liquid medication).

Based on the data in table 4.12, 71.4% of children who were required to take medication at least 14 times each week, were non-adherent, when all forms of medication are considered, compared to 44.4% non-adherent (all forms of medication) who were required to take medication 7 times each week or less.

Table 4.12. Medication taking frequency and adherence

Number of medication taking events per week	Adherent (all medication)		Total
	N	Y	
1	2	1	3
3	0	1	1
7	6	8	14
14	10	3	13
21	0	1	1
28	0	1	1
Total	18	15	33

Based on the data in table 4.13, 77.8% of children who were required to take medication at least 14 times each week, were non-adherent to solid oral medication, compared to 44.4% of children who were required to take medication 7 times each week or less being non-adherent to solid oral medication.

Table 4.13. Medication taking frequency and adherence to oral solid medication

Number of medication taking events per week	Adherent (oral solid medication)		Total
	N	Y	
1	2	1	3
7	2	4	6
14	7	1	8
28	0	1	1
Total	11	7	18

As presented in table 4.14, adherence to oral liquid medication, non-adherence is observed in just 53.8% of children required to take medication at least 14 times each week, and 33.3% where medication frequency is 7 times each week or less.

Table 4.14. Medication taking frequency and adherence to oral liquid medication

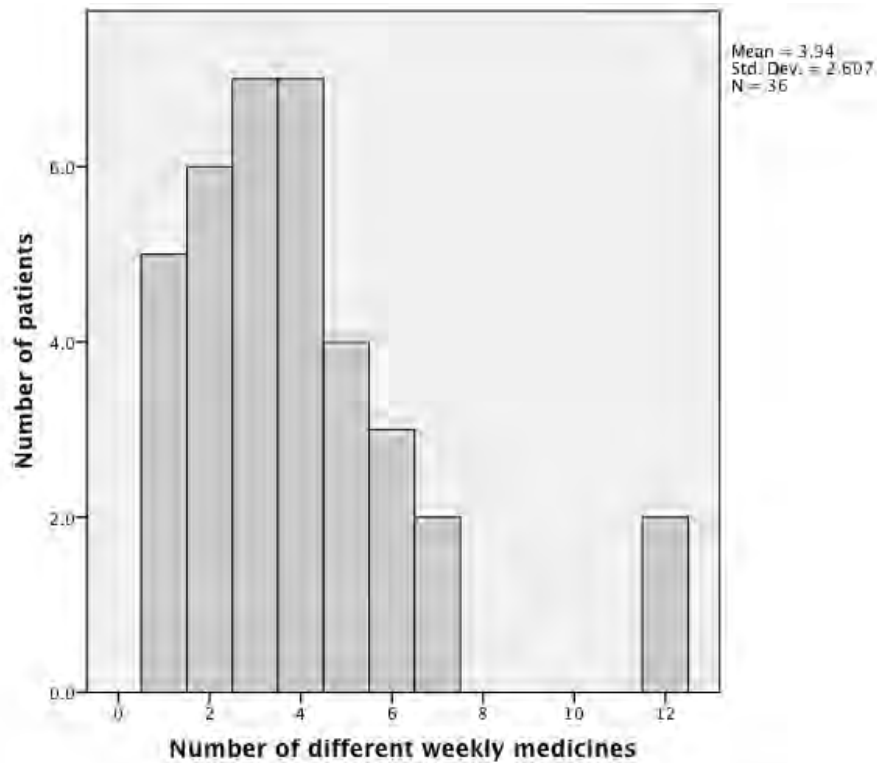
Number of medication taking events per week	Adherent (oral liquid medication)		Total
	N	Y	
1	0	1	1
3	0	1	1
7	4	6	10
14	7	4	11
21	0	1	1
28	0	1	1
Total	11	14	25

Fisher's exact analysis was conducted by categorising based on medication frequency less than or equal to 7 times each week and greater than 7 times each week. No significant difference in adherence based on frequency was observed, with p values of 0.178 (adherence across all medication dose forms), 0.167 (oral solid adherence) 0.265 (oral liquid adherence).

Considering the other aspect of medication complexity, which is the number of different medications the patient is required to take each week, Figure 4.5 shows the number of different medicines the children in the study were required to take each week.

The medication protocol for the study participants involved taking between 1 and 12 different medicines each week, the mode being 3 or 4 different medicines, and a total of 67.6% of the children took 3 or more different medicines each week.

Figure 4.5. Histogram of the number different medicines patients are required to take each week



Fisher's exact analysis showed there was a significant difference in observed outcome of medication adherence to all medication (Adherent) and adherence to [oral] liquids, with how many different medicines the child takes each week (MedAPT question 13). Adherence to all medication (Adherent) produced a p value of 0.004 and adherence to [oral] liquids a p value of 0.003 (see table 4.9.).

Of the children who took no more than 2 different medicines each week, 82% were adherent when all their medications are included in the calculation, 67% adherent to tablets and 100% adherent to oral liquids.

Of the children who took 3 or more different medicines each week 73% of them were non-adherent when all their medications are included in the calculation, 75% of them non-adherent to tablets and 65% non-adherent to oral liquids.

4.3.4.5. Analysis of MedAPT responses to whether medicines make child feel unwell

Question 9 within the MedAPT questionnaire sought to gather information on whether the medication resulted in the child feeling unwell.

Of the children in the study, 23.7% of children stated that their medicines made them feel unwell. Fisher's exact analysis of the distributions of MedAPT question 9 response and the measures of refill adherence are detailed in table 4.9. Refill adherence (all medication) produces a p value of 0.283, adherent to tablet $p=0.485$ and adherent to liquid $p=0.548$, indicating that there is not a statistically significant relationship between adherence and whether medication makes the child feel unwell.

Of the children who report that their medication makes them feel unwell, 71.4% were non-adherent when all their medications are included in the calculation, 75% of them non-adherent to tablets and 50% non-adherent to oral liquids. Of children who report that their medication does not make them feel unwell, 50% were adherent when all their medications are included in the calculation, 43% adherent to tablets and 58% adherent to oral liquids.

There was a significant relationship between the response to question 9 and the use of coping mechanisms with a p value of 0.017, providing evidence that parents may be influenced by the child's response to feeling unwell in taking their medication by using coping mechanisms to address potential aversive behaviour or to alleviate the symptoms resulting from taking the medicine. The use of coping mechanisms is explored further in section 4.3.4.6.

4.3.4.6. Analysis of MedAPT responses to use of coping mechanisms

The MedAPT questionnaire (MedAPT Question 10) asked participants to confirm whether any of the following methods were used to help the child to take their medication:

- i. Mix the medicine with food or drink
- ii. Child takes something before or after the medicine as reward or to mask taste
- iii. Physical force or restraint
- iv. Offer money
- v. Persuasion or reasoning

Each of the methods were used within the study population, with 20 (52.6%) stating that one or more of the coping mechanisms were used. Table 4.15 shows the use of coping mechanisms used in the coping mechanism population and the prevalence of coping mechanism used across the whole study population.

As can be seen in table 4.15, methodologies which involved masking the taste of the medicine by directly mixing the medicine with food or drink, or taking before or after a food or drink to mask the taste were, together with persuasion, the most commonly used.

Table 4.15. Use of coping mechanisms within the study population

Coping Mechanism	Use of coping mechanisms within the coping mechanism population (%)	Prevalence of coping mechanisms used in total study population (%)
Mix with food or drink	50	26.3
Mask taste	40	21
Physical force or restraint	10	5.3
Offer money	5	2.6
Persuasion or reasoning	45	23.7

Fisher's exact test was used to investigate whether there is a relationship between the medication factors of: dose form; frequency; number of different medicines prescribed; and choice, and the requirement for coping mechanisms to be used. This was achieved by determining whether the distributions of medication factors and coping mechanisms (from the MedAPT questionnaire response), differ. Table 4.16 summarises the results.

Table 4.16. Fisher's exact test for medication factors by use of coping mechanism

	MedAPT response variable		MedAPT 10 (Coping mechanism used)	
			Subset	P value
CLINICAL SPECIALITY	MedAPT 2 (Medical condition)	ALL/Oncology, JIA, Nephrology, n=33	Yes, n=17 No, n=15	0.356
		Dermatology, Metabolic, n=5	Yes, n=3 No, n=2	
TASTE	MedAPT 3 (Medicines taste OK?)	Yes, n=13	Yes, n=3 No, n=10	0.006
		No, n=24	Yes, n=17 No, n=7	
	MedAPT 4 (Medicines unpleasant to take?)	Yes, n=26	Yes, n=17 No, n=9	0.032
		No, n=11	Yes, n=3 No, n=8	
COLOUR	MedAPT 5 (Colours like?)	Yes, n=18	Yes, n=10 No, n=8	0.254
		No, n=19	Yes, n=10 No, n=9	
	MedAPT 6 (Colours dislike?)	Yes, n=11	Yes, n=8 No, n=3	0.100
		No, n=26	Yes, n=12 No, n=14	
DOSE FORM	MedAPT 7 (Take tablets?)	Yes, n=21	Yes, n=11 No, n=10	0.254
		No, n=16	Yes, n=9 No, n=7	
	MedAPT 8 (Take oral liquids?)	Yes, n=29	Yes, n=17 No, n=12	0.183
		No, n=8	Yes, n=3 No, n=5	
SIDE EFFECTS	MedAPT 9 (Medicines make you feel unwell?)	Yes, n=9	Yes, n=8 No, n=1	0.017
		No, n=28	Yes, n=12 No, n=16	
MEDICATION COMPLEXITY	MedAPT 12 (Medication frequency)	≤3/wk, n=5	Yes, n=4 No, n=1	0.189
		≥ 3/wk, n=32	Yes, n=16 No, n=16	
	MedAPT 13 (Diff.meds each week)	≤2, n= 12	Yes, n=8 No, n=4	0.162
		≥3, n=25	Yes, n=12 No, n=13	
CHOICE	MedAPT 14 (Choice offered?)	Yes, n=21	Yes, n=12 No, n=9	0.259
		No, n=15	Yes, n=8 No, n=7	

A significant difference in whether coping mechanisms were used was observed between positive and negative respondents to MedAPT 3 question 'Do your medicines taste OK?', with a p value of 0.006.

In response to the question exploring whether medicines are unpleasant to take (MedAPT 4), 65.4% of children who stated that their medicines were unpleasant to take, used coping mechanisms, and 72.7% who stated their medicines were not unpleasant to take did not indicate the use of coping mechanisms.

A significant difference in whether coping mechanisms were used was observed between positive and negative respondents to the question 'Are any of your medicines unpleasant or not nice to take?' (MedAPT4), with a p value of 0.032.

A significant difference in whether coping mechanisms were used was observed between positive and negative respondents to the question 'Do any of your medicines make you feel unwell?' (MedAPT 9), with a p value of 0.017.

Of the children in the study who said the medication made them feel unwell, 88.9% used coping mechanisms. Within the sub-population who stated the medicines did not make them feel unwell, the use of coping mechanisms was seen in 57.1% of children, and not used in 43.9% of cases.

Table 4.16 shows that there is a significant difference in the use of coping mechanisms between boys and girls (gender, section 4.3.3.1.1) and between different age groups (section 4.3.3.1.2.).

4.3.4.7. Analysis of MedAPT responses to the question of choice

Data collected as part of the initial CHIMP study (chapter 2), indicated choice as an influencing factor on acceptability. This was initially based on the premise that there may not be one solution to meet the needs of all children, and therefore offering a choice may provide the opportunity for the child to select the preferred dose medication dose form, and hence facilitate adherence. Data collected through the MedAPT questionnaire demonstrated that 21 of the 38 study participants (55.3%)

had been offered a choice of dose form (solid oral or liquid oral medication) for the child. What is not clear from the data is whether an active choice was made. What still remains, within the group who have been offered a choice, is the requirement for the use of coping mechanisms in 52.4% of children, which is comparable to 52.6% of all study participants who use coping mechanisms.

4.3.5. Data analysis of beliefs and behaviour questions (BBQ)

Fisher's exact test was used to investigate whether there is a relationship between the MedAPT BBQ responses (MedAPT part 2) and medication adherence, by determining whether the distributions of the MedAPT responses differ from the summary of medication adherence data. Tables 4.17, 4.18 and 4.19 summarise the results.

Fisher's exact analysis of the distributions of the patients' BBQ response scores and the three adherence measures (adherent to all medications, adherent to tablets and adherent to oral liquids) highlighted a significant difference between the oral liquid non-adherent and adherent groups, and their response to BBQ 5, with a p value of 0.072. All participants with a score of 4 or less, which indicates that the participants did not always keep the medicines close to where they need to use them, were found to be non-adherent to oral liquids, however, this is only based on 3 participants.

Fisher's exact analysis of the distributions of total combined BBQ score (sum of patient's BBQ response scores) and any of the three adherence measures (adherent to all medications, adherent to tablets and adherent to oral liquids) did not highlight a significant difference between the non-adherent and adherent groups in terms of their total BBQ score. Adherent to all medications, $p=0.956$, adherent to tablets $p=0.819$, and adherent to oral liquids $p=0.830$.

Fisher's exact analysis of the distributions of mean BBQ score (mean of patient's BBQ response scores) and any of the three adherence measures (adherent to all medications, adherent to tablets and adherent to oral liquids) did not highlight a significant difference between the non-adherent and adherent groups in terms of

their mean BBQ score. Adherent to all medications, $p=0.972$. Adherent to tablets, $p=0.789$, and adherent to oral liquids $p=0.692$.

Table 4.17. Fisher’s exact analysis of BBQ responses and Medication adherence (all medication)

MedAPT BBQ response variable		Adherent (all medication)		
	Response score	Yes	No	p value
BBQ 1 (Doctors knowledgeable)	1	0	1	0.877
	2	0	0	
	3	1	0	
	4	2	2	
	5	11	15	
BBQ 2 (Medicines unpleasant)	1	1	0	0.795
	2	2	4	
	3	3	2	
	4	3	4	
	5	5	8	
BBQ 3 (Medicines confusing)	1	0	0	0.466
	2	0	0	
	3	0	2	
	4	4	6	
	5	11	9	
BBQ 4 (Strict routines?)	1	0	0	0.603
	2	0	0	
	3	1	2	
	4	0	2	
	5	14	13	
BBQ 5 (Medicines kept close by for use?)	1	0	0	0.486
	2	0	0	
	3	0	1	
	4	0	2	
	5	15	14	
BBQ 6 (Ensure don’t run out of medicine?)	1	0	0	0.726
	2	0	0	
	3	0	0	
	4	1	1	
	5	14	16	

Table 4.18. Fisher’s exact analysis of BBQ responses and Medication adherence (tablet medication)

MedAPT BBQ response variable		Adherent (tablet medication)		
	Response score	Yes	No	p value
BBQ 1 (Doctors knowledgeable)	1	0	0	0.389
	2	0	0	
	3	0	0	
	4	1	0	
	5	6	11	
BBQ 2 (Medicines unpleasant)	1	0	0	0.679
	2	0	3	
	3	1	2	
	4	1	2	
	5	5	4	
BBQ 3 (Medicines confusing)	1	0	0	0.441
	2	0	0	
	3	0	0	
	4	1	3	
	5	6	7	
BBQ 4 (Strict routines?)	1	0	0	Not computed as BBQ4 constant
	2	0	0	
	3	0	0	
	4	0	0	
	5	7	10	
BBQ 5 (Medicines kept close by for use?)	1	0	0	0.588
	2	0	0	
	3	0	0	
	4	0	1	
	5	7	9	
BBQ 6 (Ensure don’t run out of medicine?)	1	0	0	0.669
	2	0	0	
	3	0	0	
	4	1	1	
	5	6	9	

Table 4.19. Fisher’s exact analysis of BBQ responses and Medication adherence (oral liquid medication)

MedAPT BBQ response variable		Adherent (oral liquid medication)		
	Response score	Yes	No	p value
BBQ 1 (Doctors knowledgeable)	1	0	1	0.556
	2	0	0	
	3	1	0	
	4	1	2	
	5	11	8	
BBQ 2 (Medicines unpleasant)	1	1	0	0.253
	2	4	2	
	3	3	0	
	4	2	3	
	5	3	6	
BBQ 3 (Medicines confusing)	1	0	0	0.211
	2	0	0	
	3	0	2	
	4	5	4	
	5	9	4	
BBQ 4 (Strict routines?)	1	0	0	0.199
	2	0	0	
	3	1	2	
	4	0	2	
	5	13	7	
BBQ 5 (Medicines kept close by for use?)	1	0	0	0.072
	2	0	0	
	3	0	1	
	4	0	2	
	5	14	8	
BBQ 6 (Ensure don’t run out of medicine?)	1	0	0	0.440
	2	0	0	
	3	0	0	
	4	0	1	
	5	14	10	

4.3.6. Revision of MedAPT based on study data

4.3.6.1. MedAPT Part 1

Analysis of the study data in sections 4.3.3 to 4.3.5 identified those factors, which were associated with medication adherence and non-adherence.

Whilst only those factors which produced a p value of ≤ 0.05 were considered statistically significant, there are data, discussed throughout this chapter, which indicate a potential relationship with medication adherence, and in combination with other influencing factors, should be considered. The scoring mechanism was therefore revised to reflect the strength of association based on effect size calculation, and was inclusive of all part 1 data. The effect size of a Fisher's exact test can be described by phi or Cramér's V. Cramér's V, initially published by Harald Cramér (1946), is the measure of association between two variables, with a value between 0 and +1 inclusive. The larger the value, the greater the size of the effect. The Cramér V values for each of the MedAPT response variables, with adherent (all medications) as the outcome measure were: MedAPT1 V=0.102; MedAPT2 V=0.387; MedAPT3 V=0.169; MedAPT4 V=0.167; MedAPT5 V=0.033; MedAPT6 V=0.129; MedAPT7 V=0.289; MedAPT8 V=0.043; MedAPT9 V=0.176; MedAPT10 V=0.155; MedAPT11 V=0.077; MedAPT12 V=0.034; MedAPT13 V=0.516; MedAPT14 V=0.178.

Those factors with a $V \geq 0.3$ were assigned a score of 5 or 0. A score of 5 being assigned to a non-adherence indicating response. Those factors with $V \geq 0.2$ and < 0.3 were assigned a score of 3 or 0 (3 being assigned to a non-adherence indicating response). The scoring for the remaining factors remained unchanged. Finally, the scores assigned to MedAPT 7, Do you take any tablets?, were reversed, as the data demonstrated taking tablets resulted in higher incidence of non-adherence in the study i.e. If the child took tablets they were assigned a score of 3.

Children who scored 20 points or more were predicted to be non-adherent, and those children scoring 19 or less predicted to be adherent.

The revised scores are shown in table 4.20.

Table 4.20. Revised MedAPT part 1 scores for study participants

The table is sorted by prediction correctness. The grey shaded cells highlight the predictions that were correct, based on adherence to all medication.

PIC	REVISED MedAPT Part 1 score	REVISED Predicted adherence (based on part 1)	Prediction correct? (Adherence All medication)	Medication adherence		
				All medication	Solid oral	Oral liquids
1	16	Y	CORRECT	Y	Y	Y
4	29	N	CORRECT	N	N	Y
6	15	Y	CORRECT	Y	NA	Y
7	29	N	CORRECT	N	ND	N
8	19	Y	CORRECT	Y	NA	Y
9	19	Y	CORRECT	Y	NA	Y
10	18	Y	CORRECT	Y	Y	NA
11	24	N	CORRECT	N	NA	N
12	23	N	CORRECT	N	NA	N
13	21	N	CORRECT	N	Y	N
14	29	N	CORRECT	N	N	N
15	14	Y	CORRECT	Y	NA	Y
16	19	Y	CORRECT	Y	Y	ND
18	27	N	CORRECT	N	N	N
19	25	N	CORRECT	N	NA	N
20	23	N	CORRECT	N	N	N
21	25	N	CORRECT	N	N	NA
22	20	N	CORRECT	N	N	N
23	14	Y	CORRECT	Y	NA	Y
27	24	N	CORRECT	N	N	NA
28	28	N	CORRECT	N	N	Y
29	12	Y	CORRECT	Y	Y	Y
32	14	Y	CORRECT	Y	NA	Y
34	15	Y	CORRECT	Y	Y	NA
36	27	N	CORRECT	N	N	Y
37	4	Y	CORRECT	Y	NA	Y
38	18	Y	CORRECT	Y	NA	Y
3	17	Y	INCORRECT	N	N	NA
24	20	N	INCORRECT	Y	NA	Y
25	19	Y	INCORRECT	N	NA	N
26	13	Y	INCORRECT	N	NA	N
30	14	Y	INCORRECT	N	N	NA
31	20	N	INCORRECT	Y	Y	Y
33	24	N	INCORRECT	Y	Y	NA
2	31	N	ND	ND	ND	ND
5	27	N	ND	ND	NA	ND
17	19	Y	ND	ND	ND	ND
35	22	N	ND	ND	ND	ND

The grey shaded cells highlight the correct predictions based on adherence to all medication. 79.4% of predictions were correct based on adherence to all medication.

Fisher's exact test was used to analyse the distributions of predicted adherence based on the revised part 1 score, and the measured medication adherence for all medication, solid oral medication and oral liquid medication. The results are shown in table 4.21.

Table 4.21. Fisher's analysis of revised Part 1 prediction and adherence outcome

Medication adherence prediction		Medication adherence					
		All medication		Solid oral medication		Liquid oral medication	
		Subset	P value	Subset	P value	Subset	P value
Part 1 adherence prediction	Yes (score ≤ 19)	Y, n=13 N n=4	0.001	Y, n=5 N n=2	0.067	Y, n=10 N n=2	0.019
	No (Score ≥ 20)	Y, n=3 N n=14		Y, n=3 N n=9		Y, n=5 N n=9	

A significant difference in adherence to all medication, and oral liquid medication was observed between children who scored ≥ 20 , and those who scored ≤ 19 .

4.3.6.2. MedAPT Part 2

Analysis of the BBQ responses by adherence outcome did not identify any relationship between patients' BBQ responses and medication adherence.

Therefore, revision of the scoring for part 2 was not considered possible. MedAPT part 2 has been discussed further within the discussion and conclusion section 4.4., and further within chapter 5, General Discussion.

4.4. Discussion and Conclusion

4.4.1. Study population

A total of 38 children, together with their parents from the AHCNHSFT, were recruited, completed the MedAPT questionnaire, and had their medication refill measured to determine their medication adherence.

The recruitment rate for the study was quite high (71.6%). This exceeds the 60% minimum response rate which Badger and Werrett (2005) consider acceptable. Initially 361 potential participants were identified from the electronic patients appointment system Medisec at AHCNHSFT, based on the inclusion criteria. However, on review of medication dispensing for each of the 361 children within the pharmacy department, only 71 of the patients were identified as receiving their medication consistently from the pharmacy at AHCNHSFT. This placed a limitation on the number of children eligible for recruitment. The diversity of the sample was also limited by the absence of children from some clinical specialities e.g. cardiology, HIV, respiratory gastroenterology and neurology. This was due to the dispensing of medicines within community pharmacies rather than via pharmacy at AHCNHSFT for these clinical specialities. This is part of a strategy within AHCNHSFT to move to community pharmacy dispensing where possible for repeat prescriptions. The resultant clinical specialities, through which children were recruited, were oncology, nephrology, dermatology, metabolic disorders and rheumatology.

Both adherent and non-adherent children were represented within the study population, across the three medication adherence summary categories of adherent/non-adherent to all medication, adherent/non-adherent to solid oral medication and adherent/non-adherent to oral liquid medication. The figures indicate a high level of non-adherence, with between one third and half of children non-adherent to at least one medicine within their medication regimen. Whilst this may be considered representative of the participants within the study, the study limitations, described in section 4.4.4., should be taken into account when considering how representative this figure is to the adherence level across AHCNHSFT, due specifically to the absence of children from some clinical specialities and ethnic groups.

4.4.2. Demographics

There were more boys (63.2%) than girls in the study population, which in part be explained by the incidence rates of disease within the clinical speciality groups. Nearly half of the study population comprised oncology and nephrology patients. Within these two clinical specialities the incidence of disease is predominant in boys. The oncology group comprised of 85.7% of patients with Leukaemia, which has a reported higher incidence in boys of 56% (Childhood Cancer Research Group, 2008) The Nephrology group comprised of a high proportion of boys with Nephrotic syndrome, which has been shown to affect boys twice as frequently as girls (Elsevier Clinical Key, 2012).

The ages of the children spanned the inclusion criteria age range of 3 to 11-years-old within the metabolic, nephrology, oncology and rheumatology clinical specialities, with the average age between 7 and 8-years-old. There was only one child represented within the dermatology clinical speciality.

Children from ethnic minority groups were not represented within the study. All of the children and parents/carers within the study were from the white ethnic group. The population statistics published by the Office of National Statistics (2009) estimates that Liverpool and surrounding boroughs, which the AHCNHSFT predominantly serves, are home to the following proportion of ethnic minority groups: Halton and St Helens (3.65%); Knowsley (4.3%); Liverpool (9.9%); Sefton (4.3%); Wirral (4.58%), which equates to a total population of 6% ethnic minority groups. With a sample size of 38, the expected number of children from ethnic minority groups would be 2, which was not achieved.

Whilst the number of children from ethnic minority groups attending AHCNHSFT is very small, efforts were made to identify ethnic diverse groups within the trust for recruitment. The sickle cell anaemia group being treated within the haematology clinical speciality were specifically targeted for recruitment. Sickle cell anaemia is most common among sub-Saharan Africans and is wide spread throughout the Middle East, Mediterranean Europe and India (Rees, Williams and Gladwin, 2010). There were particular issues identified in trying to recruit children within this group. In all cases (n=12), the parents chose not to participate. Their reason for refusal in

each case was stated as their unease with the medication adherence element of the study. The clinical nurse specialist for the patient group suggested that the main reason for the parents' unease, was suspicion of the motives and use of the data being gathered. It was thought that the parents felt by monitoring adherence, and questioning their child's medication-taking, the hospital were in some way using this as a method of questioning or withdrawing treatment. Additionally, some of the parents were known to be experiencing difficulties in caring for their child with sickle cell, and kept their child's condition a closely guarded secret, and could not consider discussing the condition or medication outside of the immediate clinical care team.

4.4.3. MedAPT findings

The study addressed aims IV, V and VI (section 1.10) which were to:

- IV determine whether adherence or non-adherence may be predicted through the use of the prediction tool.
- V determine whether there is a relationship between acceptability of the medicine to the child and their medication adherence.
- VI provide an evidence base to enable informed decision-making when prescribing medication for children, and help to focus pharmaceutical product development towards the production of medicines which are acceptable to the child

4.4.3.1. Aim IV

In addressing aim IV, part 1 of the prediction tool, as revised, was able to model adherence of the study participants and may be considered capable of predicting medication adherence.

Of the 14 questions that comprised part 1 of MedAPT, only clinical speciality (question 2) and the number of different medicines taken each week (question 13)

were individually statistically significant ($p \leq 0.05$) in the correlation with medication adherence.

The adherence correlation with the clinical speciality groups is likely to represent a combined effect of a number of different influencing factors, including patient, disease and regimen factors, and differences in prescribing practices between clinical specialities, which supports the findings of the CHIMP study. Dose form prescribing is affected by the prescribers experience and beliefs in the age most appropriate to switch to solid oral dose forms, and the availability of suitable dose forms, with choice often restricted.

The number of different medicines taken each week is one aspect of medication regimen complexity. The findings of the MedAPT study are supported by published literature, including the work of Gardiner and Dvorkin (2006), who state the benefit of simplified drug regimens on improving adherence in children.

For the other 12 MedAPT questions there was insufficient data to reject the null hypotheses that there was no difference between the adherent and non-adherent children for each question. However, as described in chapter 1, the correlates of adherence are both complex and wide ranging, and include patient/family factors, disease factors and regimen factors (Rapoff, 1998). Each of these aspects can influence health related behaviour, which includes medication adherence, it is therefore not unexpected that some individual question responses do not all correlate with adherence measurement. It is more likely that the interplay of contributing factors, with different strengths of association with adherence have a combined effect. The use of Cramér's V (Cramér, 1946) to determine effect size or strength of association to refine MedAPT part 1 was successful in modelling adherence prediction with measured adherence within the study population, however further evaluation in a larger and more diverse study cohort is required before the results are used to influence medicine prescribing policy.

Part 2 of the MedAPT questionnaire did not demonstrate the capability of modelling adherence within the study. When the BBQ was initially used in the CHIMP study, the complete questionnaire, comprising 30 questions, was used. In an attempt to deliver a user-friendly MedAPT questionnaire, which would be relatively quick to complete, and easy to administer, only the questions found to be significant in the CHIMP study were used in the final MedAPT (6 in total). It may be that the integrity of the questionnaire is diminished when the six questions are asked in isolation. Subsequent evaluation and refinement of the MedAPT should consider the inclusion of complete BBQ01 questionnaire on a larger study cohort.

4.4.3.2. Aim V

In addressing part V, the MedAPT questionnaire sought to determine the extent to which the child found their medication acceptable. The hypothesis being that a medication, which is considered unacceptable to the child, would present a barrier to adherence.

Whether the child found their medication acceptable was determined by asking them specific questions relating to their medication via the MedAPT questionnaire. These questions were MedAPT 3 (Do your medicines taste OK?), MedAPT 4 ((Are your medicines unpleasant to take?), MedAPT 5 (Are there any colours of medicines you like?), MedAPT 6 (Are there any colours of medicines you do not like?), MedAPT 9 (Do any of your medicines make you feel unwell?). There was insufficient data to reject the null hypotheses that there was no difference between the adherent and non-adherent children for each of the questions. However, the data indicate there may be an underlying trend, which the limited sample size was unable to confirm with sufficient statistical power. For MedAPT questions 3, 4 and 9, a negative response was associated with non-adherence.

The contribution of age, as a factor which can affect acceptance, has been confirmed, with younger children's dislike of the taste of their medication statistically significant, and the use of coping mechanisms statistically significant with younger children. Most likely as a result of the reported palatability challenges,

and extensive prescribing of oral liquids in younger children, the use of coping mechanisms was more prevalent, as the caregiver seeks to address the unacceptable palatability of their child's medication and achieve adherence. A number of coping strategies were observed, which were found to be strongly associated with whether the medicine tasted ok, or made the child feel unwell (MedAPT questions 3, 5 and 9, section 4.3.4.6). the use of coping strategies appear to be the accepted norm, as caregivers attempt to do all they can to get their child to take their medication. In the ideal world, coping mechanisms, which involved product manipulation, would not be required as there would be a selection of acceptable medication variants to offer choice to every child. In the meantime, practically, medication manipulation will remain an important mechanism to achieve acceptance by the child.

4.4.3.3. Aim VI

Aim VI focussed on gathering evidence to influence medicines prescribing and management policy, and generate data to facilitate paediatric pharmaceutical product development. The data generated through the study has provided important information, that should be considered.

The extent of non-adherence, with nearly half of children non-adherent to at least one of their medications is concerning. However, this wasn't unexpected, with figures for non-adherence within the range of 25% to 70% (Fiese and Everhart, 2006; Gardiner and Dvorkin, 2006; Costello, Wong and Nunn, 2004; Cohn et al., 2003), as described in chapter 1. It has also become the accepted norm for coping mechanisms to be used.

As discussed previously, the reasons for non-adherence are complex, however, as the MedAPT study, and CHIMP study beforehand, has shown, there is value in addressing the organoleptic factor of taste and exploring whether alternative dose forms to the classical oral liquid, including solid oral preparations, can offer a more suitable product which can facilitate adherence.

Increasing the awareness of non-adherence as an issue, which needs addressing, both in terms of the association between non-adherence and adverse clinical outcome (Bryson and Rumsfeld, 2009; Cohn et al., 2003; Ho), and the adverse effect of bad experiences with medicines on health-related behaviour (CHIMP study), is important to focus decision making in prescribing and medication development.

4.4.4. Limitations

The medication adherence measurement methodology chosen, limited the recruitment of patients, as described in section 4.4.1. The limitations of this method are described in chapter 1. The methodology requires that the patient must be consistently receiving their medication being studied, from the same pharmacy. If the patient refills their medication being measured from multiple sources, this method is practically limited unless all of the pharmacies used by the patient are known, and can be monitored. The methodology also relies on the premise that medication availability equals medication adherence, which is not consistently the case, as patients may not take their medication intentionally or unintentionally, despite it being available to take, and furthermore the oversupply of certain medications to patients in chronic disease management is a confounding factor, which may mask underlying problems.

The reason for selecting pharmacy medication refill, or repeat dispensing, was in an attempt to facilitate recruitment from all clinical specialities across AHCNHSFT without relying on provider or patient self reporting, use of invasive blood monitoring, or the use of expensive and impractical medicine container technologies. As it transpires, a combination of measures would have provided additional data for the study, including the evaluation of blood monitoring data where this was already in routine practice.

Procedures were implemented with the aim of reducing researcher bias, as described in section 4.2.2.3., including completion of the questionnaires away from the researcher, to limit researcher influence, however researcher bias is impossible to eliminate.

The study was limited to a single centre in north-west England, which raises questions regarding the applicability of the research findings in other hospital trusts, where practices and the demographics may be different.

Being based in north-west England, the representation ethnic minority participants was limited (see section 4.4.2.). Some ethnic groups have different religious beliefs regarding medical treatment, and different dietary requirements and preferences. These aspects could not be evaluated within the study cohort.

The size of the sample was small, being limited to a single centre and, as described in section 4.4.1., the requirement for children to be receiving their medication consistently from the pharmacy at AHCNHSFT.

4.4.5. Conclusion

The study addressed each of the intended aims described in section 1.10., illustrating the complexity of medication adherence in children, and the practical difficulties in accurately predicting outcome.

The data and evidence generated contribute to improving the knowledge of children's medication preferences, attitudes and behaviours, to inform further research and decision-making in paediatric pharmaceutical product development. This is discussed further in chapter 5, General discussion.

5. General Discussion

The CHIMP and MedAPT studies which comprise this thesis aimed to provide an evidence-base to enable informed decision-making when prescribing medication for children, and help to focus pharmaceutical product development towards the production of medicines which are acceptable to the child.

The knowledge gap was identified as an outcome of the literature review (see chapter 1), which concluded that evidence was limited to enable informed decision making. This conclusion was further supported by the concurrent work of van Riet-Nales et al. (2010), who conducted a systematic literature review of the effects of pharmaceutical technologies of oral medications on patient outcomes which included efficacy, tolerability, preference and adherence. The findings show that published clinical evidence to support pharmaceutical development programs is limited.

The MedAPT study evaluated the MedAPT questionnaire as a medication adherence prediction model, developed through data from the preceding CHIMP study.

The CHIMP and MedAPT studies have added to the current body of knowledge of paediatric medication preferences, acceptance and behaviours towards medication.

An original contribution to knowledge has been provided through: empirical data demonstrating that medication adherence may be predicted through the use of the MedAPT prediction tool; evidence demonstrating that there is an association between acceptability and medication adherence; and an evidence base to help focus pharmaceutical product development towards the production of medicines which are acceptable to the child, and facilitate medication adherence.

5.1. Overview of Findings

The patient's feedback through the CHIMP study provided evidence of children's preferences and dislikes, and whether their treatment protocol, which incorporated the medication, regimen and behavioural components, was acceptable to them. As the CHIMP study was not designed to measure medication adherence, the factors identified were based on feedback from the study participants in the form of retrospective self-reporting during interview.

Results from the CHIMP study suggested that medication adherence involves the interplay of patient, medication, regimen and behavioural factors. Child age, clinical speciality treatment group, medication palatability/taste, medication dose form, medication appearance, medication side effects, whether coping strategies are used, whether medication choice is offered, the complexity of the child's medication regimen and beliefs and behaviours towards treatment and medication, were found to have a reported effect on medication adherence, as described by children and their parents or carers.

The subsequent MedAPT study, sought to qualify the findings of the CHIMP study in the form of a prediction questionnaire, with medication adherence measured through pharmacy refill as the outcome measure.

Part 1 of the MedAPT questionnaire contained the patient, medication and regimen questions.

Child age was found, within the CHIMP study, to be aligned with medication adherence category, with the younger, 3 to 9-years-old age group, representing the more adherent patient population. This was not directly supported by evidence in the MedAPT study, with no statistically significant relationship found between age and adherence. This is not unexpected, as discussed in section 4.4.3.1., the reason being that the factors affecting adherence can be complex, and poor taste is relative and not an absolute term. In some children it may be feasible for taste to present a significant barrier, which alone can be the key determinant of non-adherence, whilst in other children poor taste may be less of a barrier to adherence.

Despite the lack of evidence of taste directly affecting adherence, there was evidence of a significant relationship between age and acceptability, in response to questions of taste and how pleasant the medication was to take (MedAPT questions 3 and 4). The more extensive prescribing of the, more difficult to taste mask, oral liquid medication, in the younger children may provide the explanation for the correlation between age and acceptance based on taste.

Taste masking to achieve acceptable palatability of oral medication can present significant challenges. Drug molecules dissolve in saliva and interact with taste receptors on the tongue to result in the taste modalities of sweet, sour, bitter or umami. Many traditional oral liquid medications are simple solutions or suspensions with some sweetening agents or flavours, which are often insufficient to mask the bitter taste of the active pharmaceutical ingredient. Tablets or other solid oral dose forms, with their longer salivary dissolution time if swallowed whole can largely bypass the taste receptors on the tongue are therefore less likely to present a problem with taste.

Most likely as a result of the reported palatability challenges, and extensive prescribing of oral liquids in younger children, the use of coping mechanisms was more prevalent, as the caregiver appeared to address the unacceptable palatability of their child's medication and achieve adherence.

The findings of the MedAPT study also showed that, a higher proportion of girls than boys used coping mechanisms, suggesting girls may find the taste of medication more of a problem than boys. The findings of the world's largest study on the preferences and ability of children and young people to taste, conducted by the University of Copenhagen (2008) on 8,900 Danish school children, found that girls have a better sense of taste than boys. However, there were no gender differences in responses to the MedAPT questions relating to medication palatability. This may be the result of the successful use of coping mechanisms including taste masking or mixing medication with the children's preferred food or drink resulting in improved palatability. On reflection, it would have been useful to include a question within the MedAPT questionnaire to

determine whether the children's responses to taste (MedAPT3 and 4) were based on their experiences with or without the use of taste-masking coping mechanisms.

Within the MedAPT study, adherence was shown to be significantly different between the two clinical speciality sub-groups (group 1: oncology, rheumatology and nephrology; group 2: dermatology and metabolic diseases). This aligns with the findings of the CHIMP study. The findings from the MedAPT study also showed that there are differences in dose form prescribing between clinical specialities, which support the findings of the CHIMP study. Dose form prescribing is affected by the prescribers experience and beliefs in the age most appropriate to switch to solid oral dose forms, and the availability of suitable dose forms, with choice often restricted. There is a clear need to standardise the approach, which is supported by the recent findings of the pediatric formulations task force of the American association of pharmaceutical scientists (AAPS), (Zajicek et al., 2013). The task force was established to identify paediatric, manufacturing, and regulatory issues and areas of needed research and regulatory guidance. They recognised the issue posed by poor palatability and incorrect dose form and strength for children. Dosage form and palatability standards for all paediatric ages, relative bioavailability requirements, and small batch manufacturing capabilities and creation of a viable economic model were identified as particular needs. This assessment was considered an important first step for the task force seeking creative approaches to providing more appropriate oral formulations for children.

The acceptability of medication, in terms of its organoleptic properties of palatability and dose form, has been widely reported, and accepted in literature as the key determinant of medication adherence in children. (Ernest, Elder et al. 2007; Matsui 2007; Costello, Wong et al. 2004). However, prior to the conduct of the CHIMP and MedAPT studies described herein, this hypothesis had not been the subject of empirical evaluation and confirmation. The CHIMP study provided data in support of this commonly held belief, and the qualification of the findings were sought through the MedAPT study, which indicated that palatability alone is not significantly aligned with adherence. However there was evidence that

palatability is a contributing factor in adherence, as determined through MedAPT questions 3 (Do your medicines taste OK?) and 4 (Are any of your medicines unpleasant to take?). The data showed that a negative response to medicine taste was associated with non-adherence and conversely a positive response associated with adherence.

The CHIMP study evaluated whether the preconception that liquid oral medicines are preferred in the early years was substantiated. Within the study, the youngest child taking solid oral medication was aged 5 years, however through the focus groups, children as young as 3 years were said to be routinely taking solid oral medication. This was particularly evident with antiretroviral medications (ARV), which are known to taste particularly bitter. As discussed earlier, bitter or unpleasant tasting medicines may be difficult to taste mask in solution, and a number of the children expressed a dislike for their oral liquid medication. Tablets or capsules, which enabled easier taste masking, may offer a more appropriate delivery system for children 3 to 11 years.

Within the CHIMP study, taking tablets was associated with improved adherence classification. Paradoxically, within the MedAPT study, tablets were associated with non-adherence. The conflicting results are difficult to explain, but may be a reflection of the complex interplay of other factors including behavioural effects, aversive responses or drug-induced nausea, having an increased effect on adherence within the tablet-taking group within the study cohort.

One recent study supports the conclusions of the CHIMP study. Van Riet-Nales and colleagues (2013) investigated the acceptability of different oral formulations in infants and preschool children in the Netherlands. They conducted a randomised crossover design, with tablets, suspensions and syrup placebo formulations. Tablet and syrup formulations were found to be preferred.

Similar formulation preferences are evident beyond the developed western world. Lisa Adams and colleagues (2013) conducted the national survey of administration practices and preferences of children's medicines in Tanzania (Adams et al., 2013). They found age to be the most important driver for formulation preferences, regardless of education level or whether the responses

were from the caregiver or healthcare worker. Below 6 years of age liquid formulations were chosen, and over 6 years tablets were the preferred dose form prescribed. Issues with young children vomiting tablets intended for adults has raised concerns over giving solid oral dose forms to young children. As a result the tablets are crushed and dissolved for administration, with resultant inaccurate or incomplete dosing and potentially reduced efficacy (Costello et al., 2007).

Choice as an influencing factor on medication acceptability was based on the premise that there may not be one solution to meet the needs of all children, and therefore offering a choice may provide the opportunity for the child to select the preferred medication dose form, removing one potential barrier to achieving adherence. Data collected through the CHIMP study demonstrated the value of offering choice, and a positive choice being made, to achieve acceptance by the child. Within the MedAPT study, a direct link between choice and measured adherence was not identified, due to the limitations in determining whether an active choice was made, or indeed whether alternative dose forms suitable or acceptable for the age of the child were available to enable a choice to be offered and taken. The MedAPT data indicate, that in the majority of cases, positive choices are not made or acceptable alternatives are unavailable as there still remains, within the group who have been offered a choice, the requirement for the use of coping mechanisms in over half of children.

There is evidence within the CHIMP study of the child's expression of a colour dislike being indicative of a potential aversive response to medications of that specific colour, which could be a contributing factor in acceptability and ultimately adherence. However, this finding was not supported by evidence from the MedAPT study. Further refinement of the MedAPT questions relating to colour (question 5: are there any colours of medicines you like?; question 6: are there any colours of medicines you do not like?), would improve specificity of the question, and the data which could be derived from the answers. By stating that the question relates to medicines the child currently, or within the previous 6 months has been, prescribed, this would focus answers on the prescribed medication rather than reflecting the children's wider colour preferences.

Smith et al. (2012) assessed the palatability of analgesic medicines in children, and found that children tend to prefer brightly coloured medicines. There was some evidence generated within the MedAPT study to support Smith et al.'s findings, with 75% (10 out of 15) of children who stated a specific colour preferences named a bright colour (yellow, red, pink, orange, or one child who stated "bright colours"). However, 73% (8 out of 11) of the children who stated a specific colour dislike also named a bright colour (yellow, pink or orange), although 50% of these children named yellow as a specific colour dislike and were taking yellow oral methotrexate which was identified within the CHIMP study as a medication which can result in aversive responses due to the yellow methotrexate colour-taste combination.

The process which shapes children's preferences begins from birth, with influencing factors gained through exploration of foods of different taste and appearance, and experiences with medicines and treatment, with associated colour-taste combinations (see section 1.7.1.) Unpleasant experiences have been shown within the CHIMP study to result in aversive responses to certain coloured medicines, with some further evidence within the MedAPT study as described earlier with the taste dislike of methotrexate combined with the medicine's colour yellow. Whilst no literature can be found which links the colour of a medicine with adherence (this conclusion being supported by Smith et al., 2012), in aiming to prescribe medication to children, which they feel is acceptable, it is important to establish whether a child has a specific colour aversion, to enable alternatives to be sought if available. However, as shown within the CHIMP and MedAPT studies, colour preferences alone are not necessarily the sole determinants of adherence, as the colour preference or dislike may be as a specific association between a medicine of known colour and its taste, which may not apply to a different medicine of the same colour with a different taste.

Evidence within the CHIMP study leads to the conclusion that bad experiences with medication and medical treatment can have an adverse impact on the child's behaviours towards treatment and medication. The study data presents a number of examples of the aversive responses, which can proceed bad

experiences, including aversions to certain tastes and colours, needle phobia, physical flight responses (requiring physical restraint), nausea induced by association of what is about to happen when medication is taken or medical treatment initiated.

The importance of managing the child's experiences with treatment and medication is vital if aversion is to be minimised. Within the children's hospital at Alder Hey, the network of play specialists and psychologists work as part of a multi-disciplinary healthcare team managing the child's healthcare pathway, however resource constraints can mean that preventative measures including play specialist interventions from the beginning of the child's journey are not available. The intervention of play specialists and psychologists tend to be introduced once an issue is identified e.g. needle phobia.

In an attempt to address the unacceptable palatability/taste or dose form of children's medication, a number of coping strategies were observed, which were found to be strongly associated with whether the medicine tasted OK, or made the child feel unwell (MedAPT questions 3, 5 and 9, section 4.3.4.6). The use of coping strategies appeared to be the accepted norm, as many caregivers made attempts to get their child to take their medication. In the ideal world, coping mechanisms, which involved product manipulation, would not be required as there would be a selection of acceptable medication variants to offer choice to every child. In the meantime, practically, medication manipulation will remain an important mechanism to achieve acceptance by the child.

Recent experiences of pharmaceutical manufactures progressing paediatric drug development programmes through the European Medicines Agency (EMA), demonstrates a move by the agency to require improvements to product palatability development and taste assessments, and compatibility studies with common feeds, to enable informed decisions to be made during medication administration and manipulation across the child age range as required. These requirements have been documented within the EMA's published PIP medication formulation screening criteria (EMA, 2013).

The findings of both the CHIMP and MedAPT studies highlighted the complexity of the medication regime as an important factor in adherence. In general, a simpler and less intrusive regime is more easily understood, reduces confusion, and facilitates adherence. The number of different medicines the child takes on a regular basis was found to be a statistically significant predictor of adherence. These findings concur with published literature including the findings of Gardiner and Dvorkin (2006). Children have reported medication annoyances in relation to their medication regime (Penza-Clyve, Mansell and McQuaid, 2004), whereby children complained about feeling tied down to their medication schedule. More recent work conducted by Hanghøj and Boisen (2014), who looked at self reported barriers to adherence of chronically ill adolescents found complexity of the medication regimen, measured as number of dosage units (e.g. tablets) per dose, and the perception of taking medicine too many times a day, to be adherence barriers.

The Beliefs and Behaviours questionnaire (BBQ 01) used in the CHIMP study was adapted from the George et al. (2006) validated Beliefs and Behaviour Questionnaire (George et al., 2006). George et al.'s questionnaire was validated to screen for non-adherence in adults with chronic ailments. It is a 30 item beliefs and behaviour questionnaire, which measures the beliefs, experiences and adherent behaviour on five point Likert-type scales. The questionnaire was adapted, initially for the purposes of the CHIMP study, so that it could be completed by a parent/carer of a child with a chronic illness, and identify the beliefs and behaviours from the parent/carers perspective.

In the absence of an adherence specific questionnaire validated within the paediatric population, the BBQ was selected from the published adherence specific questionnaires, as described in section 2.2.3.4. The BBQ was considered the most appropriate to use to try to understand the health beliefs and behaviours of children with chronic illnesses, on the basis that it had been validated to screen for potential non-adherence in patients with chronic ailments, is not disease specific, which was an important for the CHIMP study, where initial sampling (described in section 2.2.4.2.3.) needed to be as diverse as possible across the hospital.

Six of the BBQ 01 questions were identified as potential predictors of adherence in the CHIMP study (Chapter 2), and were incorporated into the MedAPT questionnaire (MedAPT questionnaire part 2). Analysis of the BBQ responses by adherence, measured through repeat prescribing (pharmacy refill), did not identify any relationship between patient's BBQ responses and medication adherence. This outcome was unexpected, as it did not align with the findings of the CHIMP study, which identified correlation between adherence categories and BBQ responses to the six questions within MedAPT part 2.

An explanation for the discrepancy could not be found within the data, however, theoretically this may be as a result of one or a combination of factors, which affected the responses to the MedAPT part 2 questions: In the CHIMP study the BBQ 01 questionnaire was given to the parent to complete following the semi-structured interview. The timing of this may be important, as the parent was seen to relax into the interviews, which may have put them at ease in the subsequent completion of the BBQ 01 questionnaire, hence providing more honest responses to the questions; The CHIMP study was an information gathering process which, in contrast to the MedAPT study, did not aim to measure adherence. As the feedback from some parents who declined to take part in the MedAPT study was on the basis that they did not wish for their parenting efficacy to be questioned through measuring their child's medication adherence, it is logical to conclude that responses could be affected by knowing that their answers are being critically analysed.

Furthermore, when the BBQ 01 was initially used in the CHIMP study, the complete questionnaire, incorporating 30 questions was used. In an attempt to deliver a user-friendly MedAPT questionnaire, which would be relatively quick to complete, and easy to administer, only the questions found to be significant were used in the final MedAPT (6 in total). Further work would be required to determine whether the integrity of the questionnaire was diminished when the six questions were asked in isolation. Subsequent evaluation and refinement of the MedAPT should consider the inclusion of complete BBQ01 questionnaire.

The initial scoring system for MedAPT part 1 assigned binary scores (0 or 1), whereby a response which had been found to be associated with non-adherence or non-acceptance was assigned a score of 1, and 0 assigned to a response associated with acceptance or adherence. In practice, not all factors would be expected to present equal challenges or barriers to adherence. It is more likely that there will be specific factors, which will have a more significant impact, and may stand alone as barriers to adherence, whilst the influence of other factors may only be observed in combination with a number of other less significant barriers. The initial, binary scoring mechanism did not reflect the strength of association or level of contribution one factor may present over another. For example, if a medication doesn't taste acceptable to the child, this may present a greater barrier to adherence than, say, medication frequency.

The questionnaire was refined by introducing a weighting of score based on calculation of Cramér's V values obtained through statistical analysis. Whilst part 1 of the MedAPT questionnaire was found to have the ability to predict outcome with the study subjects, further work is required before the questionnaire could be applied in routine practice. The questionnaire would benefit from further refinement of the scoring system based on size effect analysis with a broader population.

5.2. Limitations of work

There were several methodological constraints and demographical limitations within this investigation which are described in the discussion and conclusion sections of the CHIMP study (section 2.4) and MedAPT study (section 4.4). The main points are summarised below.

The CHIMP study used grounded theory methodology to evaluate and select the adherence factors for qualification within the MedAPT study. In order to minimise researcher-induced bias, the selection of study subjects was facilitated by healthcare professionals, who are experienced in approaching potential subjects and are not biased in selection. Consistency in the data collection process was achieved through the use of semi-structured interview

and focus group scripts, with questions phrased in an open style with data gathered confidentially. Specific training of the researcher (SB) ensured that the complex methodology was appropriately applied and the key coding phase involved objective evaluation of the qualitative data.

There was a reliance on patient self-report during interview and questionnaire response in both the CHIMP and MedAPT studies. It has been established that patients have a tendency to over report adherence (Soliday and Hoeksel 2000), and may adapt their answers to meet expectations of the researcher. The approach described in the last paragraph used to minimise bias from the researcher, and additionally during the MedAPT study the questionnaires were completed away from the researcher, to limit researcher influence. Despite the limitations, the methodology used was part of the initial information-gathering CHIMP study as part of grounded theory which by the nature of the method explores experiences, and was a necessary part of the MedAPT study which aimed to determine whether the self completion MedAPT questionnaire could be used to predict adherence.

Pharmacy refill (repeat prescribing) was the instrument of medication adherence measurement used in the MedAPT study. The reason for selecting pharmacy medication refill, or repeat dispensing, was in an attempt to facilitate recruitment from all clinical specialities across AHCNHSFT without relying on provider or patient self reporting, use of invasive blood monitoring, or the use of medicine container technologies which were either impractical, or too expensive to administer.

The use of pharmacy refill methodology limited the number of patients recruited, and the diversity of clinical specialities from which the patient could be recruited, as described in section 4.4.1. The methodology requires patients must to be consistently receiving their medication being measured, from the same pharmacy. If the patient receives repeat prescriptions for their medication being measured from multiple sources, this method is practically limited, unless all of the pharmacies used by the patient are known, included within the study, and can be monitored. The methodology also assumes that

medication possession equals medication adherence, which is not consistently the case, as patients may not take their medication, despite it being available to take, and furthermore the oversupply of certain medications to patients in chronic disease management is a confounding factor, which may mask underlying problems.

Despite the limitations, pharmacy databases are considered to provide a complete and accurate means of gathering dispensing data (Mabotuwana et al., 2009; Andrade et al., 2006), and the methodology has been shown to provide accurate and reliable measurements of adherence (Vink et al., 2009; Steiner and Prochazka, 1997).

For practical and financial reasons the studies were conducted within a single hospital trust, AHCNHSFT, which is based in Liverpool in the northwest of England. The hospital is one of the largest children's hospitals in Europe, treating annually over 200,000 children. Alder Hey serves a catchment area of approximately 7 million, providing secondary care for the local population of Merseyside and some neighbouring northwest counties including North Wales, Cheshire, Lancashire and Cumbria. The ethnic diversity of the catchment population has been discussed in sections 2.4.2. and 4.4.2. and demonstrate that the population is comprised of over 90% White British residents (Office of National Statistics, 2009).

All cultures have health beliefs which include ways of explaining what causes illness, how it should be treated, and who should be involved. The beliefs and behaviours, influenced by culture can affect health related behaviour. Roy, Torrez and Dale (2003) examined the attitudes of parent/carers in seeking medical treatment for their child in the USA. They evaluated the contribution of ethnicity and attitudes about traditional health beliefs in health-seeking behaviour. They discovered that there are ethnic differences irrespective of socioeconomic status. They found that African Americans were most likely to believe in home remedies and forego seeking specialist medical treatment, with Hispanics least likely to believe in the efficacy of home remedies. Ethnic differences in health seeking behaviour have also been reported by Flores et

al. (1999), who found that non-white children average fewer doctor visits than white children. This pattern is repeated within the studies presented in this thesis, with some evidence of the reluctance of ethnic minority groups to participate in the studies.

In addition to different cultural beliefs and subsequent health related behaviour across ethnic groups, religious beliefs and cultural differences in diet and tastes have been shown to affect taste perceptions and associations with medicinal value of the taste (Pieroni and Torry, 2007). This is discussed in section 1.7.1. In view of the differences across cultures and ethnicities, the relevance of the study findings, beyond the predominantly White British population of the participants, requires validation.

5.3. Implications and practical application

Within section 5.1, the findings of the studies have been summarised. The results show that nearly half of children were non-adherent to their prescribed medication, and based on the evidence, a number of different factors have been shown to interact and contribute to medication adherence in children. Increasing the levels of adherence has implications for both increasing children's benefit from medication and the economics of the healthcare system where non-adherence has been linked to adverse clinical outcome (Ho, Bryson and Rumsfeld, 2009; Cohn et al., 2003).

From the outset of the research the studies were designed to generate evidence, which could be practically applied in the clinical setting, inform the process of paediatric drug development and contribute to the academic debate. The previously limited availability of evidence to underpin clinical and pharmaceutical development decision-making has meant the outcome of the research is much needed and makes a valuable contribution in meeting the aims of the thesis, which are defined in section 1.10.

The studies have illustrated the complexity of medication adherence in children, and the practical difficulties in accurately predicting outcome. Whilst part 1 of

the MedAPT questionnaire was found to have the ability to predict outcome with the study subjects, further work is required before the questionnaire could be applied in routine practice, as described in section 5.4., future research.

The data and evidence generated contribute to improving the knowledge of children's medication preferences, attitudes and behaviours, to inform further research and decision-making in paediatric pharmaceutical product development. It is envisaged that, following the further research on an expanded population to validate MedAPT as a prediction tool, this may be used in research as a predictor of adherence, and potentially within clinical practice as a means of focussing resources and interventions to address non-adherence.

Whilst further research is warranted to validate MedAPT, there are important study findings within the thesis, which could be considered in defining medicines management and prescribing policy and advice for the pharmaceutical industry: The best practice demonstrated by some clinical specialities who consider the importance of medication adherence in a systematic manner is an important practice towards achieving acceptance, by the child, of their medication regimen; The data highlights the value of being open-minded about what children prefer, with some preconceptions questioned e.g. liquids are not always preferred by younger children; One size doesn't fit all children, and the data highlights the value of having a choice of medication dose forms and variants from which children and prescribers may choose, based on the child's needs and preferences. This raises the potential value of oral flexible dose forms, which can be taken orally as a solid or liquid.

5.4. Future research

The studies described within this thesis have examined the effect of organoleptic properties of medicines on medication adherence in children with chronic illnesses. Whilst a large number of factors have been shown to present potential barriers to children in taking their medication, the focus of the studies in terms of organoleptic aspects of the medication has identified some interesting findings, which may be practically applied.

The importance of child engagement, in identifying medication, which is acceptable to them in terms of organoleptic properties, has been highlighted. Further research should be aimed at confirming the findings of MedAPT on other patient samples within different care settings and in doing so contributing to a larger sample size on which to validate findings.

Further research to evaluate the discord between the findings of CHIMP and MedAPT in terms of the beliefs and behaviour questionnaire would be of value in strengthening the predictive value of MedAPT, and enable the important behavioural component to medication adherence to be considered.

Whilst predicting adherence is valuable in focusing improvement and intervention, it is important to have practical measures to improve adherence, and prevent issues arising in the first place. Interventional research is advocated, examining the effects of early engagement with children and their families, with adherence as an outcome measure. Furthermore, evaluation of the health economics of engagement strategies including medication choice and involvement of children in drug formulation design and taste is recommended.

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APPENDIX 1

CHIMP study ethics committee approval letters

- University of Brighton Ethics Approval
- Liverpool Children's Ethics committee (NHS Northwest 3 research ethics committee)

North West 3 Research Ethics Committee - Liverpool East

Bishop Goss Complex
Victoria Building
Rose Place
Liverpool
L3 3AN

Telephone: 0151 330 2071
Facsimile: 0151 330 2075

30 September 2009

Mr Simon P Bryson
Postgraduate Research Student
University of Brighton, School of Pharmacy
The University of Brighton
Cockcroft Building
Lewes Rd, Brighton
BN2 4GJ

Dear Mr Bryson

Study Title: The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
REC reference number: 09/H1002/72
Protocol number: 2.3

Thank you for your letter of 29 September 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

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, subject to the conditions specified below.

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" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

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).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		17 August 2009
REC application	2.2	27 August 2009
Protocol	2.2	28 July 2009
Investigator CV		29 July 2009
Participant Consent Form: Assent form Child (AF/Child/001)	1.0	03 July 2009
Participant Consent Form: Consent form Parent/Carer (CF/Parent/001)	1.0	03 July 2009
Interview Schedules/Topic Guides	Clinical and technical professional focus group (FG/Clitech/01) 2.1	03 July 2009
Statement of Indemnity Arrangements		04 June 2009
Participant Information Sheet: Child Information Sheet. Infosheet/Child/01 (Child 3-4 years inclusive)	1.1	03 July 2009
Participant Information Sheet: Child Information Sheet. Infosheet/Child/02 (5-11 years inclusive)	1.2	27 July 2009
Participant Information Sheet: Clinical and Technical Participants Information sheet (Infosheet/Clitech/01)	2.1	03 July 2009
Participant Information Sheet: Patient carer Information Sheet (Infosheet/Parent/01)	2.1	03 July 2009
Letter from Sponsor		29 July 2009
Interview Schedules/Topic Guides	Child semi structured interview and follow-up (Int/Parent/01) - 2.2	03 July 2009
Questionnaire: Non-validated, Questionnaire Parent/Carer (BBQ/Parent/01)	1.0	03 July 2009
Statement of Indemnity Arrangements		04 June 2009
Interview Schedules/Topic Guides	Parent structured interview and follow-up (int/Parent/01) - 2.1	03 July 2009
Covering Letter		29 September 2009
Protocol	2.3	29 September 2009
Participant Information Sheet: Child	1.3	29 September 2009

Participant Information Sheet: Clinical and Technical	2.2	29 September 2009
Participant Information Sheet: Parent/Carer	2.2	29 September 2009
Participant Consent Form: Parent/Carer	1.1	29 September 2009
Response to Request for Further Information		29 September 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

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 website.

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
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1002/72

Please quote this number on all correspondence

Yours sincerely

Mrs Jean Harkin
Chair

Email: adam.lewis@liverpoolpct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Professor Adrian Bone*
School of Pharmacy and Biomolecular
Brighton University



University of Brighton



Faculty of Science and Engineering

Professor Andrew W Lloyd
MA(Cantab) PhD CChem FRSC
Dean of Faculty

Cockcroft Building
Moulsecoomb
Brighton BN2 4GJ
Telephone 01273 642049
Fax 01273 642031
E-Mail a.w.lloyd@brighton.ac.uk

To Whom It May Concern:

This letter confirms that Simon Bryson has sought and been granted ethical approval from the Science and Engineering Faculty Research, Ethics and Governance Committee at the University of Brighton.

Professor Andrew Lloyd (Dean of the Faculty)

APPENDIX 2

Participant information sheet Parent, Infosheet/Parent/01

Children's preferences in taking medicines

Invitation

You and your child are being invited to participate in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to ask us if you would like more information or if there is anything that you do not understand. Please also feel free to discuss this with your friends, relatives, doctor or nurse if you wish.

We would like to stress that you do not have to accept this invitation and should only agree to take part if you want to.

Thank you for reading this.

What is the purpose of the project?

The purpose of the research is to find out whether the taste, visual appearance, smell, sound or feel/touch of your child's medicine(s) may affect their willingness to take the medicine in accordance with the advice of their doctor.

It is anticipated that this research will enable us to improve the process of developing medicines for children.

The purpose of the research is not to question the treatment your child is receiving, and the researcher will not provide medical advice. Should you require medical advice, you should ask your child's doctor.

Why have I been chosen to take part?

You have been asked to take part because your child is taking medicines on a routine basis as part of their medical treatment, and we would like to understand your experiences as a parent or carer, in routinely trying to give medicines to your child.

We would also like to speak with your child to hear their experiences in routinely taking medicines, and understand whether they have any particular likes or dislikes with the medicines they take

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. You are free to withdraw at any time without giving a reason and without any consequences to you or your child.

If you choose to take part we would also like to ask your child whether they wish to take part. We will ask your advice regarding whether you feel it is appropriate to ask them as this will depend upon your child's age.

We have an information sheet which we will use to explain the research to your child.

Parent/Carer Information Sheet
Infosheet/Parent/01
Version 2.2, 29 September 2009

If your child does not wish to participate or you decide you do not want them to participate they will not be included in the study and there will be no consequences for yourself or your child.

Should your child not participate, you may still participate should you choose to.

What will happen if I take part?

We wish to conduct a review of your child's medication history and also to gather some information regarding your child's current medical condition. The review will be conducted at the Alder Hey hospital by reviewing your child's medical records. The purpose of this review is to understand the types of medicines your child has been used to taking, as opposed to a detailed medical history. The purpose of the review is not to question the medical treatment your child is receiving.

We also wish to interview you and your child, to understand your experiences in the routine of taking medicines including any difficulties you encounter. We will ask for your permission to audio record the interview so that we can use the information that you share to enable an accurate transcription of your answers into written form, following which the audio recording will be immediately erased.

Some direct quotes you or your child provide may be used in publications, however all participants will remain anonymous.

The interview of both you and your child should last no more than an hour and will take place at Alder Hey Hospital.

As part of the interview you and your child will be asked a series of questions and in addition you will be asked to complete a questionnaire.

The questions we would like to ask your child will include asking them what they like and dislike about the medicines they take, or have taken, and how they feel about taking them.

The questions we would like to ask you include questions about what you feel your child likes and dislikes about the medicines they take, or have taken, and your experiences and involvement in the choice of medicines, in administering medicines to your child, and any difficulties encountered. The questionnaire will ask you some questions to try and understand how you feel about your child's illness and the medicines used to treat it. The purpose of the questionnaire is not to question the medical treatment or medicine(s) your child is receiving, but to understand how you feel about this.

Throughout the interviews and the questionnaires you and your child may miss questions if you choose to without giving a reason. Your responses will not be judged in any way and there are no right or wrong answers. The aim is to capture the reality of how children's medicines are used in hospital and the community and to learn from the experiences of you and your child.

Finally, in three to six months time we would like to speak with you again, by telephone for no more than 10 minutes, as a general follow-up to the initial interview.

Parent/Carer Information Sheet
Infosheet/Parent/01
Version 2.2, 29 September 2009

Will my taking part in this project be kept confidential?

All information received will be stored as anonymous information and only identified by a unique reference number which will be allocated from, and held within, a secure location at Alder Hey.

All information that you provide will be confidential and no individuals will be identifiable in any reports or publications.

No information collected will be shown to anyone apart from the research team and your child's medical team at Alder Hey.

For regulatory purposes, data from the study will be stored securely for at least 10 years following the study and destroyed as confidential waste thereafter.

The information you provide will be handled confidentially. It is however possible that during the course of the research, you or your child may disclose information which may be considered to put your child or another individual at a health risk. Should this situation arise you will be informed and your doctor at Alder Hey will be informed.

What are the possible disadvantages and risks of taking part in this research?

We do not foresee any specific risks, burdens or changes to lifestyle other than the inconvenience which you may experience in giving up your time to take part in the interviews and complete the questionnaire.

The answers you provide will not be judged, and there are no right or wrong answers. The purpose of the questions are to guide us towards understanding the experiences of you and your child, in taking and administering medicines.

It is possible that during the course of the research that you may feel uncomfortable in discussing particular aspects of your experiences. Should this occur, you are not required to provide information where you are uncomfortable in doing so, and you may omit any questions on the questionnaire should you wish to without giving a reason.

What if something goes wrong or I am unhappy with the conduct of the research?

If you are unhappy, or if there is a problem, please feel free to let us know by contacting the chief Investigator, *Mr Simon Bryson*, on 07913 048665.

If you remain unhappy or have a complaint which you feel you cannot speak about with Mr Simon Bryson, then you should contact Prof Adrian Bone, Head of Research, University of Brighton, telephone (01273 642120) or e-mail (A.J.Bone@Brighton.ac.uk). When contacting Prof. Bone, please provide details of the name or description of the study (so that it can be identified), the researcher involved, and the details of the complaint you wish to make.

Will my taking part be covered by an insurance scheme?

Participants taking part will be covered by the University of Brighton insurance

What will happen if I want to stop taking part?

You can withdraw at anytime, without explanation and without any consequences to yourself or your child. Results up to the period of withdrawal may be used, if you are happy for this to

Parent/Carer Information Sheet
Infosheet/Parent/01
Version 2.2, 29 September 2009

be done. Otherwise you may request that they are destroyed and no further use is made of them.

Who is funding the research?

The research and is being undertaken by the University of Brighton. The project has received ethical approval from the NHS National Research Ethics Service.

What will happen to the results of the research study?

This research will take place over approximately 14 months, after that time you will be given a summary of the findings from the study. The information will also be presented at academic conferences and will be published in research journals. Some direct quotes you or your child provide may be used, however, in all publications the research participants will remain anonymous.

Criminal Records Bureau check (CRB)

The researcher Simon Bryson works for the hospital and has an honorary research contract. He also has obtained an enhanced Criminal Records Bureau (CRB) disclosure and you may request evidence of the disclosure from Simon.

Contact for further information:

Should you have any questions, please contact Mr Simon Bryson, Telephone 07913 048665, e-mail S.P.Bryson@Brighton.ac.uk

What to do if you wish to participate:

You have at least 24 hours to consider whether you wish to participate.

Should you decide you wish to participate, please notify the Mr Simon Bryson (contact details above), who will then ask you to sign a consent form, and where applicable an assent form for you and your child, giving confirmation that your child has agreed to participate.

This information sheet is for you to keep. Thank you for your time and help.

APPENDIX 3

Infosheet/Child/01 for children aged 3 to 4 years inclusive

Child Information Sheet
Infosheet/Child/01
3-4 years inclusive, or as advised by parent
Version 1.1, 3 July 2009

Children's preferences in taking medicines

To be read out to the child, or used, together with the parent/carer to explain to the child.

I am talking with children to ask them what it's like taking medicines, and I would like to ask you too. If you don't want to talk to me you don't have to.

I'd like to ask you what you like and don't like about taking medicines.

Your *(insert name of parent/carer e.g. Mum/Dad/Grandma etc)* will stay with you if you want them to, and we will be asking them some questions about medicines as well.

Is it ok if I talk with you?

Thank you.

APPENDIX 4

Infosheet/Child/02 for children aged 5 to 11 years inclusive

Child Information Sheet
Infosheet/Child/02
Child 5 to 11 inclusive, or as otherwise directed by parent/carer.
Version 1.3, 29 September 2009

Children's preferences in taking medicines

To be given to child to read, or to be read out. This will be determined following consultation with parent. Alternative information sheet Infosheet/Child/01 may be used

Read from here:

Invitation

You are invited to take part in a project at the hospital. Before you decide if you wish to take part, we would like to explain what we are doing.

Please read this sheet and ask us, or the person looking after you today, if you would like more information or if there is anything that you do not understand.

Thank you.

Why are we doing this project?

We would like to find out what children like and don't like about taking medicines.

It is important that you take your medicines, so we want to find out if there is anything we can do to make better medicines for children like you who take medicines every day.

Why have I been chosen to take part?

You have been asked to take part because you know what it is like to take medicines every day so we think the information you can give us will be very useful.

Do I have to take part?

It is your choice, and it is ok to stop taking part at any time without telling us why. Just say I'd like to stop now.

What will happen if I take part?

We will look at your medical records to see what medicines you have taken and also to find out the reason why you are taking medicines.

We also wish to ask you some questions to understand what it is like to take medicines every day and to find out what you like and don't like about them.

We will ask you if it is ok to sound record our conversation so that we do not miss any of the important information you give us.

We will talk with you at the Alder Hey hospital and the person who looks after you will stay with you if you want them to.

If there are any questions which you do not want to answer it is ok, just tell us.

We will be speaking with the person who looks after you about medicines as well.

Child Information Sheet
Infosheet/Child/02
Child 5 to 11 inclusive, or as otherwise directed by parent/carer.
Version 1.3, 29 September 2009

Will my taking part in this project be kept a secret?

If you decide to take part you will be given a code number so that the information you tell us will only contain your code number and not your name. Your name will be a secret

The things you tell us will not be shown to anyone but the people involved in the project and your nurse and doctor at Alder Hey.

What will happen if I want to stop taking part?

It is ok to stop taking part at anytime and you don't need to tell us why.

What will happen to the results of the project?

We will be talking to other children and the people who look after them over one year. Once the project is over we will let you know what we have found out.

We will also tell some other grown-ups who are interested in our project about what we have found out, including some of the things you said, but we will not tell them your name.

Contact for further information:

If you have any questions, please let the person who looks after you know, or contact Mr Simon Bryson, Telephone 07913 048665, e-mail S.P.Bryson@Brighton.ac.uk

What to do if you wish to take part:

You have at least 24 hours to consider whether you wish to take part.

If you decide you wish to take part, please tell the person looking after you today or Mr Simon Bryson who will then ask you to sign a form, to say you wish to take part.

This information sheet is for you to keep. Thank you for your time and help.

APPENDIX 5

Clinical and Technical participant information sheet (CHIMP study)

Infosheet/Clintech/01

Clinical and Technical Participants Information Sheet
Infosheet/Clintech/01
Version 2.2, 29 September 2009

**Organoleptic properties of Medicines and their effect
on medication adherence in children**

Invitation

You are being invited to take part in a research study which is being carried out at the Alder Hey Children's NHS foundation trust by the University of Brighton. It is important that you understand why this research is being done and what is involved. Please feel free to ask us if you would like more information

Please take time to read the following information.

Thank you.

What is the purpose of the project?

We would like to know which organoleptic properties (taste, visual appearance, smell, sound or touch) of children's medicine(s) may affect their willingness to take the medicine in accordance with the advice of their doctor.

We will also seek to establish the child's preference of medication dose form and organoleptic properties and also seek to identify themes which may indicate whether there is an association with age, clinical condition, or other factors including previous medical interventions and life experiences.

We will also seek to establish the difficulties that parents / carers, doctors and nurses face in administering medicines to children and the reasons for this, for example, problems experienced with inappropriate presentations/dose forms of medicines which may require manipulation prior to administering to the child.

It is anticipated that a theoretical model will be developed as an outcome of this research to enhance dose form selection during medicine prescribing and paediatric pharmaceutical product development, however it is envisaged that evaluation of the model in practice will involve predicting adherence of patients prior to them taking medicines and evaluating whether predictions correlate with reported adherence. This will be subject of a separate quantitative study.

Why have I been chosen?

We want to learn from clinical and technical professionals, who have experience in routinely prescribing, selecting or administering medicines to children.

Do I have to take part?

It is up to you to decide whether or not to be involved with this research. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. You are free to withdraw at any time without giving a reason.

The study has been granted permission by Alder Hey R&D and the Liverpool Paediatric Research Ethics Committee. As a member of staff at Alder Hey, you have been granted permission to participate in the study should you wish to do so.

Clinical and Technical Participants Information Sheet
Infosheet/Clintech/01
Version 2.2, 29 September 2009

What will happen to me if I agree to take part?

We wish to carry out a series of focus groups and we are requesting that you participate in one of these. The focus groups will examine:

- the choice and range of medicine dose forms available to the prescriber.
- the extent to which the dose form and organoleptic properties of medicines are considered during medicine prescribing at Alder Hey.
- an evaluation of the involvement of the pharmacist in medicine dose form selection
- the experiences of nursing staff in consideration of the dose form and organoleptic properties of the medicine:
 - in obtaining prescriptions.
 - involvement in the choice of medicines.
 - administering medicines to the child and the factors responsible for any difficulties encountered.

We will ask for your permission to audio record the focus groups so that we can use the information that you share to enable an accurate transcription of your comments into written form, following which the audio recording will be immediately erased. Some direct quotes may be used, however the participants will remain anonymous.

As an alternative to a face-to-face focus group, you will be offered the alternative of participating in a focus group via an internet-based workspace. The workspace focus group would be hosted by the chief researcher, Simon Bryson. This enables participants to exchange views, respond to questions and views of other participants without the need to meet face to face..

Will my taking part in this project otherwise be kept confidential?

All information received will be stored as anonymous information and only identified by a unique reference number which will be allocated from, and held within, a secure location at Alder Hey.

All information that you provide will be treated as confidential and no individuals will be identifiable in any reports or publications. No information collected will be shown to anyone apart from the research team. Transcripts and recordings will be kept in a locked cabinet. Transcripts will be anonymised, and parts in which participants might be identified will be avoided in publications. For regulatory purposes, data from the study will be stored securely for at least 10 years following the study and destroyed as confidential waste thereafter.

The information you provide will be handled confidentially. It is possible that during the course of the focus group, a participant may disclose information about unsafe medical practice. Were this to occur, you will first be informed, and a senior colleague at the hospital would be consulted.

What are the possible disadvantages and risks of taking part in this research?

We do not foresee any specific risks or burdens, other than the inconvenience which you may experience in giving up your time to take part in the focus group.

The answers you provide will not be judged, and there are no right or wrong answers. The purpose of the questions is to guide us towards understanding your experiences as a clinical or technical professional involved in treating children.

It is possible that during the course of the research that you may feel uncomfortable in discussing particular aspects of your experiences. Should this occur, you are not required to provide information where you are uncomfortable in doing so.

Clinical and Technical Participants Information Sheet
Infosheet/Clintech/01
Version 2.2, 29 September 2009

What if something goes wrong or I am unhappy with the conduct of the research?

If you identify a problem with our research, please contact the Chief Investigator, *Mr Simon Bryson*, at the University of Brighton (s.p.bryson@brighton.ac.uk). If your complaint is not handled to your satisfaction then please contact Prof Adrian Bone, Head of Research, University of Brighton, telephone (01273 642120) or e-mail (A.J.Bone@Brighton.ac.uk).

Who is funding the research?

The research is being undertaken by the University of Brighton. The project has received ethical approval from the NHS National Research Ethics Service.

What will happen to the results of the research study?

This research will take place over approximately 14 months, after that time you will be given a summary of the findings from the study. The information will also be presented at academic conferences and will be published in research journals.

Some direct quotes from the study may be used, however, in all publications the research participants will remain anonymous.

Criminal Records Bureau check (CRB)

The researcher Simon Bryson works for the hospital and has an honorary research contract. He also has an enhanced Criminal Records Bureau (CRB) disclosure and you may request evidence of the disclosure from Simon.

Contact for further information:

Should you have any questions, please contact Mr Simon Bryson, Telephone 07913 048665, e-mail S.P.Bryson@Brighton.ac.uk

What to do if you wish to participate:

You have at least 24 hours to consider whether you wish to participate.

Should you decide you wish to participate, please notify the Mr Simon Bryson (contact details above), who will then ask you to sign a consent form.

This information sheet is for you to keep. Thank you for your time and help.

APPENDIX 6

Assent form Child (CHIMP study)

AF/Child/001

Assent Form Child

Study Title: Children's preferences in taking medicines

Researcher: Simon Bryson, University of Brighton School of Pharmacy

Child (or if unable, parent/guardian on their behalf) / young person to circle all they agree with

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

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

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

Have you had your questions answered in a way you understand? Yes/No

Do you understand it's OK to stop taking part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are 'no' or you **don't** want to take part, don't sign your name!

If you **do** want to take part, you can write your name below

Your name _____

Date _____

Mr Bryson who explained this project to you needs to sign too.

Print Name _____

Sign _____

Date _____

Thank you for your help.

Note: When completed 1 copy for participant and 1 copy for researcher

APPENDIX 7

Consent form Parent (CHIMP study)

CF/Parent/001

APPENDIX 8

Child Medication History Review (CHIMP study)

MHR/DTB/001

Study Title:	Child Medication adherence and organoleptic properties of medicines
Database:	Medication History review - Child
Reference:	MHR/DTB/001

Participant Identification code (From PIC/DTB/001)	Gender (M/F)	Date of Birth	Height (cm)	Weight (Kg)	Ethnic origin	Periods of hospital stay over past 12 months	Reason for admission	Past medical history	Current medical conditions	Current prescribed medication and changes over the past 12 months	Notes obtained relating to medication adherence
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APPENDIX 9

Child Semi-structured Interview outline (CHIMP study)

Int/child/01

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Semi structured interview
Participant	Child
Reference (Including version)	Int/Child/01 Version 2.2

The purpose of this document is to describe the topics for discussion and questions to be used during the semi structured interview of children involved in the study.

Overview

The parents / guardians of all patients admitted to the Alder Hey Children's NHS Foundation Trust (AHCNHSFT), aged 3 to 11 years, having a chronic illness and staying in hospital for over 24 hours 'or' attending outpatient appointments at the AHCNHSFT, aged 3 to 11 years, having a chronic illness, will be approached for recruitment of both the child and the parent/guardian to the study.

This stage will involve conducting a semi-structured interview with the child to examine:

- the child's experiences in taking medicines
- the factors which influence their adherence to the medication regime.
- investigating their likes and dislikes in relation to the medication dose form and organoleptic properties
- investigating the reasons for any difficulties encountered

Structure

The first stage of any interview with children must ensure there is sufficient time for an introduction to place the child at ease with the interviewer before proceeding with the interview.

Once the child is at ease, the intention of the interviewer will be to ask the child the questions listed below, adapted where appropriate to the age and perceived level of understanding or competence of the child.

Specific consideration must be given to the attention span of the child. Attention span is commonly calculated as $3 \text{ minutes} \times \text{age in years} \pm 3 \text{ minutes} = \text{attention span in minutes}$. Table 1 below should be considered as a guide, however, this will be dependent upon the child's developmental status.

Breaks from the interview questions should take place where necessary, using table 1 as a guide.

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Semi structured interview
Participant	Child
Reference (Including version)	Int/Child/01 Version 2.2

Table 1: Child attention span

Age (years)	Attention span range
3	6 to 12 mins
4	9 to 15 mins
5	12 to 18 mins
6	15 to 21 mins
7	18 to 24 mins
8	21 to 27 mins
9	24 to 30 mins
10	27 to 33 mins
11	30 to 36 mins

Where permissible, to minimise the influence of the parents beliefs on the child's responses, the child interview should take place without the parent/carer being immediately present, however, the parent/carer or nursing staff should be close by and able to observe the interview taking place. Where either or both parent/carer and child are uncomfortable without the immediate presence of the parent/carer or nursing staff, this must be respected.

Questions:

- Child's experiences in taking their prescribed medicines, to include:
 - Do you take your medicine without complaining?
 - Do you ever refuse your medicine(s)?
 - What do you most like and not like about the medicines you take?
 - Which medicines cause you the most problems and why?
 - Are there any particular tastes, smells, appearances which you dislike
 - Explore ways in which they take their medicines.
 - How do you take your medicines?
 - Are they changed in any way? Do your Mum or Dad have to do anything with your medicines so you can take them?
- Which types of medicines do you prefer to take? (Use visual cues in appendix A of this document)
- Have you ever taken any of these different medicines (show visual cues)? Which ones and what did you think about them?

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Semi structured interview
Participant	Child
Reference (Including version)	Int/Child/01 Version 2.2

Have you ever had a choice in which medicine you are given?

During the interview, the following aspects should be explored, but must be tailored to the age of the child. For the very young i.e <6yrs, many of the questions will be inappropriate, although this will be dependent upon the development status of the child and will be require some judgement by the chief investigator, together with the parent.

- Do you know why you need to take your medicines?
- Do you meet other boys and girls who need to take medicines similar to you?
- Do you mind taking a lot of medicines (where appropriate)?
- Is it unpleasant (e.g. taste and smell) to use some of your medications ?
- Is it physically difficult to handle some of your medications ?
- My doctors spend adequate time with me?
- Does the way you have to take medicines disrupt your life?
- Do you get confused about your medications ?
- Do you have strict routines for using regular medications ?
- Do you ever run out of medicines?
- Do you always follow the instructions of the doctors ?
- Do you make changes to fit in with your life or the way you're feeling?
- Do you sometimes put up with medical problems before telling anyone?

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Semi structured interview
Participant	Child
Reference (Including version)	Int/Child/01 Version 2.2

APPENDIX A:



A



B



C



D



E



F



G



H

APPENDIX 10

Parent/Carer Semi-structured Interview outline (CHIMP study)

Int/parent/01

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Initial semi-structured interview and follow-up interview
Participant	Parent/carer
Reference (Including version)	Int/Parent/01 Version 2.1

The purpose of this document is to describe the topics for discussion and questions to be used during the semi structured interview of parents/guardians involved in the study.

Overview

The parents / guardians of all patients admitted to the AHCNHSFT, aged 3 to 11 years, having a chronic illness and staying in hospital for over 24 hours 'or' attending outpatient appointments at the AHCNHSFT, aged 3 to 11 years, having a chronic illness, will be approached for recruitment of both the child and the parent/guardian to the study

This stage will involve conducting a semi-structured interview with the child's parent/guardian and completion of a Beliefs and Behaviours (BBQ/Parent/01) questionnaire to examine the parent/carers experiences in consideration of the dose form and organoleptic properties of the medication. The interview will examine the parent/carer's:

- experiences in obtaining prescriptions
- involvement in the choice of medication
- administering medicines to the child and the factors responsible for any difficulties encountered.

Structure

The interview must cover the following points:

- Parents experiences in administering each of the prescribed medicines to their child, to include:
 - Do they take it without complaint or refuse the medicine?
 - How do you administer each medicine, e.g. if they are prescribed tablets are these crushed and mixed with food?
 - Which medicines cause the most problems and why?
 - Are there any particular properties (e.g taste, smell, appearance) which cause more problems?
- Are there any particular medicines which your child does not like?
- Are you aware of any medicine which your child has been put off because of the way they were feeling at the time they took the medicine?
- If so, are there any medicines which may remind them of feeling sick or unwell?
- Are you aware of the range of medications available to treat your child's condition?

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Initial semi-structured interview and follow-up interview
Participant	Parent/carer
Reference (Including version)	Int/Parent/01 Version 2.1

- Have you had any involvement in selecting or choosing medicines for your child? And have you ever been offered a choice?
- Has your child expressed a positive preference or made a choice of which medicine they wish to take? Does this have an effect on whether they routinely take their medicine?
- What age do you feel that children are ready to take solid oral dose forms and reasons for this?
- What impact does your child's condition and taking regular medicines have on the family?
- How does your child's school deal with giving medicines during the school day if they are needed?
- Have there been many changes to your child's medicines? If so, what are the reasons for this?

Follow-up

Three to six months after recruitment, participants will be telephoned by SB for a brief interview to find out:

- Have there been any changes to the child's treatment since we last spoke, and if so, what effect has this had on medication adherence?
- Whether there have been any further GP visits or hospital admissions

APPENDIX 11

Beliefs and Behaviour Questionnaire (CHIMP study)

BBQ 01

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Questionnaire
Participant	Parent/Carer
Reference (Including version)	BBQ/Parent/01 Version 1.0, 3 July 2009

Parent/Carer Questionnaire

Ref. BBQ/Parent/01

Participant reference code (Assigned by Investigator)	
Date	

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Questionnaire
Participant	Parent/Carer
Reference (Including version)	BBQ/Parent/01 Version 1.0, 3 July 2009

Beliefs

	Definitely False	Mostly False	Don't know	Mostly True	True
	1	2	3	4	5
1. I have sufficient understanding about my child's illness					
2. I know what to expect from my child's illness management					
3. My child's current illness management will keep my child's illness at bay					
4. My child is receiving the best possible management					
5. The management of my child's illness is a mystery for me					
6. It is helpful to know the experiences of others with similar illness as my child					
7. Natural remedies are safer than medicines					
8. My doctors have limited management options to offer my child					
9. My child's medications are working					
10. Using any medication involves some risk					
11. My child is on too many medications					
12. I have sufficient understanding about the options for managing my child's illness					
13. I have a say in the way my child's illness is managed					
14. My doctors are very knowledgeable					

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Questionnaire
Participant	Parent/Carer
Reference (Including version)	BBQ/Parent/01 Version 1.0, 3 July 2009

Experiences

	Not at all	Slightly	Moderately	Quite a bit	Extremely
	1	2	3	4	5
15. I am concerned about the side effects from my child's medications					
16. It is unpleasant (e.g. taste and smell) for my child to use some of their medications					
17. It is physically difficult to handle some of my child's medications					
18. I am satisfied with the information my child's doctors share with me					
19. My doctors are compassionate					
20. Financial difficulties limit access to the best healthcare for my child					
21. My doctors spend adequate time with my child					
22. The management of my child's illness disrupts my child's life					

Behaviour

	Never	Rarely	Sometimes	Often	Always
	1	2	3	4	5
23. We get confused about my child's medications					
24. We have strict routines for my child in using regular medications					
25. I keep my child's medications close to where they need to use them					
26. I ensure I have enough medications so that my child does not run out					

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Questionnaire
Participant	Parent/Carer
Reference (Including version)	BBQ/Parent/01 Version 1.0, 3 July 2009

	Never	Rarely	Sometimes	Often	Always
	1	2	3	4	5
27. I push my child to follow the instructions of the doctors					
28. I make changes in the recommended management to suit lifestyle					
29. We vary the recommended management based on how my child is feeling					
30. I put up with medical problems before taking any action					

Other information

If you do not wish to answer any of the questions please leave blank.

Please tick the appropriate box:

1. What is your relationship to the child?

- a. Parent
- b. Foster parent
- c. Step parent
- d. Other (please specify) _____

2. What is your gender?

- a. Male
- b. Female

3. Which of the following age groups do you fit into?

- a. 20 or under
- d. 41 to 50

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Questionnaire
Participant	Parent/Carer
Reference (Including version)	BBQ/Parent/01 Version 1.0, 3 July 2009

- b. 21 to 30 e. 51 to 60
c. 31 to 40 f. 61 or over

4. Which ethnic group best describes you?

- a. White f. Black African
b. Indian g. Chinese
c. Pakistani h. Mixed race
d. Bangladeshi i. Other
e. Black Caribbean

5. What is your marital status?

- a. Married
b. Civil partnership
c. Living with partner
d. Single

6. What is the highest level of education that you have achieved?

- a. GCSEs / O-levels
b. A-levels
c. Degree
d. Postgraduate qualification
e. No qualifications
f. Other (please specify) _____

7. How many children do you have and / or are the guardian of?

(Please enter number of children in box)

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child Medication adherence and organoleptic properties of medicines
Intervention	Questionnaire
Participant	Parent/Carer
Reference (Including version)	BBQ/Parent/01 Version 1.0, 3 July 2009

8. Please list the ages of all children:

_____	_____	_____
_____	_____	_____

9. Would you consider yourself to have a medical background? e.g. occupation

- a. Yes
- b. No

If yes, please specify _____

10. Do you have any of the following medical conditions: (You may select more than one answer)

- a. Asthma
- b. Epilepsy
- c. Diabetes
- d. Under or overactive thyroid gland
- e. High blood pressure
- f. Any other medical condition

If you answered yes to any other medical condition, please specify _____

APPENDIX 12

Focus group outline Clinical and Technical participants (CHIMP study)

FG/Clintech/01

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child medication adherence and organoleptic properties of medicines
Intervention	Focus group
Participant	Clinical and technical professionals
Reference (Including version)	FG/Clintech/01 Version 2.1

The purpose of this document is to describe the topics for discussion and questions to be used during the focus group involving clinical and technical staff at Alder Hey involved in the study.

Overview

Doctors, pharmacists and nurses working at the Alder Hey Children's NHS Foundation Trust (AHCNHSFT) will be approached for recruitment to participate in focus groups. Informed consent will be obtained.

The following focus groups will be established:

- Nurses only, recruited across clinical disciplines;
- Doctors only, recruited across clinical disciplines
- Pharmacists only recruited across clinical disciplines (where possible)
- Group containing a mixture of doctors, nurses and pharmacists by clinical discipline/sub-discipline

The focus groups will be semi-structured and facilitated by the chief investigator, Simon Bryson.

The focus groups will examine:

- the choice and range of medication variants available to the prescriber
- the extent to which the dose form and organoleptic properties of medicines are considered during medication prescribing at The AHCNHSFT
- an evaluation of the involvement of the Pharmacist in medication dose form selection
- the experiences of nursing staff in consideration of the dose form and organoleptic properties of the medication:
 - in obtaining prescriptions
 - involvement in the choice of medication
 - administering medicines to the child and the factors responsible for any difficulties encountered

Structure

The focus groups must examine the following points:

- Experiences in administering medicines to children, to include:

Title of study (full title)	The effect of organoleptic properties of medicines on medication adherence and dose form preferences in children
Title of study (short title)	Child medication adherence and organoleptic properties of medicines
Intervention	Focus group
Participant	Clinical and technical professionals
Reference (Including version)	FG/Clintech/01 Version 2.1

- Perceptions and knowledge of level of medication adherence amongst their patients
 - Do they take it without complaint or refuse the medicine?
 - Knowledge of how parents administer each medicine, e.g. if they are prescribed tablets are these crushed and mixed with food?
 - Which medicines cause the most problems and why? Are there any particular properties (e.g taste, smell, appearance) which cause more problems?
- Awareness of the range of medications available to treat the child's condition? What is the reference text if any?
 - Do they involve the child and/or parent/guardian in selecting or choosing medicines for the child? And have they ever offered a choice? In which circumstances? What are the constraints and limitations?
 - Do children express a positive preferences or exercised choice in which medicine they wish to take? Does this have a effect on medication adherence?
 - What age do they children are ready to take solid oral dose forms and reasons for this.
 - Do they routinely review the child's medication and the reasons for this
 - Do they routinely consider the organoleptic properties of medicines and/or medication adherence during prescribing?
 - Explore each of the organoleptic properties (touch, taste, smell, visual appearance and sound) and learn from the groups whether in their experience these attributes effect medication adherence.
 - To what extent are nurses and pharmacists involved in medication selection for the child?
 - Do they experience any difficulties in obtaining prescriptions? (relates to non prescribing group)

APPENDIX 13

Adherence history and Adherence category classification table (CHIMP study)

Appendix 13: Adherence categorisation and adherence history of child participants in CHIMP study

PIC No.	Evidence for Adherence category allocation					CHIMP Allocated Adherence category	
	History of adherence (Progression of adherence over time, left to right)				Coping strategy & dose form (See footnote)		Notes
001	Adcop/Nadso More difficult in the beginning due to taste/new experience	Adcop Liquids & injections throughout	Adcop Liquid. Mask aftertaste	Adcop Initial meds i.v. traumatic. Now needle phobic	1b Oral Liq	Adcop throughout. Liquids based on taste, needles based on traumatic experience. Not tried tablets. Child indicates they might be acceptable. Parent surprised	Adcop
002	Adcop/Nadso More difficult in the beginning due to taste/new experience	Nadso Mood & medication dependent	Adcop Mood & medication dependent Given something sweet afterwards		1b, 2 Oral Liq	Nadso vs Adcop difficult to determine. Challenges based on medicine taste Tablets prescribed but parent decided child wouldn't like them so didn't try. Worries over size, spit out and thought would need to mix with food and worried if child didn't eat all food – low dose!	Adcop
003	Adcop/Nadso More difficult in the beginning due to taste/new experience	Adcop Mood & med dependent	Liquid. Mask aftertaste	Initial meds i.v. traumatic. Now needle phobic	1b Oral Liq	Appears to have been Adcop throughout. Difficult to determine. Experience with meds not pleasant, similar to other oncology patients. Tablets not tried as parent decided child taking suspension so why change.	Adcop

004	Adcop/Nadso Very difficult in the beginning due to taste/new experience. Some evidence that sickness may have resulted in missed doses	Adcop throughout	Liquid masking in yoghurt or juice		1a Oral Liq	Very difficult early experience with liquid oral medicines as with other oncology patients. Parent would not have considered giving child tablets. Confusion with sweets and preconception that children take liquids.	Adcop
005	Adcop Liquids initially	Adcop Tablets given in yoghurt as they can get stuck in throat			1a Tablets	Relatively positive experience with meds. No problems reported with liquids although child stated preference for tablets despite them sometimes getting stuck in throat	Adcop
006	Adcop	Nadso Stated non-adherence		Nadso Traumatic. Experience with i.v. Now needle phobic	4, 7 Oral Liq. (negative experience) Tablets (positive experience)	Sickness and psychological factors. Taste has a major impact which can lead to sickness and the anticipation. This extends to paracetamol. Tablets found to be better and suppository preferred to liquid oral pain relief.	Nadso
007	Adcop Difficult initial experience due to taste of the medicines				1b, 4 Oral Liq	New experience. Interview 2 months post diagnosis. Not considered tablets as thought they would be a problem for the child. Mother not comfortable with tablets	Adcop

008	Adacc Downs syndrome. taking Levothyroxine, self admin all ok	Adcop Diagnosed ALL. ALL medication problems. Physical force to achieve compliance			1a, 1b, 2, 4 Oral Liq	Levothyroxone taste wasn't ideal but acceptable due to colour. Put off previously acceptable medicine (Levothyroxine) due to amount and frequency. Tablets considered unacceptable to mum	Adcop
009	Adacc With Calpol and Keppra liquid. Keppra acquired taste but taking fine	Adcop With Oramorph taste problem, this medicine was only given for acute post operative pain relief.			Standard treatment Adacc Other (hosp Oramorph): 6 Oral Liq (nice taste)	Routine medicine, Keppra fine Unusual meds whilst in hospital proved a taste challenge. Aversive to idea of tablets	Adacc
0010	Adacc Movicol sachets generally fine. Has taken Omeprazole tablets without problem	Adcop Taste challenge with antibiotic but did take. Short course treatment.			6 Oral Liq (limited – just movicol)	Routine fine. Taste is a problem with some unfamiliar medicines when required i.e. antibiotics Slightly nervous with needles but generally fine.	Adacc
0011	Nadso Spitting liquid medicine out on occasions. Orange Calpol (strawberry ok), Lactulose, gabapentin	Adacc Move to tablets 12 months ago and all fine. Has aversion to colour orange, even tablets			4, 7 Tablets	Routinely taking tablets and adacc now. Preference for white tablets, regardless of size when offered orange smaller tablet chose white large paracetamol split into pieces	Adacc

0012	Adcop All except prednisolone down gastronomy.				5a Oral Liq. Delivered via gastrostomy	Hospitalised since birth	Adcop
0013	Adacc Initially oral methotrexate liquid. Fine for first 8 months.	Adcop After first 8 months developed stomach intolerance with oral (crushed tablets in yoghurt or oral liquid)	Adcop Receiving methotrexate by injection during weekly outpatient visit		1a, 7 Oral Liq to i.v.	Also takes or has taken calpol, ibuprofen, ondansetron (with oral methotrexate) as required and routine folic acid solution which is taken fine Issue with this child is the nausea associated with methotrexate	Adcop
0014	PIC code allocated following informed consent. Participants did not return to clinic for interview.						
0015	Adacc On initial diagnosis grandparent recalls ease with which child would take oral medicines (Liquid)	Nadso An bad tasting antibiotic prescribed for anal sore resulted in aversive response to oral medication	Nadso Masking in foods didn't resolve issue	Adcop Nasogastric tube inserted and happily taking medicines via tube	5b Oral Liq (Nasogastric tube delivery)	needle phobia	Adcop

0016	Nadso Liquid medicines and some tablets discarded due to bad taste of liquid or lack of belief on effect of both				4, 6 Oral Liq	Aversive behaviour based on belief of effect and taste of liquid	Nadso
0017	Adcop Liquid methotrexate bad taste. No masking, just took anyway.	Adcop Now on tablets but still experiencing nausea			6, 8 Tablets (Side effect nausea)	Takes Ondasetron tablets to help relieve nausea induced by methotrexate	Adcop
0018	Nadso Initial liquid medicines masked in bottles of milk and tea. Not always finishing the drink so full dose not always being administered.	Adcop Taking tablets but some taste issues remain			1a, 3, 4, 7 Tablets		Adcop

0019	Adcop Started on liquid and didn't like taste	Adacc Tablets of methotrexate well tolerated and preferred to the liquid	Adcop Now on methotrexate injection		7 i.v		Adcop
0020	Adacc Liquid medicines taken fine. No reported problems	Adacc Transition phase aged 3 yrs where tablets tried and started to dissolve in mouth. Left until child ready to try again some time later and transferred fine	Adacc Takes tablets happily now. Up to 3 at a time.		9 Tablets	Child has been comfortable with medication throughout as part of a well managed process	Adacc
0021	Nadso Liquid taste issues at first	Nadso Now takes tablets but issues with steroid tablets which are not coated due to taste and texture. No known coping mechanism to achieve adherence with non coated	Nadso Alternate dose form acceptable and takes powder inhalers under sufferance. Sick with prednisolone		Tablets, inhalers	Taste and texture aversion a significant problem with liquids, tablets and dry powder inhalers If given non-coated tablets requests coated. Powder inhalers taken under sufferance as no alternative First tried tables at 7. Steroids from birth as dissolvable tablet and from 8 as oral tablet Difficulty with solids	Nadso
0022	Adcop Taste not ideal, and initial difficulty due to quantity of CF medications required	Adcop Problems remain due to texture, taste and quantity			1a, 1b, 4		Adcop

0023	Adcop Taken despite taste not ideal as liquid	Adacc Takes despite taste of some. CF meds taken with water.			6,9 Tablets	Now mainly tablets but some liquids. Takes meds well, just taste. Tablets from 4 yrs. Straightforward progression	Adacc
0024	Adcop Up to age 4 mainly liquids, some of which required taste masking in choc mousse	Switch to tablets at 4 yrs. Aversion for a while when one small tablet would become stuck in throat, but returned to them at fine now	Adacc All except vit k are tablets and are well tolerated and accepted Adcop Vit K is taken but taste dislike –brushes teeth immediately afterwards		1a Tablets Oral liq.	Has needle phobia	Adacc
0025	Adcop Taste masked liquid antivirals	Adacc Tablets (anti-virals) taken quite happily			1a Tablets		Adacc
0026	Adcop Oral methotrexate liquid taste aversion and associated nausea	Adcop Methotrexate injection weekly			6,7 i.v.	Hasn't tried taking tablets. Has aversion to the thought of taking them. States that he's 'not good at taking tablets'. View reinforced by mother.	Adcop

0027	Adcop Amlodipine, half tablets dissolved in juice. Not tried solid as mother thinks child would refuse. Codeine liquid taste aversion and nausea. Ranitidine liquid taste aversion and omeprazole mups considered handling problem		Preference for amoxicillin (banana), Sanimigram and Calpol		1a Oral Liq	Not been offered or tried solid oral	Adcop
0028	Adcop Prednisolone tablet, cyclosporine and ranitidine liquid		Likes Calpol		6, 8 Oral Liq	No change. Copes but no masking as such. Ranitidine to manage reflux associated with meds	Adcop
0029	Adcop Liquids taken but stated preference for tablets so in process of switching.				1a, 1b, 4	Move to tablets not yet complete	Adcop
0030	Adcop	Adacc Takes tablets happily. Did take liquids but child said she'd prefer tablets and switched.			6,7 tablets		Adacc
0031	Adcop Less of a problem now than early days with a routine and method for taking the meds in place. Tacrolimus, prednisolone, loperamide liquid/tablet dissolved in water. Taken with water.			Child has gastrostomy	1b, 5a Oral Liq	Move to tablets has not yet been successful despite several attempts. Makes child gag.	Adcop

0032	Adcop Previous meds adapted, crushed and given with milk	Nadso Child chooses sometimes not to take a tablet which she states does help her feel better after food.			1a Tablet		Nadso
0033	Adcop Initially liquids which were taste masked with chocolate buttons taken after to disguise taste	Adcop Now mix of tablets and liquids, with liquids given down gastronomy. Most of tablets fine to be taken orally, with preference for coated tablets which are easier to swallow			1b,5a Oral Liq. via gastrostomy	Switch to tablets occurred in line with transplant due to need to take tacrolimus	Adcop

Key (Coping strategies classification):

1. Taste mask
 - a. Mixed with masking agent
 - b. Taste mask given before or after medicine to mask
2. Physical force
3. Bribery
4. Persuasion
5. Operative procedure to bypass (enteral feeding tube)
 - a. Gastrostomy
 - b. Nasogastric tube
6. Under sufferance: Not ideal but child takes medicine anyway
7. Move to alternate dose form/special product
8. Other medication to manage side effects

APPENDIX 14

NRES ethics approval letter , Alder Hey site-specific R&D approval and University of Brighton ethics approval email for MedAPT study

NRES Committee North West - Greater Manchester East

3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7820
Facsimile: 0161 625 7299

03 September 2012

Mr Simon Bryson, PhD Research Student and Alder Hey Research Fellow
Alder Hey Children's NHS Foundation Trust
R&D Mulberry House, Eaton Road
West Derby
Liverpool
L12 2AP

Dear Mr Bryson

Study title: Evaluation of the children's medication adherence prediction tool (MedAPT)
REC reference: 12/NW/0687
IRAS protocol no: 112765
Protocol number: RP/AHCNHSFT/002

The Proportionate Review Sub-committee of the NRES Committee North West - Greater Manchester East reviewed the above application on 03 September 2012.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

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" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System 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 approvals from host organisations.

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).

Approved documents

The documents reviewed and approved were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Evidence of insurance or indemnity		20 June 2012
Investigator CV	Mr S Bryson	
Investigator CV	Dr A Macadam	
Assent form for child	1.0	25 June 2012
Literature review		
Patient ID coding		
E-mail with clarification concerning recruitment		03 September 2012
Participant Consent Form: Parent/carer	1.0	25 June 2012
Participant Information Sheet: Parent/carer	1.0	10 July 2012
Participant Information Sheet: Child 3-4 years	1.0	25 June 2012
Participant Information Sheet: Child 5-11 years	1.0	25 June 2012
Protocol	1.2	11 May 2012
Questionnaire: MedAPT	1.0	09 August 2012
REC application	3.4	22 August 2012

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

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 NRES 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 website.

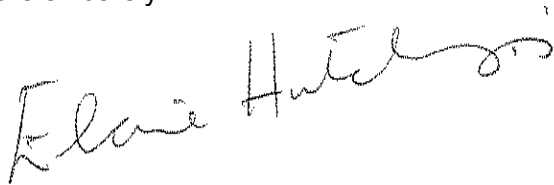
Further information is available at National Research Ethics Service website > After Review

12/NW/0687

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely



pp

Mr Francis Chan
Chair

Email: elaine.hutchings@northwest.nhs.uk

Enclosures: List of names and professions of members who took part in the review

"After ethical review – guidance for researchers"

Copy to: Dr Angela MacAdam, University of Brighton

Professor A Bone, University of Brighton

Dr Matthew Peak, R&D, Alder Hey NHS Foundation Trust

NRES Committee North West - Greater Manchester East

Attendance at PRS Sub-Committee of the REC meeting on 03 September 2012

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Dr Michael Hollingsworth	Retired Senior Lecturer in Pharmacology	Yes	
Professor Janet Marsden	Professor of Ophthalmology and Emergency Care	Yes	Vice Chair
Mr Howard Shilton	Clinical Nurse	Yes	

Department Name

Direct Line: 0151 252 5673
Direct Fax No: 0151 252 5673
Email: Matthew.Peak@alderhey.nhs.uk
Dot.Lambert@alderhey.nhs.uk
Katherine.Jopson@alderhey.nhs.uk
Emma.Masango@alderhey.nhs.uk

Eaton Road
Liverpool
L12 2AP
www.alderhey.com
Main Switchboard
0151 228 4811

Mr Simon Bryson
Alder Hey Children's NHS Foundation
Trust

4th September 2012

Our ref: 12/46/RE
Your ref:

Dear Simon,

RE: Evaluation of the Children's Medication Adherence Prediction Tool (MEDAPT)

Thank you for submitting the above application to the Research & Development Office. It has been reviewed in accordance with the requirements of the Research Governance Framework for Health & Social Care and relevant legislation. I am pleased to confirm approval for it to go ahead within Alder Hey Children's NHS Foundation Trust.

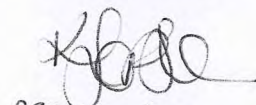
This Trust is performance managed by the National Institute of Health Research (NIHR) in terms of the NIHR Higher Level objective of increasing the number of patients recruited to clinical trials. Our Trust investigators are supported by a number of data managers. You will be contacted by a member of that team who will advise you on the time and format in which data should be submitted. **R&D approval is conditional upon these data being submitted in a timely fashion each month.**

It will be the responsibility of the Chief Investigator to comply with the responsibilities laid down, in the Research Governance Framework for Health and Social Care (2001 and 2005), by the Department of Health. Please see the enclosed leaflet for further information.

A full copy of the Research Governance Framework for Health and Social Care can also be obtained from the Department of Health website at www.dh.gov.uk, the R&D Office, or the Alder Hey Children's NHS Foundation Trust Intranet.

If you are using the Trust's standard Research Consent and Assent forms, please contact the R+D Administrator, Katherine Jopson on ext 2673 to arrange a time for collection.

Yours sincerely



pp Dot Lambert
Research & Development Manager



INVESTOR IN PEOPLE

RESEARCH GOVERNANCE FRAMEWORK FOR HEALTH AND SOCIAL CARE

RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

It is the principal investigator's responsibility to ensure that:

- The dignity, rights, safety and well being of participants are given priority at all times by the research team.
- The research is carried out in accordance with the research governance framework.
- When a study involves participants under the care of a doctor, nurse or social worker for the condition to which the study relates, those care professionals are informed that their patients or users are being invited to participate and agree to retain overall responsibility for their care.
- When the research involves user or carer or a child, looked after or receiving services under the auspices of the local authority, that the agency director or her deputy agrees to the person (and/or their carer) being invited to participate and is fully aware of the arrangements for dealing with any disclosure or other relevant information.
- Unless participants or the relevant research ethics committee request otherwise participants' care professionals are given information specifically relevant to their care which arises in the research.
- The study complies with all legal and ethical requirements.
- A Material Transfer Agreement is in place with the receiving organisation for any samples sent outside of the Trust.
- Each member of the research team is qualified by education, training and experience to discharge his/her role in the study.
- Students and new researchers have adequate supervision, support and training.
- The research follows the protocol approved by the research committee.
- Any proposed changes or amendments to or deviations from the protocol are submitted for approval to the ethics committee, the research sponsor and any other appropriate body.
- Procedures are in place to ensure collection of high quality, accurate data and the integrity and confidentiality of data during processing and storage.
- Arrangements are made for the appropriate archiving of data when the research has finished.
- The findings from the work are opened to critical review through the accepted scientific and professional channels.
- Once established, findings from the work are disseminated promptly and fed back as appropriate to participants.
- All data and documentation associated with the study are available for audit at the request of an auditing authority.

From: Pabs Ethics Committee <Pabs.Ethics@brighton.ac.uk>
Subject: RE: **Simon Bryson ethics application (NRES REC12/NW/0687)**
Date: 11 September 2012 11:39:00 BST
To: [REDACTED]
Cc: [REDACTED]

Dear Simon

Thank you for sending through details of your research project (“Evaluation of the children’s medication adherence prediction tool”). We have recorded that this project received favourable ethical review from the NRES Committee North West – Greater Manchester East and wish you all the best with your research.
Best wishes

Sian Williams
Chair of PABS Ethics Committee.

APPENDIX 15

Participant information sheet Parent (MedAPT study)
Infosheet/parent/02



MedAPT

A study to evaluate the Medication Adherence Prediction Tool for children

Parent/Carer Information
(Infosheet/parent/02)



Invitation

You and your child are being invited to participate in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to ask us if you would like more information or if there is anything that you do not understand. Please also feel free to discuss this with your friends, relatives, doctor or nurse if you wish.

We would like to stress that you do not have to accept this invitation and should only agree to take part if you want to.

Thank you for taking the time to read this.

What is the purpose of the project?

The purpose of the research is to find out whether certain factors relating to your child's medication and treatment influence your child's medication taking in accordance with the advice of their doctor.

It is anticipated that this research will enable us to improve the process of developing medicines for children and provide information to help in prescribing.

The purpose of the research is not to question the treatment your child is receiving, and the researcher will not provide medical advice. Should you require medical advice, you should ask your child's doctor.

Why have I been chosen to take part?

You have been asked to take part because your child is taking medicines on a routine basis as part of their medical treatment, and we would like to ask you some questions based on your experiences as a parent or carer, in routinely trying to give medicines to your child.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. You are free to withdraw at any time without giving a reason and without any consequences to you or your child.

If you choose to take part we would also like to ask your child whether they wish to take part. We will ask your advice regarding whether you feel it is appropriate to ask them as this will depend

upon your child's age.

We have an information sheet which we will use to explain the research to your child. If your child does not wish to participate or you decide you do not want them to participate they will not be included in the study and there will be no consequences for yourself or your child.

What will happen if I take part?

We wish to ask you and your child some questions in the form of a questionnaire, and also conduct a review of your child's medication taking. The review will be conducted at the Alder Hey hospital by reviewing your child's pharmacy records. The purpose of this review is to understand the pattern of your child's medication taking. The purpose of the review is not to question the medical treatment your child is receiving.

Completion of the questionnaire should take no more than 10 minutes.

The questionnaire comprises 20 questions. The questions relate to your child's current medication and treatment. The purpose of the questionnaire is not to question the medical treatment or medicine(s) your child is receiving, but to gather information which may help us to understand which factors are important to your child in adhering to the medication regime in accordance with the advice of their doctor.

Your responses will not be judged in any way and there are no right or wrong answers. The aim is to capture the reality of how children's medicines are used in hospital and to learn from the experiences of you and your child.



Will my taking part in this project be kept confidential?

All information received will be stored as anonymous information and only identified by a unique reference number which will be allocated from, and held within, a secure location at Alder Hey.

All information that you provide will be confidential and no individuals will be identifiable in any reports or publications.

No information collected will be shown to anyone apart from the research team and your child's medical team at Alder Hey.

For regulatory purposes, data from the study will be stored securely for at least 10 years following the study and destroyed as confidential waste thereafter.

The information you provide will be handled confidentially. It is however possible that during the course of the research, you or your child may disclose information which may be considered to put your child or another individual at a health risk. Should this situation arise you will be informed and your doctor at Alder Hey will be informed.

What are the possible disadvantages and risks of taking part in this research?

We do not foresee any specific risks, burdens or changes to lifestyle other than the inconvenience which you may experience in giving up your time to complete the questionnaire.

The answers you provide will not be judged, and there are no right or wrong answers.

It is possible that during the course of the research that you may feel uncomfortable in disclosing particular aspects of your experiences. Should this occur, you are not required to provide information where you are uncomfortable in doing so, and you may omit any questions on the questionnaire should you wish to without giving a reason.

What will happen if I want to stop taking part?

You can withdraw at anytime, without explanation and without any consequences to yourself or your child. Results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and no further use is made of them.

What will happen to the results of the research study?

This research will take place over approximately 12 months.. The information will be presented at academic conferences and will be published in research journals. Some direct questionnaire responses you or your child provide may be used, however, in all publications the research participants will remain anonymous.

What if something goes wrong or I am unhappy with the conduct of the research?

If you are unhappy, or if there is a problem, please feel free to let us know by contacting the chief Investigator, *Mr Simon Bryson*, on 07913 048665. If you remain unhappy or have a complaint which you feel you cannot speak about with Mr Simon Bryson, then you should contact Prof Adrian Bone, Head of Research, University of Brighton, telephone (01273 642120) or e-mail (A.J.Bone@Brighton.ac.uk). When contacting Prof. Bone, please provide details of the name or description of the study (so that it can be identified), the researcher involved, and the details of the complaint you wish to make.



Will my taking part be covered by an insurance scheme?

Participants taking part will be covered by the University of Brighton insurance

Who is funding the research?

The research and is being undertaken by the University of Brighton. The project has received ethical approval from the NHS National Research Ethics Service.

Criminal Records Bureau check (CRB)

The researcher Simon Bryson works for the hospital and has an honorary research contract. He also has obtained an enhanced Criminal Records Bureau (CRB) disclosure and you may request evidence of the disclosure from Simon.

Contact for further information:

Should you have any questions, please contact Mr Simon Bryson, Telephone 07913 048665, e-mail simon.bryson@alderhey.nhs.uk

What to do if you wish to participate:

You have at least 24 hours to consider whether you wish to participate.

Should you decide you wish to participate, please notify the Mr Simon Bryson who will then ask you to sign the consent form on the next page, and where applicable an assent form for you and your child, giving confirmation that your child has agreed to participate.

This information sheet is for you to keep. Thank you for your time and help.

APPENDIX 16

Participant information sheet child 3-4 years (MedAPT study)
Infosheet/child/03

Child Information Sheet
Infosheet/Child/03
3-4 years inclusive, or as advised by parent
Version 1.0, 25 June 2012

Children taking medicines

To be read out to the child, or used, together with the parent/carer to explain to the child.

I am talking with children to ask them about their medicines and I would like to ask you too. If you don't want to talk to me you don't have to.

I'd like to ask you and your (*insert name of parent/carer e.g. Mum/Dad/Grandma etc*) some questions about your medicines, how you take them, and what you like and don't like about them.

Your (*insert name of parent/carer e.g. Mum/Dad/Grandma etc*) will write your answers on a sheet of paper I give them, and I will be asking them some questions about medicines as well.

Is it ok if I talk with you?

Thank you.

APPENDIX 17

Participant information sheet child 5-11 years (MedAPT study)
Infosheet/child/04

What will happen if I want to stop taking part?

It is ok to stop taking part at anytime and you don't need to tell us why.

What will happen to the results of the project?

We will be talking to other children and the people who look after them over one year. Once the project is over we will let you know what we have found out.

We will also tell some other grown-ups who are interested in our project about what we have found out, including some of the things you said, but we will not tell them your name.

Contact for further information:

If you have any questions, please let the person who looks after you know, or contact Mr Simon Bryson (Contact information below)



What to do if you wish to take part:

You have at least 24 hours to consider whether you wish to take part.

If you decide you wish to take part, please tell the person looking after you today or Mr Simon Bryson who will then ask you to sign a form, to say you wish to take part.

This information sheet is for you to keep. Thank you for your time and help.

MedAPT

A study to evaluate the Medication Adherence Prediction Tool for children

Infosheet/child/04 (5-11yrs)

Contact information

Simon Bryson
Tel: 07913 048665
Email: simon.bryson@alderhey.nhs.uk

Alder Hey Children's 
NHS Foundation Trust



Invitation

You are invited to take part in a project at the hospital. Before you decide if you wish to take part, we would like to explain what we are doing.

Please read this sheet and ask us, or the person looking after you, if you would like more information or if there is anything that you do not understand.

Thank you.



Why are we doing this project?

We are working with children at Alder Hey who, like you, take medicines regularly and would like to find out about you and the medicines you take. It is important that you take your medicines, so we want to find out what you think about taking your medicines and whether you are able to take them when you are supposed to. We would like to use what you tell us to make better medicines for children like you who take medicines regularly.

Why have I been chosen to take part?

You have been asked to take part because you know what it is like to take medicines every day so we think the information you can give us will be very useful.

Do I have to take part?

It is your choice, and it is ok to stop taking part at any time without telling us why. Just say I'd like to stop now.

Will my taking part in this project be kept a secret?

If you decide to take part you will be given a code number so that the information you tell us will only contain your code number and not your name. Your name will be a secret

The things you tell us will not be shown to anyone but the people involved in the project and your nurse and doctor at Alder Hey.

What will happen if I take part?

We wish to ask you some questions to understand a little about you, the medicines you take and what you think about the medicines you take each day. The person who looks after you will help you, and we'll ask you to write your answers on a paper form and hand this back to us.

If there are any questions which you do not want to answer it is ok, just tell us. It should take no more than 10 minutes to answer the questions. It is important that you answer the questions truthfully. There are no right or wrong answers, and you will not get into trouble for any answers you give us.

Once you give us your completed form back, we will look at some information from the Alder Hey Pharmacy about the medicines you take, and how often you take them.

APPENDIX 18

Assent form child (MedAPT study)
AF/child/02

Assent Form Child

Study Title: Evaluation of the children's medication adherence prediction tool (MedAPT)

Researcher: Simon Bryson, University of Brighton School of Pharmacy

Child (or if unable, parent/guardian on their behalf) / young person to circle all they agree with

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

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

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

Have you had your questions answered in a way you understand? Yes/No

Do you understand it's OK to stop taking part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are 'no' or you **don't** want to take part, don't sign your name!

If you **do** want to take part, you can write your name below

Your name _____

Date _____

Mr Bryson who explained this project to you needs to sign too.

Print Name _____

Sign _____

Date _____

Thank you for your help.

Note: When completed 1 copy for participant and 1 copy for researcher

APPENDIX 19

Consent form parent (MedAPT study)
CF/parent/02

APPENDIX 20

Medication Adherence Prediction (MedAPT) questionnaire
MedAPT 001



MedAPT

Medication Adherence Questionnaire
MedAPT 001

09/08/2012 version 1.0

Question	Response	(admin use only)
How old are you (Child)?		
Medical condition		
Do all your medicines taste ok?	Y/N	
Are any of your medicines unpleasant or not nice to take?	Y/N, which one(s)	
Are there any colours of medicines you like?	Y/N, which one(s)	
Are there any colours of medicines you do not like?	Y/N, which one(s)	
Do you take any tablets?	Y/N, which one(s)	
Do you take any oral liquids?	Y/N, which one(s)	
Do any of your medicines make you feel unwell?	Y/N, which one(s)	
<p>Do you use any of the following to help you/your child take their medicines? (please tick each that apply):</p> <ul style="list-style-type: none"> <input type="checkbox"/> Mix the medicine with food or drink <input type="checkbox"/> Child takes something before or after the medicine as reward or to mask taste? <input type="checkbox"/> Physical force or restraint <input type="checkbox"/> Offer money <input type="checkbox"/> Persuasion or reasoning 		
Does your child have a		
Gastronomy	Y/N	
Nasogastric tube	Y/N	
How frequent does your child need to take their medicines?	<ul style="list-style-type: none"> < once a week 3 times/week every day >2 times each day 	
How many different medicines do you regularly (total each week) take?		
Have you ever been offered a choice of type of medicines (tablets or liquids) for your child?	Y/N	

	Definitely False	Mostly False	Don't know	Mostly True	True
My doctors are very knowledgeable					
	Not at all	Slightly	Moderately	Quite a bit	Extremely
It is unpleasant (e.g. taste and smell) for my child to use some of their medications					
	Never	Rarely	Sometimes	Often	Always
We get confused about my child's medications					
We have strict routines for my child in using regular medications					
I keep my child's medications close to where they need to use them					
I ensure I have enough medications so that my child does not run out					

Please add any further comments you wish to make: