

DETERMINING THE PREVALENCE AND NATURE OF ORAL
FORMULATION-RELATED BARRIERS TO MEDICINES ADMINISTRATION
IN PAEDIATRIC PATIENTS SUFFERING FROM CHRONIC CONDITIONS

by

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A systematic review identified limited studies exploring oral formulation-related barriers to medicines administration in children. Owing to the lack of licensed medicines suitable for use in children, manipulation is often required to deliver a specific dose or to facilitate medicines administration. Little is known regarding the prevalence and nature of issues encountered when administering medicines to children in the domiciliary setting.

This study adopted a pragmatic approach to determine the nature and prevalence of oral formulation-related barriers to medicines administration in children suffering from a range of chronic conditions. Problems reported by healthcare professionals, patients and their parents/carers were identified to inform future pharmaceutical development and improve children's medicines.

Focus groups (n=4) were conducted with healthcare professionals in the West Midlands and semi-structured face-to-face interviews (n=278) were conducted with parents/carers/young people at University Hospitals Coventry and Warwickshire. Questions explored barriers to medicines administration, refusal and manipulation.

In total, 31% of interview respondents reported medicines refusal. Taste was the most commonly reported barrier to medicines administration. Almost one fifth (19%) of medicines administered to children were reported to require manipulation. Findings indicate that age-appropriate medicines are required to provide both suitable dose units and acceptable taste for paediatric patients.

For my loved ones

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GLOSSARY

A and E- Accident and Emergency

ADR- Adverse Drug Reaction

AIDS- Acquired immune Deficiency Syndrome

ARV- antiretroviral

AZT- zidovudine

BBC- British Broadcasting Corporation

BCH- Birmingham Children's Hospital

BNFC- British National Formulary for Children

CF- Cystic Fibrosis

ddl- didanosine

DNA- Did not attend

DOH- Department of Health

EFV- efavirenz

EMA- European Medicines Agency

EUPFI- European Paediatric Formulation Initiative

FIND OUT- REC no 10/H1207/47 Acronym given to this study (**Formulation aNd Development**)

FormPIC- REC no 13/NE/0020 Acronym given to further study (**Formulation Preference In Children**)

GCP- Good Clinical Practice

GMP- Good Manufacturing Practice

GOSH- Great Ormond Street Hospital

GP- General Practitioner

HIV- Human Immunodeficiency Virus

IBM SPSS statistics- statistical package for the social sciences

IMD 2010- Index of multiple deprivation 2010

IRAS- Integrated Research Application System

JRA- Juvenile Rheumatoid Arthritis

Losec MUPS- Multiple Unit Pellet Systems

LSOA- Lower super output area

MAM- Medical Adherence Measure

MCRN- Medicines for Children Research Network

MEMS- Medication Event Monitoring Systems

MHRA- Medicines and Healthcare products Regulatory Agency

MMAS- Modified Morisky Adherence Scale

MODRIC- Manipulation Of Drugs In Children

MP- Medical practitioner

NEWT- North East Wales NHS Trust

NG- Nasogastric

NHS- National Health Service

NHSBSA- National Health Service Business Services Authority

NIAID- National Institute of Allergy and Infectious diseases

NICE- National Institute for Health and Care Excellence

NIHR- National Institute of Health Research

NPSA- National Patient Safety Agency

NVP- nevirapine

PACTG- Paediatric AIDS Clinical Trial Group

PALS- Patient Advice and Liaison Service

PCT- Primary Care Trust

PEG- Percutaneous endoscopic gastrostomy

PI- protease inhibitor

PICOS- Participants, Interventions, Comparisons, Outcomes and Study design

PIL -Patient Information Leaflet

PIP- Paediatric Investigation Plan

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QSR NVivo 8- thematic analysis package

RCPCH- Royal College of Paediatrics and Child Health

REC- Research Ethics Committee

RDS- Research Design Service

RPS- Royal Pharmaceutical Society

RV- Rebecca Venables

SCI- Science Citation Index

SIGN- Scottish Intercollegiate Guidelines Network

SLE- Systemic Lupus Erythematosus

TIP- Treatment Interview Protocol

UTA- Unable to attend

UHCW- University Hospitals Coventry and Warwickshire

VAS- Visual Analogue Scale

WHO- World Health Organisation

WM-MCRN West Midlands- Medicines for Children Research Network

YPG- Young Persons Group

3TC- lamivudine

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1 BACKGROUND TO THE THESIS

Approximately 200 million prescriptions are issued annually for children and young people in the UK (Costello *et al.*, 2004). It has been estimated that 5 - 10% of young people worldwide suffer from chronic, impairing health conditions (Newacheck *et al.*, 2000).

Adherence is defined as

‘the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.’ (WHO, 2003)

There is evidence to suggest that adherence with prescribed medication is lower amongst adolescents and children than in adults (Staples and Bravender, 2002). Medication adherence rates between 11% and 93% in paediatric patients have been reported (Winnick *et al.*, 2005). A median rate of 58% medicine adherence in youth has been estimated (Burkhart and Dunbar-Jacob, 2002).

Adherence is a multi-factorial phenomenon (WHO, 2003) resulting from multiple influencing factors. There is little indication of the true prevalence of adherence issues caused by inappropriate formulations for children, yet it is a problem that is highlighted by many parents and healthcare professionals (Lowey and Jackson, 2008). Several studies have investigated medicines adherence in children, however they have not explored all of the potential barriers to achieving adherence. A greater understanding of why carers of children find some medicines more difficult to administer, and why some are refused is required.

Children with long-term conditions often need to follow a complex medication regimen. They require medicines to be given in accurate dosages often at specific times and/or time

intervals for critical conditions, using drugs with potentially serious adverse profiles and those with a narrow therapeutic index.

It is well known that many medicines prescribed for children in the UK are used without a medicines licence (unlicensed) or outside the terms of a medicines licence (off-label).

A survey of unlicensed and off-label drug use on paediatric wards across five European countries reported that 46% of prescribed medicines were either unlicensed or off-label (Conroy *et al.*, 2000). Reports from the primary care setting found that between 10% and 28.9% of medicines prescribed to children were unlicensed or off-label (Jong *et al.*, 2002, Stevenson, 2008).

Issues with adult formulations used in children including taste and the size of solid unit dosage forms have been identified to cause clinical problems (Kendall and Mehta, 2006). This often necessitates the use of unsuitable formulations in children which may lead to inappropriate modifications to medicines to facilitate medicines administration. The manipulation of dosage forms can be the cause of drug errors (Florence, 2008). The therapeutic effects of many medicines rely on the integrity of the dosage form in which they are presented, thus altering or damaging these can lead to unexpected or inappropriate outcomes e.g. crushing sustained release tablets can cause inappropriate release of large amounts of medication.

Studies have shown how crushing tablets can affect efficacy and compliance (Cornish, 2005). Adding medicines to fruit juices or milk in order to mask the flavour can affect the bioavailability of a drug (Akinleye *et al.*, 2007). However, limited information is available regarding how children and carers adapt various prescribed medicines to increase

acceptability, and the effects that these actions may have on the drug formulation and its pharmacokinetics and pharmacodynamics (Winnick *et al.*, 2005). This may be a decision parents, carers and patients make independently or following recommendation from a healthcare professional.

Studies investigating medicine manipulations in children have reported that approximately 10% of medicines for children are manipulated in a ward environment to administer medicines to children (Skwierczynski and Conroy, 2008) and to obtain accurate doses (Richey *et al.*, 2011). However, a paucity of evidence is available exploring the prevalence and nature of medicines manipulation for the purpose of administering a specific dose or to facilitate medicines administration to children in the domiciliary setting.

Limited data is available regarding the impact of oral formulation properties (i.e. organoleptic, taste, texture, smell, colour/appearance and physical, size and difficulties with swallowing) of individual medicines on child acceptance. Poor acceptance could lead to child resistance or medicines refusal. However, the palatability of paediatric oral medicines is one of the most important factors with potential to influence adherence to therapeutic regimens and outcomes (Salunke *et al.*, 2011). The importance and great incentive to study palatability was discussed in the reflection paper (EMEA, 2006) and endorsed in the latest European Paediatric guideline on pharmaceutical development of medicines for paediatric use (EMA, 2013). In the Paediatric Investigation Plan (PIP) guidelines, taste-masking and palatability are at the forefront in the implemented development of new paediatric medicines (European Commission, 2008).

International studies have explored oral formulation-related barriers to medicines administration in specific disease groups (e.g. antiretroviral medicines in Human immunodeficiency virus - HIV patients) (Boni *et al.*, 2000, Gibb *et al.*, 2003, Goode *et al.*, 2003, Marhefka *et al.*, 2004, Pontali *et al.*, 2001, Wrubel *et al.*, 2005). Further studies compare the acceptance and flavour preferences of a spectrum of drugs from one class (e.g. antibiotics) using a 'one-off' taste test method, commonly with the aid of a visual analogue scale (VAS) and often in healthy children or adults (Bagger-Sjöbäck and Bondesson, 1989, Chan *et al.*, 1997, Cohen *et al.*, 2009, El-Chaar *et al.*, 1996, Samulak *et al.*, 1996, Toscani *et al.*, 2000).

It was necessary to conduct a pragmatic study, exploring oral formulation-related problems with individual oral medicines in a large paediatric population suffering from different chronic conditions. Determining the nature and prevalence of oral formulation-related barriers to medicines administration and their influence on medicines refusal by children was needed.

It was anticipated that study findings would direct drug formulation development with the objective of improving future medicines for children, maximising cost-benefit of effort. As most of the formulation properties of interest to the present study (i.e. taste, smell, texture, volume, size, and swallowing solid dosage forms) relate predominantly to administering oral medicines, investigation of oral medicines was pertinent to this study.

2 INTRODUCTION

2.1 Compliance, Adherence and Concordance

The term compliance is defined as 'The extent to which the patient's behaviour matches the prescriber's recommendations' (Haynes and Sackett, 1979) and involves the patient playing a passive role, following the instructions of a medical professional. The term adherence has been adopted from compliance, to include the active role of a patient in their health care, in which healthcare professional, patient and parent/carer form a partnership. The term adherence implies that the patient/parent/carer is free to choose whether they follow the advice of a healthcare professional and they should not be blamed if they decide against this (Horne *et al.*, 2005).

Often the terms compliance and adherence are used interchangeably, however this is inappropriate as adherence implies that patient, parent/carer, and medical professional are collaboratively involved in healthcare decisions unlike compliance (Matsui, 2007b). Concordance indicates a consensual agreement about taking medicines formed between patient and practitioner in which the beliefs of the patient are of paramount importance (Haynes *et al.*, 2008).

To summarise, the key difference when considering the concepts concordance, compliance and adherence, is that adherence involves patients, parents and carers taking an active, rather than a passive role in decision-making before following a medication regimen. By defining adherence as a concept that encompasses both elements of concordance and compliance, healthcare professionals are able to understand and consider interactions with

patients, to provide ways to help patients overcome barriers to their medication regimes and to quantify a level of adherence (Lehane and McCarthy, 2009). The term adherence will be used throughout this thesis.

2.2 Medicines adherence

Adherence is intended to be a statement of fact, and non-judgemental, not to blame treatment, prescriber or patient (Haynes *et al.*, 2008). To promote adherence, shared decision-making between healthcare professional and parent/carer and child is needed and this is not always achieved. To support adherence it is important to ensure effective communication between healthcare professionals and parents/carers/patients, that parents/carers/patients are involved in decision-making and that patients understand their condition/s and treatment and make an informed choice based on this (NICE, 2009).

Medicines adherence rates in paediatric patients ranging from 11 to 93% have been reported (Winnick *et al.*, 2005) with a median rate of 58% (Burkhart and Dunbar-Jacob, 2002). Rates of medicines adherence in young people and children are generally below 50% (Quittner *et al.*, 2008).

Adherence is a multidimensional phenomenon involving five factors related to the health system and healthcare team, condition, patient, therapy, and social/economics (WHO, 2003). These factors are displayed in Figure 1.

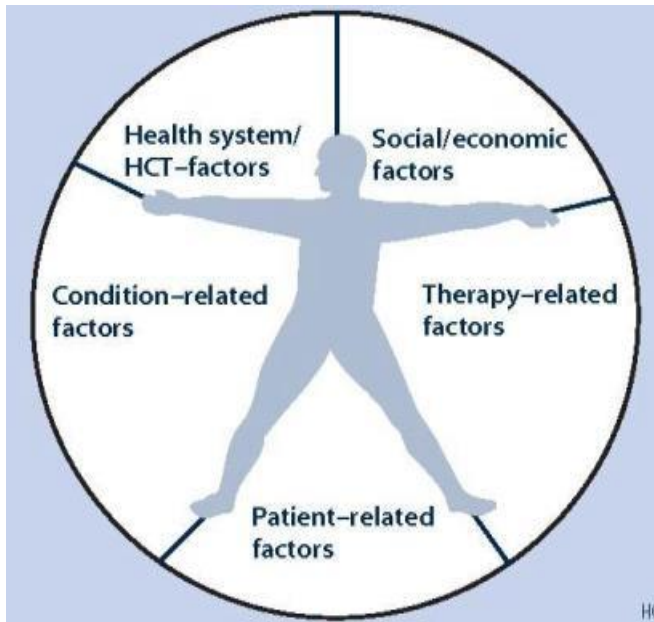


Figure 1 The five factors of adherence (WHO, 2003).

The factors affecting medicines adherence in children and young people are similar to those in adults, yet in children, medicines adherence is more complex due to the added dimension of a patient's family (Osterberg and Blaschke, 2005).

Parents and carers can influence medicines adherence in children as often they are responsible for administering medicines until a child begins to take more responsibility. Generally parents take full responsibility for a young child, and this changes to a shared medication management routine as a child becomes more independent at school age to a complete self-management stage at adolescence. However, the age at which a young person becomes fully responsible for self-administration varies on an individual basis, and is not related to age, rather more maturity (WHO, 2003).

It is important for healthcare professionals to understand how families manage the responsibility of administering medicines as this may influence medicines adherence.

Investigating whether parents, carers and young people are independently responsible for administering medicines or if the role is shared is vital when exploring medicines adherence.

Medicines adherence can be affected by varying levels of parental supervision, busy lives and dysfunctional families (Matsui, 2007b). Several paediatric studies in patients with chronic conditions have indicated that family-related factors can affect medicines adherence (Gau *et al.*, 2006, Mackner and Crandall, 2005, Mellins *et al.*, 2004, C.A. Shah, 2007).

Adherence to medicines can be challenging for young people (Osterberg and Blaschke, 2005). Factors affecting medicines adherence in young people include cognitive, emotional and psychological factors, patient education, family functioning, peer influence, healthcare team (i.e. communication style), the healthcare setting, complexity of the therapeutic regimen and interference of the treatment with needs and lifestyles of the young person (Michaud *et al.*, 2004). Particularly, research on juvenile diabetes, haemophilia and rheumatoid arthritis has revealed the potential vulnerability of young people to medication non-adherence (WHO, 2003).

2.2.1 Measuring medicines adherence

The level of medicines adherence critical for effective disease control varies across different chronic conditions, even though optimal adherence is always 100%, except when drug-plasma levels indicate otherwise. Zelikovsky and co-workers (2008) studying young people listed for a renal transplant suggest an 80% - 90% adherence cut-off to classify adherent patients. A higher adherence cut-off of 95% has been reported in adult HIV guidelines in order to optimise therapeutic outcomes (Carpenter *et al.*, 2000).

Adherence can be measured using indirect and direct methods. Drug assays, and body fluid levels of drug or markers are examples of direct methods. These produce quantifiable data and are objective methods, however there are disadvantages to these such as cost, drug interactions (including foodstuff-drug interactions) affecting results, individual drug metabolising abilities and drug absorption rates (Riekert and Drotar, 2000).

Other direct methods include 'pill counts' and electronic monitoring. Electronic monitoring involves attaching electronic devices to containers of liquids or solid dosage forms, metered dose inhalers and nebulisers, which create a record of the time and date each time they are opened or used respectively. This data can be evaluated and the level of adherence calculated (Butz, 2006). Problems with these exist, for example patients failing to return solid dosage forms that they have not taken, or opening containers but discarding the contents. In spite of this, electronic monitoring has become the gold standard for measuring adherence (Riekert and Drotar, 2000). There are limitations to using this technique in a pragmatic study, these include cost, patients being made aware that they are being monitored and the inability to provide information on the type of non-adherence behaviour.

Indirect methods of assessing adherence include self-reports (e.g. face-to-face interviews, questionnaires), i.e. questioning whether a patient has taken medicines or not and physician rating. These are low cost interventions and easier to perform. Concerns have been raised with regard to the validity of indirect methods as adherence may be overestimated because of social desirability (i.e. reporting to a clinician 'what they want to hear') (Butz, 2006).

However, findings from studies comparing indirect and direct assessment methods to measure adherence have reported similar results when using different methods (Riekert and

Drotar, 2000). One example is an adult study by Haynes and co-workers (1980) in which, 75% of patients adherent to their anti-hypertensive medication based on tablet counts were correctly identified as adherent through direct questioning. In addition, 90% of patients reporting that they were non-adherent were non-adherent according to tablet counts (Haynes *et al.*, 1980).

2.2.2 Non-adherence

Non-adherence can be unintentional or intentional. An explanation of both concepts is provided in Figure 2 below.

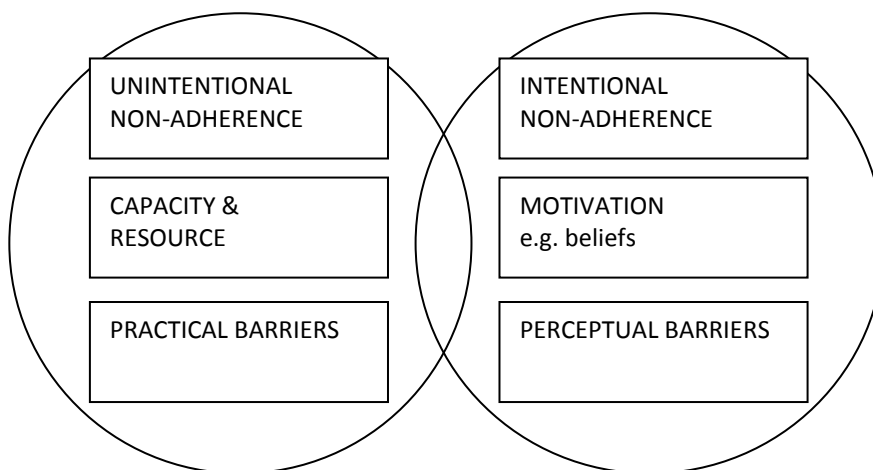


Figure 2 A diagram displaying the factors that influence unintentional and intentional non-adherence (Adapted from Horne and co-workers (2005)).

2.2.2.1 Unintentional non-adherence

Ability and resource barriers may impede adherence, these include forgetfulness, physical difficulties with opening containers or using inhalers, not understanding the concept of obtaining a repeat prescription and issues with medicines administration affecting normal daily activities. Practical aspects causing unintentional non-adherence include administration

difficulties such as if the patient is physically unable to swallow solid dosage forms (Horne *et al.*, 2005).

2.2.2.2 Intentional non-adherence

Intentional non-adherence is a deliberate act, in which a patient may be described as a rejector, (i.e. does not take medicines at all) or a modifier (changes the dose or frequency of medicines administration) (Horne *et al.*, 2005).

2.3 Introduction to oral formulation-related barriers to medicines administration

There are many reasons related to drug therapy that could reduce adherence to a prescribed treatment plan. Instructions may be misunderstood or misinterpreted, medicines forgotten and adverse effects perceived to be worse than the disease itself (notably in the case of asymptomatic conditions). Worries about becoming dependent upon medicines, believing that medication will not help to improve the condition and denial of the disease itself are all potential reasons for sub-optimal adherence (WHO, 2003).

Oral medicines may be refused by children for a variety of reasons. Reasons for refusing oral medicines are displayed in Figure 3 below.

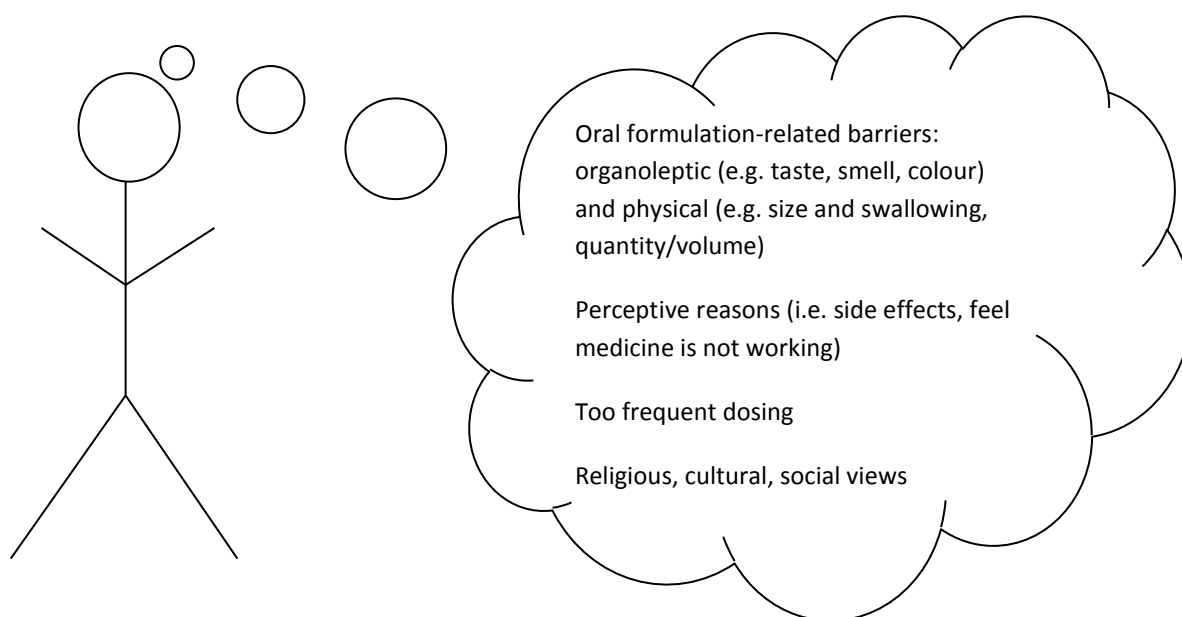


Figure 3 Reasons for child refusal of oral medicines.

Poor child acceptance of medicines may not result in complete omission of a dose of medicine, yet delay administration or cause unnecessary stress for parent or carer and child. According to the European Medicines Agency (EMA) (EMA, 2006), the palatability of paediatric oral medicines is considered one of the most important factors with potential to influence adherence to therapeutic regimens and outcomes.

In several studies, palatability has been reported to affect acceptance of or adherence to medicines in children. However these studies conducted one-off taste-tests with healthy children or adult volunteers (Bagger-Sjöbäck and Bondesson, 1989, Chan *et al.*, 1997, Cohen *et al.*, 2009, El-Chaar *et al.*, 1996, Samulak *et al.*, 1996, Toscani *et al.*, 2000) or investigated problems with organoleptic properties of medicines in specific paediatric populations (e.g. children with HIV) (Boni *et al.*, 2000, Gibb *et al.*, 2003, Goode *et al.*, 2003, Marhefka *et al.*, 2004, Pontali *et al.*, 2001, Wrubel *et al.*, 2005).

2.4 Licensing of Medicines

To understand the existence of oral formulation-related barriers to medicines administration it is necessary to have a good understanding of the problems associated with the licensing of medicines for children.

European and UK legislation provides marketing authorisation of medicines to ascertain the efficacy, safety and quality of medicines.

A licensed medicine is a medicine that is given a Marketing Authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA) once quality, safety and efficacy have been assured. For these medicines the manufacturer has responsibility for adverse events (Buckham 2010).

A survey carried out by Neubert and co-workers (2008) confirmed the need for a common definition for unlicensed and off-label medicine use which should be incorporated in to European legislation. The survey agreed that drugs with a Marketing Authorisation used in an unapproved manner should be termed 'off-label' and those without a Marketing Authorisation termed 'unlicensed' (Neubert *et al.*, 2008).

2.4.1 The prevalence of unlicensed medicines use and off-label prescribing in children

Developing age-appropriate medicines is both time-consuming and technically challenging. Stages to drug development include: identifying problematic drugs, using specific technologies such as taste-masking, and conducting pharmacokinetic, bioavailability and dose-ranging studies (Milne and Bruss, 2008). Additionally, financial and ethical reasons

restrict many pharmaceutical companies from performing clinical trials in children (Wong, 2003).

The majority of medicines prescribed to children have not been licensed (unlicensed) or are medicines used outside of the terms of their licence (off-label) and are commonly adult medicines (A. Nunn, 2003).

Studies conducted in the UK suggest that the use of unlicensed medicines on paediatric wards accounts for between 25% and 65% of medicines use (Cuzzolin *et al.*, 2003). Unlicensed medicines are also used to treat paediatric patients in general practice. Approximately 11% of medicines used in primary care for treating children in the UK are off-label or unlicensed according to McIntyre and co-workers (2000).

2.4.2 Specials medicines

Healthcare professionals may consider it necessary to prescribe or advise the use of an unlicensed medicine when no licensed, suitable alternative is available, in which case the medicine will often be prepared in a pharmacy by, or under the supervision of a pharmacist (extemporaneous medicine) or ordered from a Specials manufacturer (Specials medicine).

Medicines legislation (specifically, The Medicines for Human Use Marketing Authorisations Etc Regulations 1994/SI 3144) states that medicinal products require a licence before they are marketed in the UK (MHRA).

Some patients have special clinical needs that cannot be met by licensed medicinal products and therefore, the law allows manufacture and supply of unlicensed medicinal products (commonly known as 'Specials') subject to fulfilling the following conditions:

- There is a bona fide unsolicited order
- The product is formulated in accordance with the requirement of a doctor or dentist registered in the UK
- The product is for use by their individual patients on their direct personal responsibility.

A manufacturer's Specials licence issued by the MHRA must be held if a Specials medicine is procured in the UK. Advertisement of Specials medicines is not permitted, and a Special should not be supplied if an equivalent licensed product is available and suitable. Essential records must be kept and serious adverse drug reactions (ADRs) reported to the MHRA (MHRA).

Obstacles to the commercial availability of Specials medicines still prevail. These include short shelf-lives and specific storage conditions, creating increased frequency of re-ordering, waste medicines, cost and longer time elapses to obtain the medicine from point of ordering (Standing and Tuleu, 2005). The inconvenience for parents travelling frequently to and from pharmacies and hospitals is a common issue surrounding the supply of Specials medicines.

When comparing the procurement of Specials and extemporaneous medicines, manufacturers of Specials follow quality assurance systems (i.e. record keeping trail and tracking of batch numbers, ADR reporting, good manufacturing practice (GMP) and regular inspections from legal authorities), to minimise the risk of production errors (Yeung *et al.*, 2005). Such procedures are not required when dispensing extemporaneously.

2.4.3 Extemporaneous medicines

The compounding of ingredients to prepare an unlicensed medicine for an individual patient describes extemporaneous dispensing (A. Nunn, 2003). The preparation of extemporaneous medicines does not require a Manufacturer's Specials licence and can be performed in a registered pharmacy (according to section 10 exemption of the Medicines Act) under the supervision of a pharmacist (RPS, 2010).

Extemporaneous medicines are often prepared instead of Specials medicines, owing to problems with the supply of Specials medicines. Yeung and co-workers (2005) reported that greater than 50% of extemporaneously procured liquids in UK specialist hospitals were available to order as Specials. The restrictions on advertising Specials medicines for manufacturers (resulting from the lack of regulatory approval on clinical trials regarding dosing, efficacy and safety) across the UK make obtaining Specials difficult (Standing and Tuleu, 2005).

It is recognised that children are administered portions of adult doses and tablets crushed or capsules opened to ensure that a child receives medicine, although this is inaccurate and unsafe practice (WHO, 2009). The manipulation of medicines by parents, carers, young people and nurses may be classed as extemporaneous dispensing (Standing and Tuleu, 2005).

2.4.4 The problems and risks associated with unlicensed medicines

Appropriate prescribers are permitted to prescribe unlicensed medicines or medicines off-label subject to their individual clinical competence, the professional codes and ethics of

their statutory bodies, and the prescribing policies of their employers. Additional risks should be carefully considered when prescribing an unlicensed medicine or in an off-label manner, including: reduced product quality, adverse reactions, inconsistent product information or labelling (e.g. absence of Patient Information Leaflets (PILs) and unlicensed imports with patient information in a foreign language). Patients and carers can easily become confused when a PIL is contradictory with a medicine's off-label use (MHRA, 2009).

Unlicensed medicines have a poor quality evidence base in comparison to licensed, marketed medicines (Lowey and Jackson, 2008). They may be prepared using a formulation in a pharmacopoeia, in other published work or in a local formulary and additionally research on chemical, microbiological and physical stability may or may not have been carried out (A. Nunn, 2003). The poor evidence base available for extemporaneous medicines is associated with risks including the production of non-standardised formulations resulting in a lack of uniformity of dosing and possible overdose or underdose (Lowey and Jackson, 2008).

A considerable risk of error exists when preparing extemporaneous medicines. Such errors can have serious consequences. One example is the death of a baby following the use of concentrated chloroform water by a pre-registration pharmacist (Baby dies after peppermint water prescription for colic, 1998). This particular case resulted from the lack of quality assurance standards required to prepare medicines extemporaneously. Additionally, unsuitable facilities, lack of equipment and materials and the declining expertise of pharmacists in pharmaceuticals and formulation contribute to risks involved with extemporaneous procurement (Lowey and Jackson, 2007). When preparing extemporaneous

medicines, calculation errors pose a further risk as units of strength vary (i.e. milligrams, micrograms and nanograms) and complex calculations may be needed (Lowey and Jackson, 2007).

Both unlicensed and licensed medicines are available in a range of strengths. As unlicensed medicines are ordered through specific requests, the variety of strengths is greater. This could be perceived as an advantage to administering a specific dose. However, a 10-fold difference in available strengths can create confusion and lead to serious dosing errors (Koren *et al.*, 1986). One such example involved a child receiving a 10-fold overdose of spironolactone following a community pharmacy supplying a formulation ten times stronger than a hospital pharmacy (Checking paediatric dosing, 2003).

Specials production is not a standard reproducible procedure between manufacturers; It may vary significantly, so changing suppliers could alter clinical outcomes (Stevenson, 2008). Mulla and Co-workers (2007) reviewed captopril liquid formulations used to treat children in hospitals and paediatric cardiac centres in the UK. The results indicated that a variety of unlicensed liquid captopril formulations were used interchangeably. Concerns regarding the bioequivalence of inconsistent captopril liquid formulations and thus the risk of drug toxicity were highlighted. Further variations between the formulations were found related to half-lives, excipients used and solubilities (Mulla *et al.*, 2007).

Errors occurring during unlicensed medicines administration leading to underdosing or overdosing have also been recorded. This could be clinically significant and could cause therapeutic failure or toxicity. Liquids prepared extemporaneously or procured as Specials come in a variety of strengths (as discussed earlier in this section) which can create

confusion for parents. Poor or inconsistent labelling can promote confusion and result in errors during medicines administration (Lowey and Jackson, 2008). It should be noted that this risk is not confined to the administration of unlicensed medicines. Similar errors can occur when administering licensed medicines.

The risk of experiencing an ADR is higher when using an unlicensed preparation (Turner *et al.*, 1999). Often, unlicensed oral medicines are prescribed to patients who are more vulnerable to ADRs (i.e. children, infants, premature neonates, and those fitted with nasogastric - NG tubes) (Lowey and Jackson, 2007). Close clinical monitoring of ADRs is required in such patients who may be unable to alert healthcare professionals of the event (Lowey and Jackson, 2007). As there is insufficient evidence for the safety, efficacy and quality of unlicensed medicines, the prescriber risks litigation following adverse events (Buckham 2010).

A study conducted with 1,000 members of the public (including 610 parents) in Northern Ireland, found that 86% of participants had no previous knowledge of unlicensed medicines use in children. The proportion of parents who felt unlicensed medicines were unsafe increased from 1.8% to 62.4% after being informed of unlicensed medicine use (Public unaware of unlicensed drug use in children, 2009). Parents and carers need to be more aware of unlicensed medicine use and alert to the risks associated with this (Public unaware of unlicensed drug use in children, 2009).

2.4.5 The cost of Specials medicines

Specials medicines also incur additional costs as they are procured on a 'produced to order' basis. The limited stability evidence and shortened expiry dates contribute to the medicine bill wastage.

A British Broadcasting Corporation (BBC) report released in September 2010 revealed that the cost of Specials to the National Health Service (NHS) increased from £57m to £160.5m in four years in England. Data revealed on the inconsistency of pricing showed that 25mg/5mls captopril liquid Special had cost Coventry Primary Care Trust between £50 and £1,556. Omeprazole liquid Special was reported to cost between £50 and £997. Internal NHS sources stated that if each Special had a limit of £75 a saving of almost £72m would be possible (Paduano, 2010).

As of November 2011, changes in reimbursement for Specials medicines ordered to pharmacies means that pharmacies are now encouraged to source Specials medicines more carefully as those most commonly dispensed are reimbursed based on a Specials tariff (NHSBSA, 2011), in attempt to reduce profits. However this will not diminish the problems with cost altogether as this does not cover all Specials medicines.

2.5 Medicines manipulation

2.5.1 Introduction

As a result of the lack of appropriate paediatric medicines, healthcare professionals and parents often opt to manipulating medicines (T. Shah *et al.*, 2008).

Manipulation techniques used to administer medicines are associated with the highest risk of errors in extemporaneous dispensing as no compatibility or stability data is available, dose bioavailability is unpredictable and they are difficult to monitor (RCPCH, 2004). Medicines may be manipulated by nurses at ward level and by parents and carers in the community to either facilitate medicines administration (e.g. to improve palatability) or for the purpose of administering a specific dose.

Common examples of manipulation techniques used to administer specific doses of medicines to children include diluting concentrated preparations designed for adults and segmenting (halving or quartering) tablets (RCPCH, 2004). The limited data that is available on manipulating prior to administration is designed for treating geriatric patients or adults with difficulties swallowing. The North East Wales NHS Trust (NEWT) guidelines include guidance on preparing solid dosage forms for tube administration, however do not report evidence for mixing medicines with foodstuffs (Smyth, 2012).

2.5.2 The prevalence of medicines manipulation

Skwierczynski and Conroy (2008) investigated drug manipulations performed by nurses on paediatric wards in two UK hospitals. They concluded that 9.6% of drugs administered were manipulated and 10% of children were administered a manipulated drug. An observational study (part of Manipulation Of Drugs In Children - MODRIC study) investigating medicines manipulation to obtain accurate doses on wards, revealed that 10.1% of medicine administrations required manipulation of a medicine or measurement of a small volume (less than 0.2ml) (Richey *et al.*, 2011).

An audit conducted in 2001 at Great Ormond Street Hospital in London (GOSH), revealed that medicine manipulations (including capsule opening, tablet crushing and cutting) were needed to administer 26% of oral doses administered to inpatients (Data unpublished, cited by Standing and Tuleu (2005)).

Tomlin (2007) suggested that parents disguise up to 40% of medicines given to young children by putting it in to foods such as jam, honey and yoghurt. However, limited data is available on the prevalence and nature of manipulation techniques used to administer medicines to children in the domiciliary environment by parents, carers and young people.

2.5.3 Physicochemical and bioavailability changes associated with medicines manipulation

Manipulating medicines could help to promote adherence, however it could equally compromise bioavailability, stability, and safety of a medicine. Several studies have reported that splitting, crushing or tampering with solid dosage forms prior to administration can lead to inaccurate dosing.

Teng and co-workers (2002) demonstrated that when a tablet is split, the weight can range from 50 to 150% of the desired half-tablet weight. Similarly, Cook and co-workers (2004) studied the effects of splitting tablets and found that the fragment weight of unscored cyclobenzaprine tablets using a tablet cutter may range between 69.4% and 130.2% of the anticipated weight. These examples highlight the risk of unpredictable dosing when segmenting tablets which could affect the therapeutic response of a drug.

Breitkreutz and co-workers (1999) reported that drug absorption can be affected if tablets are crushed. Similarly, crushing tablets was found to increase drug potency in a study by Cornish (2005). Additionally, when non-soluble solid dosage forms are dispersed in liquids, poor uniformity of the drug in solution can lead to inaccurate dosing resulting from the poor solubility of dosage form excipients.

Certain solid dosage forms should not be manipulated prior to administration, specifically controlled release preparations and enteric coated tablets. This can significantly alter drug bioavailability and affect clinical response (Lowey and Jackson, 2007). The manipulation of solid dosage forms promotes further risks including the inhalation of dusts and powders during the process, leading to exposure of parents and carers to potentially harmful substances, e.g. carcinogenics (RPS, 2011).

Although it is known that parents and carers mix medicines with various foodstuffs prior to administration to improve child acceptance, it has been acknowledged that for the vast majority of substances utilised to increase palatability and medicines adherence, there is no data available (Craig *et al.*, 2009). There is limited published data regarding the pharmaceutical effects of adding drugs to various foodstuffs (Akinleye *et al.*, 2007, Cacek, 1986, Carrier *et al.*, 2004, Fay *et al.*, 2005, Johnson *et al.*, 2003, Notterman *et al.*, 1986, T. Shah *et al.*, 2008, Wells and Losin, 2008).

The BNFC provides recommendations on mixing 11 medicines (e.g. topiramate sprinkle capsules) with foods (soft foods, honey, yoghurt, apple sauce or jam) and at least 8 medicines (e.g. Losec MUPS) with fruit juice (BNF for Children, 2011-2012). Additionally, some PILs include guidance on mixing with foodstuffs, e.g. Losec MUPS (AstraZeneca, 2011)

and also some detailed leaflets, e.g. Movicol paediatric plain (Norgine Pharmaceuticals Ltd, 2009). To ensure the bioavailability and safety of a manipulated medicine such guidance should be supported by robust scientific evidence. A section of the PIP suggests that proposed studies for paediatric drug development include those investigating drug stability and compatibility when mixed with foodstuffs (European Commission, 2008).

It is important to recognise that the time elapse from adding a medicine to a foodstuff until administration of a dose could increase the drug-foodstuff binding capability and pharmacokinetics of the drug; thus drug-foodstuff binding may alter therapeutic response. The drug-foodstuff interaction is not the only concern. If a child does not consume the entire drug-foodstuff mixture, a reduced dosage will be consumed. Similarly if a child associates certain foods or beverages with an adulterated taste as a result of mixing with an unpalatable drug, it may discourage a child from consuming the foodstuff used (Cabaleiro, 2003).

Altering gastric-transit time in children will also affect the bioavailability of a drug. Studies have found that the administration of different liquids causes greater variations in gastric emptying time compared to when solids are administered. The reason for this probably results from differences in solution parameters including calorific contents, osmolarities and viscosities (Bowles *et al.*, 2010).

Medicines that are administered via NG and percutaneous endoscopic gastrostomy (PEG) tubes do not always require manipulation. However, Skwierczynski and Conroy (2008) concluded that medicines required manipulation four times more often in children with a feeding tube compared to those without. Patients with NG/PEG tubes often have complex

dosing regimens including multiple medicine and nutritional formulations. This increases the risk of incompatibilities involving drug-drug and drug-nutrient interactions. Sedimentation of drugs and electrolytes could lead to caking, which may alter drug uniformity and also the pharmacokinetic profile of a drug. This could detrimentally affect therapeutic response.

There is limited data investigating healthcare professionals' knowledge of the physicochemical effects of mixing medicines with foodstuffs. Akram and Mullen (2012) explored the knowledge of 30 paediatric nurses regarding mixing medicines in to foodstuffs using a questionnaire. Study findings revealed that mixing medicines with foodstuffs was a common activity amongst the nurses, yet over one quarter of the participants did not feel sufficiently knowledgeable about problems with drug stability (Akram and Mullen, 2012).

2.6 Oral formulation-related barriers to medicines administration

The background and objective section of the reflection paper, Formulations of choice for the paediatric population (EMA, 2006) acknowledged limited data regarding child acceptance of dosage forms (in relation to age and developmental status) and also the limited availability of licensed medicines suitable for administration to children.

Formulation work performed so far in pharmaceutical companies has shown that liquids appear to be more popular with the younger population (infant age), oral dispersing tablets may be favoured by those who are older, and in the adolescent sub-group, tablets and capsules may be more appropriate and convenient (T. Nunn and Williams, 2005). These findings suggest that a wide range of dosage forms of different pharmaceutical strengths are required to suit all paediatric sub-groups (T. Nunn and Williams, 2005). Investigating if

factors (e.g. child age) influence dosage form preference across paediatric patients is important.

The palatability of a medicine is one of the most important issues affecting adherence to drug regimens (Salunke *et al.*, 2011). This is supported by the PIP guideline which identified that taste-masking and palatability information is required when licensing new paediatric medicines (European Commission, 2008).

As the physiological development of children changes markedly with age, they should not be regarded as 'miniature men and women' (WHO, 2007), therefore involving children in studies investigating problems with paediatric medicines is essential. This is supported by the Royal College of Paediatrics and Child Health (RCPCH), who suggest that the views of children with regard to taste need to be investigated owing to differing perspectives between adults and children (RCPCH, 2004).

Taste is defined as 'the sensation of flavour perceived in the mouth and throat on contact with a substance.' (Oxford Dictionaries, 2013b)

A food or drink that is described as palatable is 'pleasant to taste.' (Oxford Dictionaries, 2013a)

Taste is perceived by humans through taste buds which are concentrated on the top of the tongue and found in smaller numbers on the roof of the oral cavity, the larynx and pharynx. Taste buds are constituted of taste receptor cells which contain microvilli referred to as taste hairs. Protein structures within plasma membranes of taste hairs serve as receptors which bind with food molecules once dissolved in water. Receptor cells, followed by sensory nerves are stimulated, transmitting impulses from taste buds to the brain (Chiras, 2011).

Sweet, salty, sour and bitter are the four basic taste modalities, with a fifth modality described more recently as 'meaty' 'substantial' or 'delicious' (Llorens, 2004). The sensation of taste is a relatively early development in the foetus (Lawless, 1985). By the seventh or eighth week of gestation specialised taste cells are present and by weeks thirteen to fifteen taste buds are structurally mature (Lawless, 1985). Flavour preferences vary throughout childhood. Sweet-tasting substances are preferred in childhood (Lawless, 1985), whilst taste preferences resembling those that predominate in adults are seen in the later adolescent years (Liem and Mennella, 2002).

Reported studies in children have shown that often fruity, sweet formulations are preferred. Citrus and red berry flavours are preferred across Europe, liquorice in Scandinavia, whilst bubblegum and grape flavours are reported to be preferred in the US (EMEA, 2006). In contrast to these general findings, some children may prefer flavours that do not follow the general trend. A study by Bennetto and co-workers (2007) acknowledged discrepancies of taste preference in autistic children. Personal communication with a parent of an autistic child preferring bitter to sweet flavours supports this (Personal communication, Paediatric consultant).

Genetic and cultural effects can also influence taste and flavour preferences (Mennella *et al.*, 2005). Lipchock and co-workers (2012) reported that children with a bitter-sensitive allele were more likely to have experienced solid dosage forms than bitter-insensitive children. This suggests that genotype may play a vital role in child acceptance of liquid medicines that are bitter tasting.

Additionally, taste preferences may be influenced by factors such as religious beliefs, gender and diet (Craig *et al.*, 2009). Some medical treatments can also affect taste recognition. A study in oncology patients whom had started chemotherapy treatment identified significantly greater taste recognition errors (Matsui, 2007a). Such findings reinforce that all healthcare professionals should consider palatability before making any prescribing or supply choices to paediatric patients. Although some individuals have very specific taste preferences it is not possible to procure medicines that are well-accepted by all children universally. However, when prescribing in particular patient groups (e.g. autistic children and children receiving chemotherapy) palatability should be at the forefront of prescribing decisions.

Other formulation-related barriers to medicines administration have not been extensively studied, and additionally not in relation to child acceptance of a medicine.

Poor aftertaste of a medicine creates a taste-related problem for which there is a paucity of published data. In the European Paediatric Formulation Initiative's (EuPFI) 2nd conference commentary, 'Formulating better medicines for children', Dr Menella reported that the binding of bitter receptors with bitter agents in the throat could be responsible for the taste that occurs after swallowing a medicine and that the dissolution time of a particular drug can affect this (Salunke *et al.*, 2011).

Further organoleptic properties (i.e. smell, texture and colour) of a medicine may alter how it is perceived. These properties could affect child acceptance of a medicine and also reduce medicines adherence. The RCPCH (2004) suggested that research should be performed to

investigate child acceptability of tastes, textures, volumes and colours of medicines to promote improved medicines adherence.

Physical properties (the number of solid dosage forms of an individual drug or volume of a liquid or powder required at one dosing interval, the size of or aversion to/difficulty swallowing a solid dosage form) may be problems perceived by children resulting in poor child acceptance of a medicine. 'Pill-swallowing' studies conducted in children and young people with HIV have identified that young people fear that solid dosage forms may 'get stuck' or cause choking (Czyzewski *et al.*, 2000, Garvie *et al.*, 2007). In addition to children perceiving that they are not capable of swallowing solid dosage forms, some children may be unable to swallow due to physical or mental impairments. In these circumstances they may be fitted with an NG/PEG tube.

This thesis examines some of the problems associated with the administration of oral medicines to children suffering from a variety of chronic conditions in the domiciliary setting, focussing on the influence of barriers to the administration of oral formulations.

3 AIMS AND OBJECTIVES

3.1 Primary Aims

- To review literature investigating oral formulation-related barriers to medicines administration in paediatric patients suffering from chronic conditions
- To establish the prevalence and nature of oral formulation-related barriers to medicines administration
- To identify the medicines most commonly associated with oral formulation-related barriers to medicines administration, on an individual level and according to drug therapeutic class
- To determine if a relationship exists between oral formulation-related barriers to medicines administration and child refusal of medicines
- To determine the prevalence of medicines manipulation to facilitate medicines administration or for the purpose of giving a specific dose, by parents/carers/children
- To identify the ways that parents/carers/children manipulate oral medicines to facilitate medicines administration or for the purpose of giving a specific dose

3.2 Secondary Aims

- To explore the problems experienced with oral medicines in paediatric patients from the perspectives of medical practitioners, nurses and pharmacists using focus groups
- To identify additional barriers to medicines administration (i.e. those not directly associated with oral formulations).

3.3 Primary Objectives

- To perform an international systematic review of literature using relevant sources updated on 10th January 2013
- To conduct semi-structured face-to-face interviews with parents, carers and young people to identify the prevalence and nature of: i) oral formulation-related barriers to medicines administration ii) manipulations to oral medicines
- To determine if oral-formulation related barriers to medicines administration influence medicines refusal using appropriate statistical analyses.

3.4 Secondary Objectives

- To conduct focus groups with medical practitioners, nurses and pharmacists to:
 - (i) Inform design of semi-structured face-to-face interviews with parents, carers and young people
 - (ii) Explore and compare their views on perceived problems associated with oral medicines prescribed to paediatric patients
- To conduct semi-structured face-to-face interviews with parents, carers and young people to identify additional barriers to medicines administration that are not directly associated with oral formulations.

4 SYSTEMATIC REVIEW

4.1 Introduction to Systematic Review

There is limited information regarding the prevalence and nature of oral formulation-related barriers to medicines administration in children with chronic conditions.

Personal communication with the Young Persons Group (YPG) at Birmingham Children's hospital (BCH) and the Youth Council at University Hospitals Coventry and Warwickshire (UHCW) indicated that some organoleptic and physical properties of medicines may serve as barriers to medicines adherence amongst children suffering from chronic conditions (see Appendix 1). Healthcare professionals at UHCW during the pre-study period highlighted problems with some oral medicines prescribed to paediatric patients (see Appendix 2).

Palatability has been described as a crucial factor influencing adherence to therapeutic regimens and outcomes (Salunke *et al.*, 2011). In the latest guideline developed by the panel on antiretroviral therapy and medical management of HIV-infected children, the appropriateness (including palatability) and availability of drug formulations were reported as important factors to be considered when initiating or changing antiretroviral therapy (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected children, 2011).

Further properties of formulations that may influence child acceptance include: texture, colour/appearance and smell (can influence perception of its flavour), volume of a dose (typical target dose volumes: less than 5ml for children under 5 years and less than 10ml for those 5 years and older (EMA, 2006)), quantity of solid dosage forms, size of solid dosage forms or aversion to/difficulty swallowing medicines.

Individuality influences the age at which children are able to swallow intact solid dosage forms. In conjunction, support and training from healthcare professionals can influence this, and anecdotal evidence suggests that with help, children 6 years and below can learn to swallow solid dosage forms (EMA, 2006). In addition, some children are physically unable to swallow as discussed earlier in section 2.6.

Owing to the limited availability of medicines suitable for use across the paediatric spectrum, often medicines require manipulation to facilitate medicines administration or to provide a specific dose.

4.2 Objective of Systematic Review

The refined review objective was to identify and examine the oral formulation-related barriers to medicines administration in paediatric patients suffering from chronic conditions.

The primary outcome measure was defined as, 'the influence that oral formulation-related barriers to medicines administration have on child acceptance of or adherence to a medicine'.

The secondary outcome of this systematic review was discussion of medicines manipulation techniques used to administer oral medicines to paediatric patients. Study inclusion criteria (see Table 1) were based on the primary outcome measure. Studies meeting inclusion criteria of the review question were further evaluated for reports of medicines manipulation.

4.3 Methods

4.3.1 Introduction to methods

In August 2009, a mind-map was created (see Appendix 3) using guidance from Buzan and Buzan (2006). This was developed using themes identified in early literature searches, problems with medicines highlighted by children in the YPG at BCH and also healthcare professionals at UHCW (see Appendices 1 and 2). The terms in the mind-map were used to inform broad searches. Searches were made on the databases: PubMed (Medline), Science Direct, Wiley and Interscience, The Cochrane library and Pharm-line (now part of the National electronic Library of Medicines - NeLM).

These searches retrieved a plethora of studies exploring general medicines adherence in children. However, limited literature investigating oral formulation-related barriers to medicines administration in children suffering from chronic conditions was retrieved. Although providing valuable background information to underpin the study, refinement of the search strategy was necessary.

A systematic review aims to answer a research question by identifying, appraising and synthesising all of the empirical evidence that meets the pre-defined eligibility criteria (The Cochrane Collaboration, 2013). It was decided that a systematic review would be conducted with the purpose of providing more reliable findings that could be used to inform decision making (The Cochrane Collaboration, 2013).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist as reported by Moher and co-workers (2009) was used to guide the reporting of this review.

This was adapted to allow for appropriate reporting of qualitative data and the heterogeneity of the quantitative study results in this review.

4.3.2 Eligibility criteria

Criteria for inclusion and exclusion of relevant studies were developed using the refined review objective:

- To identify and examine the oral formulation-related barriers to medicines administration in paediatric patients suffering from chronic conditions.

This systematic review considered studies conducted in children of all ages prescribed oral medicines for chronic conditions (defined as long-term - at least 4 weeks). This time period was chosen to permit the inclusion of families with experience of administering medicines in a domiciliary setting and the exclusion of 'one-off' taste studies. This review examined oral formulation-related barriers to medicines acceptance or adherence, therefore only studies exploring formulation-related problems with orally ingestible medicines were included. Reports of children, parents and carers (including parent/carer/child reports documented by healthcare professionals) were pertinent to this review.

The inclusion and exclusion criteria as listed in Table 1 below, were used to screen studies retrieved in systematic searches using the refined search strategies provided in sections 4.3.4.1 - 4.3.4.4, based on Participants, Interventions, Comparisons, Outcomes and Study design (PICOS) (Moher *et al.*, 2009).

Table 1 Inclusion and exclusion criteria used to screen studies for inclusion in the review based on PICOS (Moher *et al.*, 2009).

Inclusion criteria	Exclusion criteria
<p>Participants:</p> <ul style="list-style-type: none"> • 0-<18years (pre-term to adolescent) • Outpatients and inpatients • All nationalities, demographics, socio-economic groups, ethnic groups 	<p>Participants:</p> <ul style="list-style-type: none"> • Studies examining issues in ≥ 18 years (including studies investigating paediatric medicines tested in an adult population)
<p>Interventions:</p> <ul style="list-style-type: none"> • Prescribed oral medicine long-term (defined as at least four weeks) 	<p>Interventions:</p> <ul style="list-style-type: none"> • Short-term treatment (i.e. 'one-off' taste test studies) • Comparative/medication crossover trial
<p>Comparisons:</p> <ul style="list-style-type: none"> • Studies with or without a control were considered 	<p>Comparisons:</p> <ul style="list-style-type: none"> • Studies were not excluded based on absence of a control.
<p>Outcomes:</p> <ul style="list-style-type: none"> • Investigating oral formulation-related barriers to medicines administration (organoleptic and physical properties) on child acceptance of or adherence to medicines. 	<p>Outcomes:</p> <ul style="list-style-type: none"> • No reference to oral formulation-related barriers to medicines administration
<p>Study design:</p> <ul style="list-style-type: none"> • Self-report (child parent/guardian/caregiver) including such data documented by a healthcare professional 	<p>Study design:</p> <ul style="list-style-type: none"> • Studies that did not adopt a self-report tool i.e. just clinical laboratory results

4.3.3 Information Sources

The refined search strategy was conducted using the University of Birmingham e-library and databases listed below. These databases were selected to encompass all relevant literature.

- MEDLINE (includes PubMed (Ovid)) 1946 to 29th May 2012, including also in-process and other non-indexed citations (covers life sciences, with a strong focus on biomedicine)
- EMBASE (EMBASE CLASSIC and EMBASE 1947 to 29th May 2012) (a biological and pharmacological database, with a strong coverage of drug and pharmaceutical research)

- CINAHL Plus (EBSCO) (1937 TO 29th May 2012) (provides nursing and allied health literature)
- NeLM (includes Pharm-line) (includes literature covering pharmacy practice and the clinical use of drugs).

Searches were saved and re-run regularly to ensure up-to-date literature was not omitted. Systematic searches were updated as of January 10th 2013 and results are reported in the search flow diagram guided by Moher and co-workers (2009), see Figure 4.

In addition, hand searches within specific journals (Paediatric Drugs, Archives of Disease in Childhood and the Pharmaceutical Journal) were performed.

Further sources of relevant information were also used. This involved checking professional and regulatory bodies' websites, and conference reports. Also, the researcher maintained a professional and active role in the field of research and presented at the Royal Pharmaceutical Society (RPS) conference 2012 (Venables *et al.*, 2012a).

Full-texts were obtained through libraries at UHCW, Aston University and University of Birmingham. Further sourcing involved inter-library requests and the help of the British Library, London. Non-English papers were translated with help from colleagues at the University of Birmingham if abstracts were relevant and met inclusion criteria.

References cited by studies included in this review and additionally those citing the studies in this review were retrieved for screening using Science Citation Index (SCI).

4.3.4 Search

Subject headings based on the key search terms were identified for each database searched. Free-text terms were also used in the search strategies to maximise the retrieval of relevant literature. A systematic search strategy for each database where possible was created based on the participants, intervention, problem associated with intervention and outcomes, as reported in the inclusion criteria (see Table 1). The search strategies are detailed in sections 4.3.4.1 - 4.3.4.4 below.

4.3.4.1 Search strategy used in OVID EMBASE

Participants

exp adolescent/ OR exp child/ OR exp infant/ OR exp Pediatrics/ OR (adolescen* OR child* OR teen* OR youth* OR young* OR bab* OR neonat* OR infan* OR pediatric* OR paediatric*)

AND

Intervention

("drug formulation" OR "drug manipulation" OR "drug administration" OR "drug adaptation" OR medic* formulation" OR "medic* manipulation" OR "medic* adaptation" OR "medic* administration") OR drug administration/ OR exp drug dosage form/ OR *drug combination/ OR exp drugs, essential/ OR exp drugs, generic/ OR exp nostrums/ OR exp pharmaceutic aids/ OR exp adjuvants, pharmaceutic/ OR exp pharmaceutical vehicles/ OR exp preservatives, pharmaceutical/ OR *solutions/ OR *hypertonic solutions/ OR *hypotonic solutions/ OR *isotonic solutions/ OR exp pharmaceutical solutions/

AND

Problems associated with intervention

exp organoleptic property/ OR exp swallowing/ OR refus* OR acceptability OR side effect OR (preference* OR like OR dislike) OR exp taste/ or exp "smelling and taste"/ OR exp palatability/

AND

Outcome

health behavior/ OR exp patient compliance/ OR exp treatment refusal/ OR (barrier OR "medication adherence" OR "patient compliance" OR "medication compliance" OR "patient adherence") OR *health care organization/

4.3.4.2 Search Strategy used in OVID Medline

Participants

exp adolescent/ OR exp child/ OR exp infant/ OR exp Pediatrics/ OR (adolescen* OR child* OR teen* OR youth* OR young* OR bab* OR neonat* OR infan* OR pediatric* OR paediatric*)

AND

Intervention

("drug formulation" OR "drug manipulation" OR "drug administration" OR "drug adaptation" or medic* formulation" OR "medic* manipulation" OR "medic* adaptation" OR "medic* administration") OR exp dosage forms/ OR *drug combinations/ OR exp drugs, essential/ OR exp drugs, generic/ OR exp nostrums/ OR exp pharmaceutical aids/ OR exp adjuvants, pharmaceutical/ OR exp pharmaceutical vehicles/ OR exp preservatives, pharmaceutical/ OR *solutions/ OR *hypertonic solutions/ OR *hypotonic solutions/ OR *isotonic solutions/ OR exp pharmaceutical solutions/

AND

Problems associated with intervention

Organoleptic OR palatability OR exp swallowing/ OR refus* OR acceptability OR side effect OR (preference* OR like OR dislike) OR exp taste/ OR exp smell/

AND

Outcome

health behavior/ OR exp patient compliance/ OR exp treatment refusal/ OR (barrier OR "medication adherence" OR "patient compliance" OR "medication compliance" OR "patient adherence") OR health care organization

4.3.4.3 Search strategy used in EBSCO CINAHL plus

Participants

(MH "Child") OR "child" OR (MH "Adolescence") OR (MH "Infant") OR MJ adolescen* OR child* OR teen* OR youth* OR bab* OR infan* OR neonat* OR paediatric* OR pediatric*

AND

Intervention

TX "pharmaceutical preparations" OR "dosage forms" OR "drug combinations" OR "herbal drugs" OR "generic drugs" OR "essential drugs" OR "nonprescription drugs" OR "investigational drugs" OR "nostrums" OR "pharmaceutic* aids" OR "prescription drugs" OR "pharmaceutical solutions" OR "drug administration" OR "drug formulation" OR "drug manipulation" OR "drug adaptation" OR "medicine formulation" OR "medicine administration" OR "medicine manipulation" OR "medicine adaptation" OR (MH "Dosage Forms+") OR (MH "Drug Combinations+") OR (MM "Drugs, Essential") OR (MM "Drugs, Generic") OR (MM "Drugs, Investigational") OR (MM "Drugs, Non-Prescription") OR (MM "Drugs, Off-Label") OR (MM "Drugs, Prescription") OR (MM "Prodrugs") OR (MH "Delayed-Action Preparations+") OR (MH "Powders+") OR (MH "Solutions+") OR (MH "Drug Administration+")

AND

Problems associated with intervention

TX ("taste" OR "palatab*" OR "prefer*" OR "accept*" OR "dislike" OR "like" OR "smell*" OR "organoleptic" OR "aftertaste*" OR "deglutition" OR "swallow*" OR "side effect*") OR (MM "Deglutition") OR (MH "Taste")

AND

Outcome

(MM "Health Behavior") OR (MM "Allied Health Organizations") OR (MH "Patient Compliance+") OR (MM "Treatment Refusal") OR TX "health behaviour" OR "patient compliance" OR "medic* adherence" OR "treatment refusal" OR "barriers" OR "medic*compliance" OR "patient adherence" OR "health care organisation"

Boolean operators 'AND' and 'OR' were used to structure the search strategy. An asterisk (*) denotes a term searched as a wildcard. Speech marks ("") are used to surround and identify a string of terms together. The text 'exp' preceding a subject heading term means that the term is exploded to retrieve narrower, related terms during the search.

4.3.4.4 Search strategy for NeLM

The NeLM database does not permit complex specific searches. Combinations of key terms were used to retrieve publications: child*, infan*, adolescen*, bab*, drug administration, dosage form, formulation, manipulation, adaptation, taste, palatab*, swallow*, deglut*, flavour, flavor, organoleptic, refuse, adherence, compliance.

4.3.5 Study Selection

The citations retrieved from systematic searches were imported in to, and managed using the reference manager Endnote X3 (Thomson Reuters). Duplicate studies were identified and deleted. Citations of the retrieved studies were screened against the inclusion and exclusion criteria listed in Table 1.

Screening was initially based on title, then abstract and finally full-text. When studies seemed to meet inclusion criteria or when a decision to include a study could not be made based solely on review of the title or abstract, full-text copies were obtained. The reference lists of the included review studies and studies that had cited these were examined to identify any further relevant studies as discussed in section 4.3.3. The search flow diagram details the rigorous identification process (see Figure 4).

4.3.6 Data collection process

Studies identified as potentially eligible for inclusion were validated independently by RV and a pharmacist with experience in paediatrics and clinical pharmacy. The decision to include the final 27 studies was agreed by consensus.

4.3.7 Data outcomes

For the included review studies, authors, year of publication, study site, medication type, study population characteristics (age of child and number and type of interview participants), methodology of the study tool of interest, and findings of interest to this review were identified and are reported in Table 2. The full content of the review studies were critically examined by RV and the pharmacist with experience in paediatrics and clinical pharmacy, and themes were derived based on the oral formulation-related barriers explored in the studies, following review of the key search terms and review objectives. The themes were categorised and formed the narrative study review. The review studies were assessed for quality. Analysis of study outcomes for the narrative review was informed by Pope and co-workers (2000).

4.3.8 Quality assessment and risk of bias in review studies

Randomised controlled trials are positioned in the top rank of the hierarchy of evidence (SIGN, 2008). In this systematic review, it was acknowledged that the methodology of included studies used to generate the review outcomes would be considered lower in the hierarchy of clinical evidence. Assessing study quality using rigorous methods as reported by Moher and co-workers (2009) was not feasible, owing to heterogeneity across methodologies and reported outcome measures relevant to this review.

Quality of the studies was assessed with guidance from the critical appraisal skills programme (Public Health Resource Unit, 2006). The studies were critiqued based on the following factors: appropriate research design, sampling recruitment strategy met aims of research (how participants were selected, why people chose not to participate), defined

clearly how the data was collected, discussed risk of researcher bias/drug company funding, reported rigorous and critical data analysis (considered both arguments and explicitly explained how data was analysed) and transparency of findings and value of research linking to future research. Critique of the qualitative data was also guided by Mays and Pope (2000).

4.3.9 Summary measures

The review outcome measures form the structure of the narrative results section.

Primary outcome measures:

- Oral formulation-related barriers to medicines administration
- The influence of oral formulation-related barriers to medicines administration on child acceptance of or adherence to a medicine.

Secondary outcome measure:

- Medicines manipulation techniques used to administer oral medicines to paediatric patients.

4.4 Results

4.4.1 Study selection

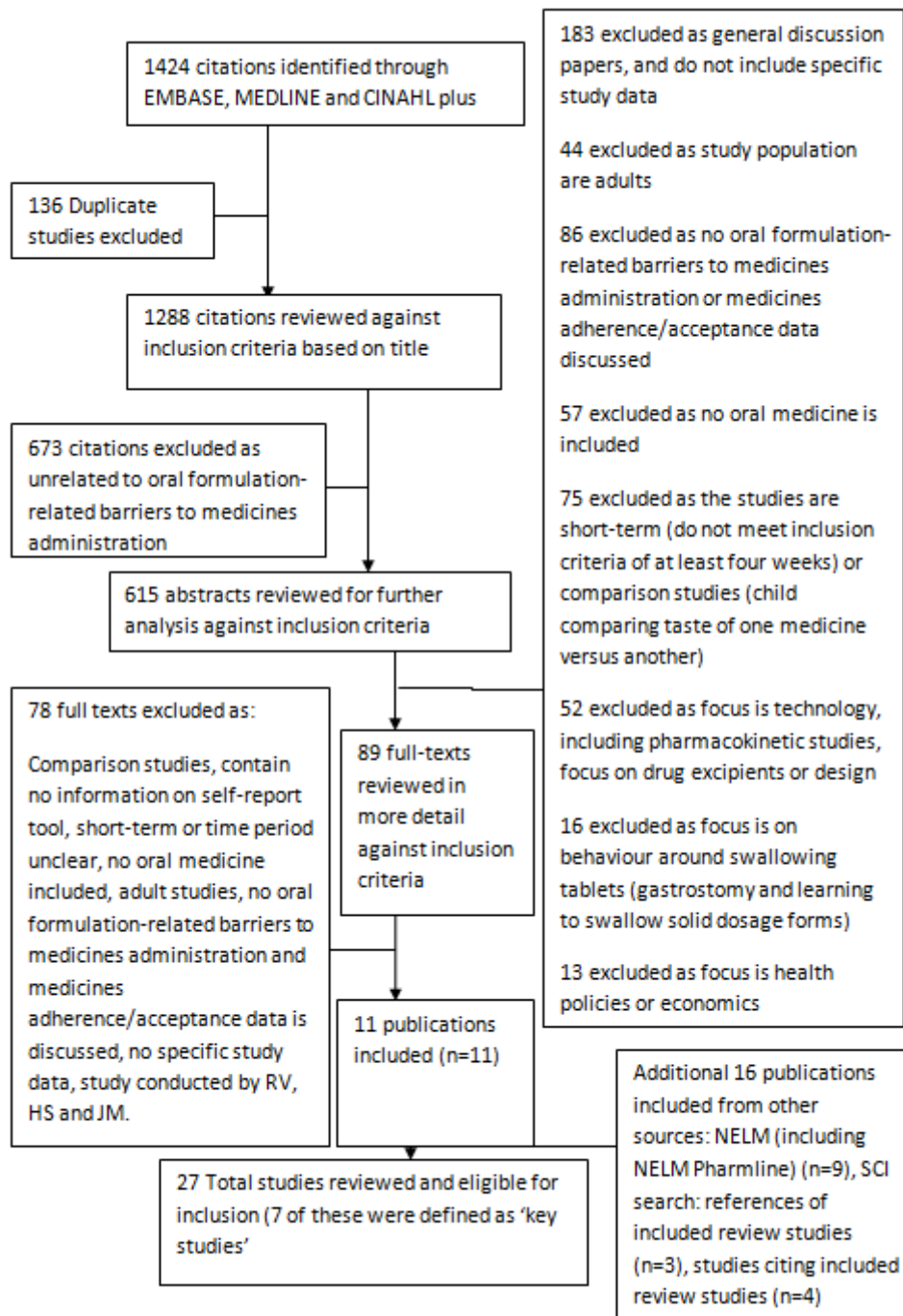


Figure 4 A search flow diagram to show the study screening process, in accordance with the PRISMA system (Moher *et al.* 2009).

4.4.2 Study Characteristics

Table 2 Study characteristics of the 27 studies included in this systematic review.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Shemesh <i>et al.</i> , 2004)	Medication adherence in pediatric and adolescent liver transplant recipients	A paediatric liver transplant clinic , Mount Sinai Medical Centre, New York, USA	Liver transplant patients (except those on ciclosporin)	2 -21y	Analysis of 81 cases	Caregivers and children questioned independently with a list of reasons (for non-adherence) (plus an open option for any other reason)	Caregivers report Tastes bad: 4.9% (n=4/81).
(Tucker <i>et al.</i> , 2002)	Associations with medication adherence among ethnically different pediatric patients with renal transplants	African American and European American patients recruited from four South eastern Paediatric Nephrology Clinics, USA	Renal transplant patients	6-21y	68 paediatric patients (African American and European origin) with renal transplants and their caregivers	Primary caregiver and child together. Medication aversion scale with Likert scale (closed questions)	Neither group of patients agreed that they dislike taking their medicines because they tasted bad or may make them sick. Neither group agreed that swallowing was an issue due to tablet size either. Among both groups, perceived characteristics of their medication regimen, including pill size, pill taste and medication complexity, were found to have significantly low to moderate associations with medication adherence.
(Zelikovsky <i>et al.</i> , 2008)	Perceived barriers to adherence among adolescent renal transplant candidates	A large transplant centre in the North East USA	Renal transplant patients	11-18y	56 Caucasian adolescents listed for a kidney transplant, and their carers	Semi-structured interviews 'The Medical Adherence Measure (MAM)' (closed questions)	Approximate results from histogram: 17% reported taste as a reason for non-adherence 2% reported 'hard to swallow.' Those who identified "hate the taste" as a barrier missed more doses, $z = -2.4$, $p = 0.02$ (average ranks 39.81 vs. 25.36) and took more doses late, $z = -2.7$, $p = 0.007$ (average ranks 40.44 vs. 24.61). Some barriers had a low rate of endorsement (e.g. hard to swallow pills) and therefore there was not sufficient power to examine the relationship between these barriers and adherence.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Christiansen <i>et al.</i> , 2008)	Oral chemotherapy in paediatric oncology in the UK: problems, perceptions and information needs of parents	Two paediatric oncology centres: Great Ormond St hospital (GOSH) and University College Hospital (UCLH) London, UK	Oral chemotherapy (methotrexate and mercaptopurine)	<18y (60% younger than 7y)	55 caregivers	Semi-structured questionnaire via face-to-face interviews with primary caregivers (open-ended questions)	75%, (n = 41) faced some kind of problem or difficulty when dealing with oral chemotherapy: Unpleasant taste of the liquid (n=10) Capsules dispensed were too big to swallow (n=1). Approximately one quarter of parents (24%, n = 10) had at least at some point during treatment crushed tablets prior to administration and evidence of dosage form manipulation was evident in responses to open-ended questions. Breaking capsules in to ice-cream and crushing tablets on cornflakes were described by two fathers in the study.
(Ingerski <i>et al.</i> , 2010)	Barriers to Oral Medication Adherence for Adolescents with Inflammatory Bowel Disease	Two paediatric IBD centres in the Northeast or Midwest regions, USA	Inflammatory bowel disease prescribed mercaptopurine/azathioprine and/or 5-ASA	13-17y	74 adolescents and their primary caregivers together	Medical Adherence Measure MAM: semi-structured interview (closed questions)	Hate the taste: 10.8% (all reported by Crohn's patients) Hard to swallow: 10.8% (all reported by Crohn's patients). 'Children resisting, refusing, spitting out drugs (because of bad taste?) (32%).'
(Modi and Quittner 2006)	Barriers to Treatment Adherence for Children with Cystic Fibrosis and Asthma: What Gets in the Way?	Two paediatric pulmonary clinics in Florida, USA	Oral enzyme capsules (patients with CF or asthma) (Review only considers oral medicines)	6-13y	73 children and parents separately	The disease management interview-CF (DMI-CF) - 51-item self-report measure of adherence behaviours for patients with CF that was modified from the treatment adherence questionnaire-CF (TAQ-CF). The DMI-Asthma is a 28-item questionnaire which asks when, how often, and how much of each medication they took (open-ended questions also) Barriers to Adherence	Taste was reported as a barrier for taking oral antibiotics. Children with CF also identified difficulty swallowing solid dosage forms as a key barrier to taking oral medications (like oral antibiotics and enzymes). Barriers to oral enzymes: CF Children reports swallowing (13%) CF Parent reports of oppositional behaviours (11%) Barriers to Nutrition medicines: CF Parent reports taste (17%) Barriers to Allergy medicines: Asthma parent reports (14%) swallowing Barriers to oral antibiotics: CF parent reports Taste (16%), Oppositional behaviours (11%) CF children reports Swallowing (25%) Asthma parent reports Taste (24%).

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Boni <i>et al.</i> , 2000)	Compliance to combination antiretroviral therapy in HIV-1 infected children	Department of Infectious Diseases, University of Genoa, Italy	Antiretroviral medicines	Mean age 8.2y	Parents/legal guardians of 25 children	Questionnaire: Results presented as 'Problems pointed out by parents or legal guardians in administration of antiretroviral treatment' (open questions)	Too many medicines/tablets to take: 36% Difficulty swallowing: 32% Bad taste: 24% Child resists/refuses/spits out medicine 32% (unknown reason).
(Buchanan <i>et al.</i> , 2012)	Barriers to Medication Adherence in HIV-Infected Children and Youth Based on self- and caregiver report	Multicentre USA	Antiretroviral medicines	8-18y	Children/youth with perinatally acquired HIV and their parents/caregivers (n = 120 dyads)	Children and their caregivers independently: Questionnaire about 19 potential barriers to adherence to the child's antiretroviral therapy regimen. (closed list)	Barriers to adherence, reasons for missing medicines in previous month: Child: Taste, can't get it down, or keep it down (pill or liquid) (18%), Child refused (20%) Too much medication (9%). Adult reports (also reported in bar chart): Taste, can't get it down, or keep it down (pill or liquid) (8%), Child refused (12%), Too much medication (2%). Significant agreement between child and caregiver reports on the barrier of taste/cannot get it down as a barrier, based on a kappa statistical test, $k = 0.44$, ($P < 0.001$).
(Byrne <i>et al.</i> , 2002)	Achieving Adherence With Antiretroviral Medications for Pediatric HIV Disease	The Women and Children Care Center (WCCC) of New York Presbyterian Hospital, USA	Antiretroviral medicines	4 months to 18y (average, 7.5y)	Primary caregivers of 42 children	The interview guide contained 48 questions on clinical, family, and child factors related to adherence drawn from the literature on paediatric adherence and clinical experience with paediatric ARV adherence (list of barriers plus other open-ended question option)	In response to specific questions, caregivers reported as barriers to adherence: taste (10%), volume of medicine (10%). Strategies related to improving taste or taking away unpleasant aftertaste were somewhat more frequently reported (29% and 24%, respectively).

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Esteban Gomez <i>et al.</i> , 2004)	Influencia de las características del tratamiento antirretroviral en la adherencia del paciente pediátrico	Servicio de Farmacia. Unidad de Inmunodeficiencias Pediátricas. Hospital Universitari, Madrid	Antiretroviral medicines	4-16y	28 caregivers of 32 paediatric patients undergoing active antiretroviral therapy	Subjective numeric scale-based questionnaire. The questionnaire aimed to assess on a scale from 0 (no difficulty for adherence) to 5 (maximal difficulty) a number of treatment-related factors: a) number of drugs and dosage regimen; b) organoleptic properties of drugs; c) treatment administration; d) adverse events; and e) antiretroviral therapy effectiveness perceived by caregiver. (closed questions)	Caregivers evaluated the following factors as entailing moderate to high difficulties for correct adherence: number of drugs in the antiretroviral combination, organoleptic properties (smell, taste) of protease inhibitors (PI), PI-related deglutition problems, and PI-related immediate gastrointestinal adverse events. These factors may be considered potential obstacles for adequate adherence to antiretroviral therapy in paediatric patients. Grading of organoleptic difficulties based on average values of scores of carers: Syrups and Liquids reverse transcriptase inhibitor, protease inhibitor: taste: 0.3, 4.5 smell: 0.3, 2.1 deglutition: 0.1, 2.3 Solid pharmaceutical forms: taste: 0.3, 1.6 deglutition: 0.75, 1.8 Mentions texture. The only factor assessed as high adherence difficulty was the flavour of the protease inhibitors in liquid form. For solid dosage forms, the aspects with a highest score (within that none of them reached the score corresponding to moderate difficulty), were the flavour and the difficulties in swallowing of the PI.
(Farley <i>et al.</i> , 2003)	Assessment of Adherence to Antiviral Therapy in HIV-Infected Children Using the Medication Event Monitoring System, Pharmacy Refill, Provider Assessment, Caregiver Self-Report, and Appointment Keeping	University of Maryland School of Medicine, Baltimore, USA	Antiretroviral medicines	<13y	20 caregivers completed the Pediatric Adherence Questionnaire (PACTG)	Caregiver self-report interviews completed periodically physician/nurse questionnaire Paediatric AIDS Clinical Trial Group (PACTG) Paediatric Adherence Questionnaire (list of barriers plus other specify open question option)	'Problems with adherence' 6 caregivers reported barriers to adherence. Taste (n=3/20) Child refuses (n=4/20).

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Feingold <i>et al.</i> , 2000)	Protease Inhibitor Therapy in HIV-Infected Children	1The Children's Regional Hospital, Camden, New Jersey. 2The Children's Hospital of Philadelphia, Pennsylvania	Protease inhibitors	Median age 82.9 months (range 5–204 months)	Chart review of 70 children	A retrospective chart review of open-label PI containing combination therapy	10 changes were made because of patient preference or poor adherence. Primary reasons for medicine change included medications not being palatable or patient's inability to swallow pills or capsules.
(Hammami <i>et al.</i> , 2004)	Integrating Adherence to Highly Active Antiretroviral Therapy Into Children's Daily Lives: A Qualitative Study	A Belgian paediatric acquired immune deficiency syndrome referral centre	Antiretroviral medicines	Adherent mean age: 8.5y (0.25-17.25) Less adherent mean age: 13y (6.70-18.75)	11 primary caregivers of 18 children	Semi-structured interviews about 60 minutes long (open questions)	Almost all caregivers mentioned a history of opposition from their child as a result of bad taste and side effects. Adherent patients demonstrated creativity in solving such problems. One parent discussed offering "nice tasting things" at the same time as administering the medicine to facilitate child acceptance of the medicine.
(Leprevost <i>et al.</i> , 2006)	Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children	Paediatric clinic at St. Mary's Hospital, Paddington and Great Ormond Street Hospital NHS Trust, London UK	Antiretroviral medicines (Lamivudine and abacavir specifically)	2-13y	Caregiver reports of 24 children	Adherence questionnaire. Acceptability was also assessed (open questions)	Acceptability questionnaires: 9/24 (38%) of caregivers commented that taste of medications had been a problem for their children during the study.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Marhefka <i>et al.</i> , 2004)	Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP)	Urban, public, university-affiliated, PACTG affiliated paediatric HIV speciality clinics in Gainesville, Florida, Jacksonville, Florida, and Baltimore, Maryland US	Antiretroviral medicines	2-12 y (mean=8.7 6 SD=3.06)	51 Participants (parents or primary caregivers)	A new caregiver self-report assessment tool (the Treatment Interview Protocol; TIP)- a caregiver-completed structured interview (open questions)	Barriers to adherence endorsed: Pills are too big to swallow (n=5) Medication tastes bad (n=5) Child isn't able to swallow pills (n=1) Too many pills (n=3) Child doesn't drink all the medicines (n=1). Described difficulties experienced by a caregiver when preparing a solution. However no more details were reported.
(Paranthaman <i>et al.</i> , 2009)	Factors influencing adherence to anti-retroviral treatment in children with human immunodeficiency virus in South India- a qualitative study	Non-profit medical care and research institution based in Chennai, India	Antiretroviral medicines	<12y	A convenience sample of 14 caregivers	Interview (semi-structured) Qualitative in-depth (open-ended questions)	Medication related factors that influence adherence are mainly associated with side effects, size of tablets, Palatability and tablet regime. Crying because of the 'bitter taste of the medicines' was reported by a caregiver of a non-adherent child. "It was difficult to break the tablets into exact doses. Once they prescribed 1/3 rd of the tablet but it is difficult to give. For this, syrup would have been better. I feel it is difficult because we are unable to break the tablet correctly. I have the feeling that I am not giving the correct dosage."
(Plipat <i>et al.</i> , 2007)	Evaluation of a practical method to assess antiretroviral adherence in HIV-infected Thai children	Siriraj Hospital Paediatric Clinic, Bangkok, Thailand	Antiretroviral medicines	<7-14y	137 caregivers	PACTG adherence questionnaire (list plus open-ended question option to specify additional barriers)	One hundred and thirty-seven (85%) caregivers completed their questionnaires. Reasons commonly attributed to poor adherence were forgetfulness, bad taste and interruption of the child's rest.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Pontali <i>et al.</i> , 2001)	Adherence to Combination Antiretroviral Treatment in Children	Department of Infectious Diseases, University of Genoa, Genoa, Italy	Antiretroviral medicines	Mean age 9.4y	Caregivers of 44 children	Questionnaire to caregivers (closed question list)	Problems when administering medicines to children: Swallowing (29.5%), Bad taste (20.5%), Child resists/refuses/spits out (25%), Too many medicines/pills (34%). List of main problems reported: Less than 6 years 1. Taking medicines at school or out of home 2. Child resists/refuses/spits out, 2. Child complains of bad taste, 2. Food interactions, 2. Vomiting From 6 to 10 years 1. Difficulty swallowing pills 2. Too many medicines/pills 3. Child complains of bad taste, 3. Food interactions, 3. Change in routine (holidays, weekend) More than 10 years 1. Too many medicines/pills 2. Food interactions 3. Difficulty swallowing pills 4. Taking medicines at school or out of home, 4. Running out of medicines.
(Roberts, 2005)	Barriers to antiretroviral medication adherence in young HIV-infected children	Flyers in HIV/AIDS clinics and community-based organizations located throughout Los Angeles, California, USA	Antiretroviral medicines	6-12y (mean 9.5y)	9 children interviewed with guardians and guardians (alone) of 5 additional children	Face-to-face in-depth interview (open-ended questions)	As soon as I put them in my mouth, they dissolve and taste nasty." "When you put them in your mouth . . . it tastes all nasty." "It's hard because they're too big for me. Because when it goes down like this, it goes 'dush, dush, dush.' It hurts my throat." "He started having problems taking it, like if he looks at it or smells it, then he's just coughing and gagging..." Some guardians reported giving their children various foods or beverages (e.g., pudding) to make the medications more palatable.
(Wrubel <i>et al.</i> , 2005)	Pediatric adherence: Perspectives of mothers of children with HIV	Multisite USA	Antiretroviral medicines	1-18y (Range) 8.3y (Mean)	71 caregivers provided one or more accounts	Primary caregivers interviewed (open-ended questions)	The mothers did not present taste a central difficulty, but rather as a challenge to be mastered. 32% of the mothers described the ways they made the medication palatable as part of the process of giving the medication, for example, mixing it with some food to disguise the taste, or giving a sweet drink immediately after giving the medication.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Bunupuradah <i>et al.</i> , 2006)	Use of taste-masking product, FLAVORx, to assist Thai children to ingest generic antiretrovirals	Thailand	Antiretroviral medicines	Mean age was 5.2 ± SD 1.9y (range=1-9.8y)	Caregivers of 30 children	Open label, one arm, cohort study – flavour masking. Children were followed twice, one month apart. At each visit, the caregivers were asked to complete the approved Thai version of the NIAID Pediatric AIDS Clinical Trial Group (PACTG) Standard International Questionnaire. (barrier list and additional open-ended questions)	<p>“At the first visit, all thirty caregivers answered that the child had never missed any antiretroviral medicine dose and that they did not experience problems with administering the medicine on time every day.”</p> <p>However, during the interview, most caregivers reported that the child disliked taking antiretroviral medicines because of the bitter taste especially generic AZT syrup, 3TC syrup, ddl powder, NVP crushed tablet and EFV opened capsule.</p> <p>At the final visit, caregivers gave the same answers for the PACTG adherence questionnaire with no reported problems or occurrence of poor adherence. From the interview, 24 caregivers reported that, after using FLAVORx, their children had an easier time taking antiretroviral medicines with FLAVORx. FLAVORx did not affect adherence as full adherence was reported in all children despite the problem of bitter antiretroviral medicines.</p>
(Davies <i>et al.</i> , 2008)	Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study	A tertiary care institution in Cape Town, South Africa	Antiretroviral medicines	37 (16-61) months at start of ART	Caregivers of 122 children	A questionnaire was administered to caregivers after 3 months of treatment to assess experience with giving medication and self-reported adherence (PACTG with open-ended questions element)	Experience with giving medication: Poor palatability of medication was the most common problem (21.8% of caregivers), 68% of these attributed to ritonavir.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Gibb <i>et al.</i> , 2003)	Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial	Centres in Europe and Brazil	Antiretroviral medicines	3 months to 16y	At least one caregiver questionnaire returned for 108 children	Adherence questionnaire to caregivers (open-ended questions)	Reasons why a child had difficulty taking medicines were given by caregivers of 65 children and could be divided into 2 main groups: comments on taste/palatability/volume of drug(s); and social situations. The largest number of responses (n = 48) was in the first group and included comments on taste/flavour/smell, size of tablets, consistency of medicine, causing vomiting/nausea and difficulty in swallowing. "Difficulties with unpleasant flavor"; "Taste causes nausea"; "Hates the taste and smell"; "Child vomits due to taste"; "Bad smell and a big tablet" (referring to NFV); and "Difficulties with quantities."
(Goode <i>et al.</i> , 2003)	Adherence issues in children and adolescents receiving highly active antiretroviral therapy	Australia	Antiretroviral medicines	4-14.5y (mean 7.6y)	18 parents (12 of which were also treated for HIV on HAART regimens)	Telephone interview (open-ended questions)	Qualitative reports indicated overwhelmingly that difficulties with administering medicines were due to: Taste (44%) Procedural factors (i.e. mixing and preparation) (reported by 28% of respondents).
(Lin <i>et al.</i> , 2011)	Palatability, adherence and prescribing patterns of antiretroviral drugs for children with human immunodeficiency virus infection in Canada†	HIV clinic at the Hospital for Sick Children, Toronto, Canada	Antiretroviral medicines	0-18y	119 children	Chart review Cross-sectional survey of physicians caring for the children	Ritonavir was the least palatable drug compared with other antiretroviral medicines (p = 0.01); 50% of children have refused its consumption because of poor taste, and in 27% of children, drug change was required. Authors suggested adding FLAVORx to opened capsules to improve palatability.

Authors	Study title	Study Setting	Medication type	Age of children	Study population	Method	Oral formulation-related barriers to medicines administration and medicines manipulation techniques
(Reddington <i>et al.</i>, 2000)	Adherence to medication regimens among children with human immunodeficiency virus infection	Multisite USA	Antiretroviral medicines	1-14y (median age 7.9y)	90 caregivers	Caregivers interviewed (79 face- to-face, 11 telephone) (difficulties with medicines reported by patients. Open-ended questions?)	Better tasting medicines were rated 'very helpful' by 81% of caregivers. Reasons for difficulty in administration were primarily the size of the nelfinavir pill, taste and consistency of nelfinavir powder and the taste of both the pill and liquid form of ritonavir.
(Van Dyke <i>et al.</i>, 2002)	Reported Adherence as a Determinant of Response to Highly Active Antiretroviral Therapy in Children Who Have Human Immunodeficiency Virus Infection	Multicentre USA	Antiretroviral medicines	4 months-17y	125 children	PACTG Modules Questionnaires of subjects (if responsible for medicines) or caregivers (list plus other open-ended question option)	The main reasons stated for non-adherence were taste (16%) and child refuses (16%) for ritonavir and taste (9%) for nelfinavir. 'The large volume and unusual texture of the nelfinavir powder is particularly challenging for parents to administer.'

Seven key studies are highlighted in bold font.

Drug names in Bunupuradah and co-workers (2006) AZT= zidovudine, 3TC= lamivudine, ddI= didanosine, NVP= nevirapine, EFV= efavirenz.

4.4.3 Introduction to Results

In total, 27 studies were retrieved which met the pre-defined review inclusion criteria (see Figure 4). In 7 of the included studies, findings were reported on an individual drug level. These will be referred to as the 7 'key studies' as reporting of findings was more complete in these studies. All 7 'key studies' investigated antiretrovirals. Figure 5 below shows the classification of the included review studies according to chronic conditions.

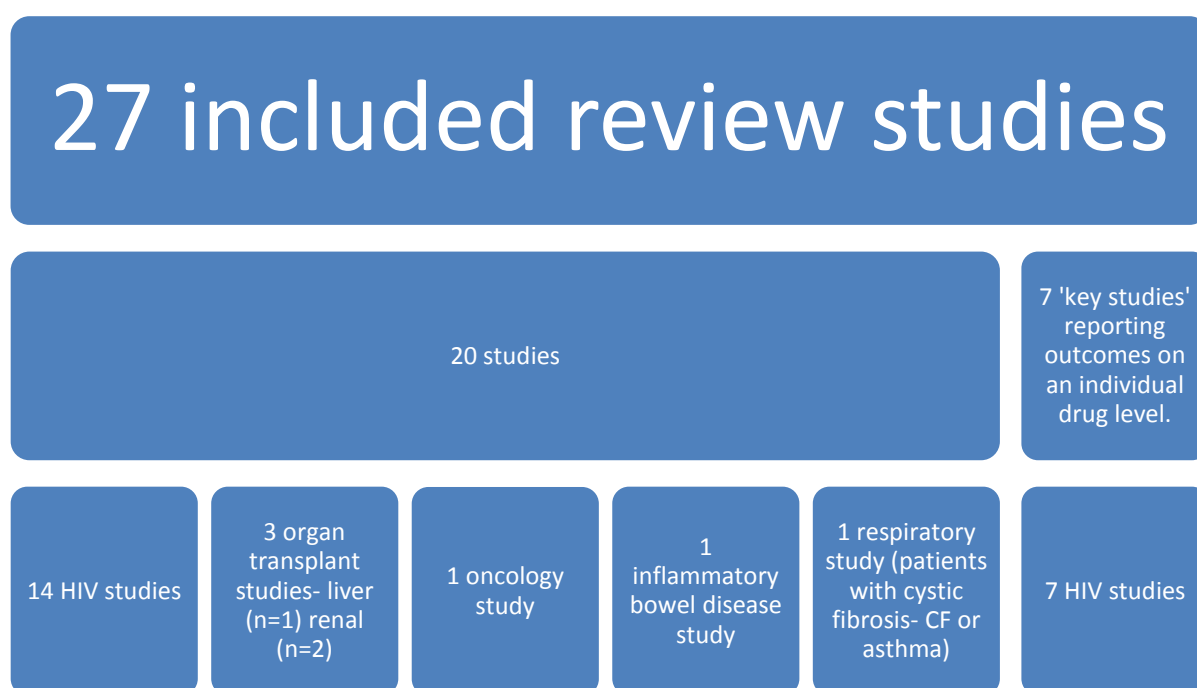


Figure 5 The classification of the 27 included review studies by chronic condition.

In 25 of the 27 studies an interview or questionnaire was utilised as a self-report tool to ascertain potential barriers to medicines administration. In 12 of these 25 studies, a closed question approach defining a 'choice list' of barriers to medicines acceptance or adherence was reported (Buchanan *et al.*, 2012, Byrne *et al.*, 2002, Davies *et al.*, 2008, Esteban Gomez *et al.*, 2004, Farley *et al.*, 2003, Ingerski *et al.*, 2010, Plipat *et al.*, 2007, Pontali *et al.*, 2001,

Shemesh *et al.*, 2004, Tucker *et al.*, 2002, Van Dyke *et al.*, 2002, Zelikovsky *et al.*, 2008). Several of these studies gave an additional option to list a further barrier that was not stated in the list.

The remaining 13/25 studies adopted a more 'open-ended question' approach to explore barriers to medicines acceptance or adherence in detail, revealing a plethora of qualitative data and some individual quotations (Boni *et al.*, 2000, Bunupuradah *et al.*, 2006, Christiansen *et al.*, 2008, Gibb *et al.*, 2003, Goode *et al.*, 2003, Hammami *et al.*, 2004, LePrevost *et al.*, 2006, Marhefka *et al.*, 2004, Modi and Quittner, 2006, Paranthaman *et al.*, 2009, Reddington *et al.*, 2000, Roberts, 2005, Wrubel *et al.*, 2005).

The final 2/27 studies provided results based on review of medical records. As relatively few studies have explored oral formulation-related barriers to medicines administration in children with chronic conditions, studies reviewing medical records were included in this review. Figure 6 below shows the classification of study methodologies across the included review studies.

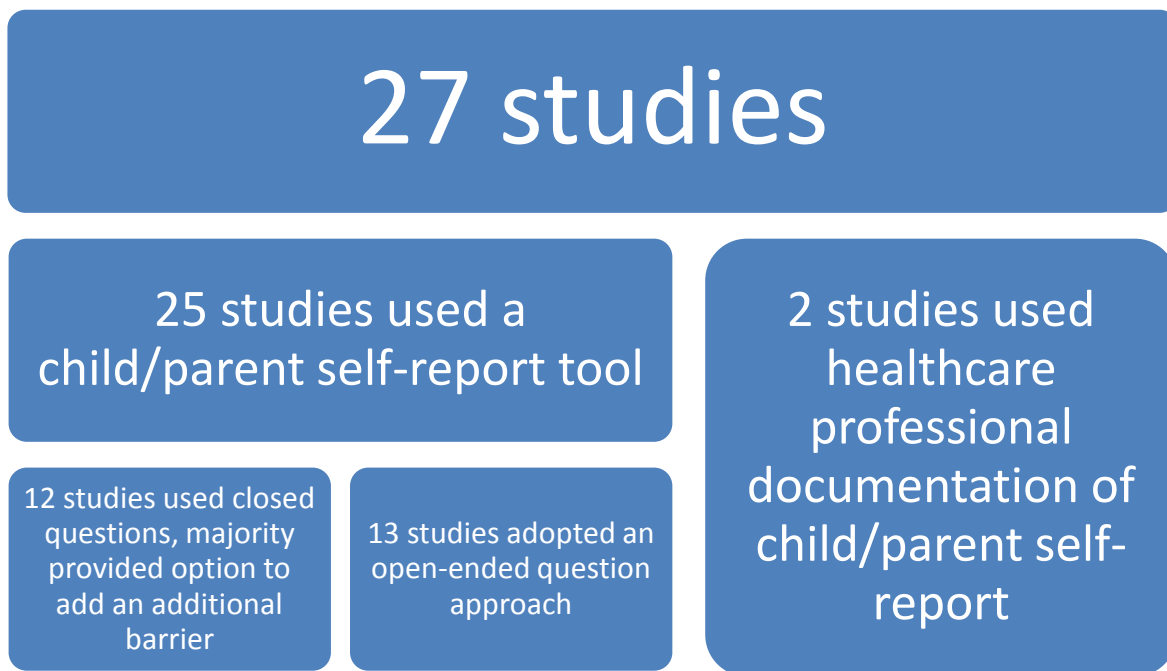


Figure 6 The methodological designs of the 27 included review studies.

4.4.3.1 Introduction to the 7 'key studies'

Of the 7 'key studies', 3 studies (Bunupuradah *et al.*, 2006, Gibb *et al.*, 2003, Van Dyke *et al.*, 2002) conducted randomised trials and adopted multi-method design. The interview components within these studies revealed relevant data for this review. Randomised controlled trials are of higher hierarchical study design quality as discussed earlier (see section 4.3.8), however it was the interview and medical record data that was investigated in this review. Davies and co-workers (2008) and Lin and co-workers (2011) used multi-method design and the questionnaire component and chart review were of interest to this review. Goode and co-workers (2003) and Reddington and co-workers (2000) adopted a single-method design consisting of a telephone survey and interview correspondingly.

Qualitative, open-ended questions reveal the most detailed and useful data for this review as they permit exploration of the obstacles to medicines administration. Of the 7 'key

studies', 3 studies adopted the Pediatric Adherence Clinical Trials Group - PACTG (NIAID) questionnaire as the self-report data collection tool (Bunupuradah *et al.*, 2006, Davies *et al.*, 2008, Van Dyke *et al.*, 2002). This includes closed-style questions with a limited list of barriers ending with an option of 'other'. Gibb and co-workers (2003) and Goode and co-workers (2003) used open-ended questions in their studies. In the study by Reddington and co-workers (2000) the style of all questions could not be interpreted from the study report, however results suggest that difficulties with medicines were explored using open-ended questions.

Lin and co-workers (2011) adopted a different methodological approach, involving the review of patient records. Data collected from patient records should mirror a retrospective recorded qualitative interview format, although it is probable that detail recorded regarding problems with medicines may vary.

4.4.4 Results: A narrative review

All 27 included review studies were screened for oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines and the relevant data was extracted. A thematic analysis approach was adopted by RV, as guided by Pope and co-workers (2000). Thematic study findings for primary and secondary outcome measures were categorised under the subsequent subheadings:

- Report on oral formulation-related barriers to medicines administration: Taste (including aftertaste), size or swallowing (size of solid dosage form or medicine described as difficult to swallow), quantity or volume (of solid dosage forms or liquid/powder), texture, smell and colour (including appearance)

- Report on the influence of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines
- Report on medicines manipulation techniques used to administer medicines.

In the 7 'key studies', at least one oral formulation-related barrier to medicines administration was associated with a specific drug (some with a specific formulation reported). Where specified drugs or formulations were associated with a particular oral formulation-related barrier these are reported at the end of the appropriate themed section.

4.4.4.1 Taste

All 27 studies discussed reports of taste and/or aftertaste problems. Taste was identified as a key obstacle to medicines administration in 25/27 of the included studies. Data is summarised in Table 2.

Of the 27 studies, 3 studies investigated antiretrovirals and reported data in a qualitative manner, revealing participant quotes (Hammami *et al.*, 2004, Paranthaman *et al.*, 2009, Roberts, 2005).

Hammami and co-workers (2004) revealed a taste problem highlighted by a parent, and the way that the parent dealt with it, offering 'nice tasting things' at the same time as administering the medicine to facilitate child acceptance of the medicine.

Roberts (2005) reported childrens' views on medicines poorly accepted as a result of disliking the taste.

Crying because of the ‘bitter taste of the medicines’ was reported by a caregiver of a non-adherent child according to Paranthaman and co-workers (2009).

In 2/27 studies, taste was not reported to be a main obstacle to medicines administration.

Wrubel and co-workers (2005) reported that the mothers of the children in their study did not portray taste issues as a “central difficulty,” rather a “challenge to be mastered.” Tucker and co-workers (2002) studied results from patients of different ethnic origins (African American and European) and found that neither ethnic group disliked taking their medicines ‘because they tasted bad or may make them sick,’ however properties of their medicines including pill taste was found to have low to moderate significant associations with adherence measures.

Caregiver reports of main problems when administering medicines to children were ranked based on frequency of reporting and stratified according to age range of the child (<6 years, 6-10 years and >10 years) in only one of the 27 studies (Pontali *et al.*, 2001). Across the three age categories ‘child complains of bad taste’ was the highest rated oral formulation-related barrier amongst children younger than 6 years (see Table 2 for ranked results across age ranges).

Buchanan and co-workers (2012) interviewed both children and caregivers independently and found significant agreement between their reports of the barrier: ‘taste/cannot keep it down (pill/liquid)’ based on a kappa test ($k=0.44$, $P<0.001$), as reported in Table 2.

Frequencies of reported oral formulation-related barriers to child acceptance or medicines adherence were not provided in all of the study reports. Where frequency was reported this is detailed in Table 2.

All 7 'key studies' investigated antiretroviral medicines. Taste problems associated with ritonavir and/or nelfinavir were highlighted in 6 of these. It was anticipated that commonalities would be observed across these studies as they only considered a narrow range of medicines. Of the 7 studies, only 3 studies reported the formulation of the drug concerned, these are reported in Table 3 below.

Table 3 'Key studies' reporting taste problems with specific drug formulations.

Authors	Sample size	Taste problems with specific drug formulations
Bunupuradah and co-workers (2006)	Caregivers of 30 children	The reason for a child disliking to take their medicines was the bitter tastes of: opened efavirenz capsules, crushed nevirapine tablets, didanosine powder, lamivudine syrup and generic zidovudine syrup.
Reddington and co-workers (2000)	Caregivers of 90 children (Tablets 20% of the children (18 of 90) Liquids 30% (27 of 90) combination for 50% (45 of 90))	Reasons for difficulties in administration were the 'taste and consistency of nelfinavir powder and the taste of both the pill and liquid form of ritonavir.'
Van Dyke and co-workers (2002)	Caregivers of 125 children	The main reasons reported for non-adherence: included the bad taste of ritonavir liquid, 16% and nelfinavir powder/tablets, 9% (note- results for nelfinavir powders and tablets were pooled).

4.4.4.2 Size or swallowing

4.4.4.2.1 Size of solid dosage form

Problems relating to the sizes of solid dosage forms or swallowing medicines were investigated in 16/27 studies (Boni *et al.*, 2000, Buchanan *et al.*, 2012, Christiansen *et al.*, 2008, Esteban Gomez *et al.*, 2004, Feingold *et al.*, 2000, Gibb *et al.*, 2003, Ingerski *et al.*,

2010, Lin *et al.*, 2011, Marhefka *et al.*, 2004, Modi and Quittner, 2006, Paranthaman *et al.*, 2009, Pontali *et al.*, 2001, Reddington *et al.*, 2000, Roberts, 2005, Tucker *et al.*, 2002, Zelikovsky *et al.*, 2008).

Frequencies of size or swallowing reports are provided in Tables 4 – 7 for studies in which this data is revealed.

Of the 16 studies, 8 referred to the size of the solid dosage form, as reported in Tables 4 and 5. The dimensions of the solid dosage forms were not specified in these reports.

Table 4 Problems reported with the size of solid dosage forms.

Authors	Sample size	Reports of problems with the size of solid dosage forms
Buchanan and co-workers (2012)	Children/youth with perinatally acquired HIV and their parents/caregivers (n = 120 dyads)	'Taste, can't get it down/keep it down (pill/liquid)' reported as a barrier to adherence grouped with taste (reason for missing medicines in previous month).
Christiansen and co-workers (2008)	55 caregivers	'Capsules too big to swallow' was a problem or difficulty reported by 1 parent when dealing with oral chemotherapy.
Marhefka and co-workers (2004)	51 Participants (parents or primary caregivers)	'Too big to swallow' reported by 5 caregivers as a barrier to adherence.
Paranthaman and co-workers (2009)	A convenience sample of 14 caregivers	'Size of tablets' was reported as a medication related factor influencing adherence.
Roberts (2005)	9 children interviewed with guardians and guardians (alone) of 5 additional children	A 7-year-old boy revealed: "It's hard because they're too big for me. Because when it goes down like this, it goes 'dush, dush, dush.' It hurts my throat."
Tucker and co-workers (2002)	68 paediatric patients with renal transplants and their caregivers	No patients agreed that taking their pills or medications was difficult because of 'Size.'

Buchanan and co-workers (2012) indicated that the size of solid dosage forms was a barrier to medicines adherence, but this was not clear in the questionnaire methodology and therefore was difficult to interpret. The barrier: 'Taste, can't get it down or keep it down'

suggests a problem which could be related to the size of a solid dosage form but this was not clarified in the study.

Tucker and co-workers (2002) concluded that neither African Americans nor European Americans reported problems swallowing tablets resulting from the size of tablets, however this had low to moderate significant associations with adherence measures.

Data on size problems with individual solid dosage forms was detailed in 2 of the 7 ‘key studies’. This is provided in Table 5 below.

Table 5 Problems reported with the size of individual solid dosage forms in ‘key studies.’

Authors	Sample size	Reports of problems with the size of solid dosage forms
Gibb and co-workers (2003)	At least one caregiver questionnaire returned for 108 children	Large size of nelfinavir tablets reported as a reason why a child had difficulty with taking medicines grouped with other oral formulation-related barriers.
Reddington and co-workers (2000)	Caregivers of 90 children (Tablets 20% of the children (18 of 90) Liquids 30% (27 of 90) combination for 50% (45 of 90))	Large size of nelfinavir tablets reported as a reason for difficulty with administration.

4.4.4.2.2 Difficulties with swallowing medicines

In 8/16 of the studies, reports on difficulties with or aversion to swallowing medicines were provided (see Tables 6 and 7).

Table 6 Reported difficulties with swallowing solid dosage forms and liquids.

Authors	Sample size	Reports of difficulties with swallowing solid dosage forms
Boni and co-workers (2000)	Parents/legal guardians of 25 children	'Difficulty swallowing' was a problem pointed out by 32% of parents or legal guardians in administration of antiretroviral treatment.
Esteban Gomez and co-workers (2004)	28 caregivers of 32 paediatric patients undergoing active antiretroviral therapy	'Deglutition' reported as a difficulty with adherence. Average scores of 0.1 (low difficulty) and 2.3 (moderate difficulty) for liquid reverse transcriptase inhibitors and protease inhibitors respectively. Average scores of 0.75 (low difficulty) and 1.8 (low difficulty) for reverse transcriptase inhibitors and protease inhibitors respectively in solid dosage forms.
Feingold and co-workers (2000)	Chart review of 70 children	'Inability to swallow pills or capsules' was reported as a reason for changing medicines.
Ingerski and co-workers (2010)	74 adolescents and their primary caregivers together	'Hard to swallow' was reported as a barrier to adherence by 10.8% of Crohn's patients.
Modi and Quittner (2006)	73 children and parents separately	'Swallowing' reported by 13% and 25% of CF children regarding oral enzymes and oral antibiotics respectively, and 14% of parents of asthmatics regarding allergy medicines.
Pontali and co-workers (2001)	Caregivers of 44 children	'Swallowing' reported by 29.5% of caregivers as a problem when giving medicines to their child.
Zelikovsky and co-workers (2008)	56 adolescents listed for a kidney transplant, mean age and their carers	'Hard to swallow pills' reported by 2% of adolescents as a reason for difficulty with medicines/ an obstacle that may cause non-adherence.

Esteban Gomez and co-workers (2004) reported moderate difficulty with adherence to liquid protease inhibitors resulting from child aversion.

Pontali and co-workers (2001) found that 'Difficulty swallowing pills' was a main problem with medicines administration reported by caregivers of children over 6 years of age (see

Table 2). Caregivers of children less than 6 years did not report difficulty with swallowing tablets as a main problem as syrups and suspensions were available (Pontali *et al.*, 2001).

Zelikovsky and co-workers (2008) reported that the barrier to adherence: ‘hard to swallow pills’ had a low rate of endorsement in their study, thus the authors concluded that there was insufficient power to examine the relationship between this barrier and adherence.

In one of the seven ‘key studies’, Lin and co-workers (2011) reported records of ‘cannot swallow’ for several antiretroviral drugs (see Table 7 below). The specific formulations were not reported, this is a study limitation.

Table 7 The number of prescriptions refused resulting from documented reports that patient ‘cannot swallow’ in the ‘key study’ by Lin and co-workers (2011).

Authors	Sample size	Drug and number of prescriptions refused
Lin and co-workers (2011)	Chart review of 119 children	Abacavir 1 Amprenavir 0 Didanosine 1 Efavirenz 1 Indinavir* Lamivudine 0 Lopinavir/ritonavir 0 Nelfinavir 0 Nevirapine* Ritonavir 1 Saquinavir* Stavudine 1 Zalcitabine* Zidovudine 0 Total= 5/72 of prescribed medicines refused resulted from patient report ‘cannot swallow’ as documented in medical records.

*= no medicines refused because of any factors related to palatability.

4.4.4.3 Quantity or volume

4.4.4.3.1 Problems with the quantity of solid dosage forms

Problems associated with the quantity of solid dosage forms were discussed in 6 of the 27 studies (see Table 8 below).

Table 8 Reported problems associated with the quantity of solid dosage forms.

Authors	Sample size	Reports of problems with the quantity of solid dosage forms
Boni and co-workers (2000)	Parents/legal guardians of 25 children	'Too many medicines/tablets to take' was a problem pointed out by 36% of parents or legal guardians in administration of antiretroviral treatment.
Buchanan and co-workers (2012)	Children/youth with perinatally acquired HIV and their parents/caregivers (n = 120 dyads)	'Too much medication' reported by 9% of children and 2% of caregivers (data from reported histogram).
Christiansen and co-workers (2008)	55 caregivers	'There were a lot of tablets to take at once' reported by 3 parents as a problem or difficulty when dealing with oral chemotherapy.
Gibb and co-workers (2003)	At least one caregiver questionnaire returned for 108 children	"Difficulties with quantities" was a reason reported for a child having difficulty taking medicines grouped with other oral formulation-related barriers
Marhefka and co-workers (2004)	51 participants (parents or primary caregivers)	'Too many pills' reported by 3 caregivers as a barrier to adherence.
Pontali and co-workers (2001)	Caregivers of 44 children	'Too many medicines/pills' was a problem experienced by 34% of caregivers when administering medicines to children. Main problems stratified to age ranges <6 years, 6-10 years and > 10 years. Too many medicines/pills was listed as a main problem for children over 6 years.

Gibb and co-workers (2003) did not report the drug formulation/s for which difficulties with quantities were reported. Also, the frequency of reports of difficulties with quantities was not revealed by Gibb and co-workers (2003).

4.4.4.3.2 Problems with the volume of liquids or powders

Comments on the volume of antiretroviral liquids or powders were reported in 3 of the 27 studies (see Tables 9 and 10 below).

Table 9 Reported problems associated with the volume of liquids or powders.

Authors	Sample size	Reports on the volume of antiretroviral formulations
Byrne and co-workers (2002)	Primary caregivers of 44 children	10% of respondents identified volume as a barrier to administering medicines to children.
Marhefka and co-workers (2004)	51 participants (parents or primary caregivers)	Revealed medicine volume as a barrier to adherence, reported by a single respondent 'child doesn't drink all the medicines.'

In one of the seven 'key studies', difficulty with the volume of a drug formulation was specified as provided in Table 10 below.

Table 10 Reported problems associated with the volume of a specific drug formulation in the 'key study' by Van Dyke and co-workers (2002).

Authors	Sample size	Reports of problems with volume of a specific drug formulation
Van Dyke <i>et al.</i> (2002)	Caregivers of 125 children	The 'large volume' of nelfinavir powder was reported to be challenging for parents to administer.

It is unclear as to whether the problem reported with the volume of nelfinavir powder was an assumption as data from parents was not provided to support this finding. However, the discussion reported that an average 6 year old is required to take 25 scoops of nelfinavir powder with food twice a day (actual volume not reported) (Van Dyke *et al.*, 2002).

4.4.4.4 Texture

Problems with the texture of medicines were reported in 4 of the 27 studies (Esteban Gomez *et al.*, 2004, Gibb *et al.*, 2003, Reddington *et al.*, 2000, Van Dyke *et al.*, 2002). See Tables 11 and 12 below for reported problems with texture.

Table 11 Reported problems with the texture of medicines.

Authors	Sample size	Reported problems with texture
Esteban Gomez and co-workers (2004)	28 caregivers of 32 paediatric patients undergoing active antiretroviral therapy	Acknowledged the need to improve textures of medicines, however did not include study data on texture to support this.
Gibb and co-workers (2003)	At least one caregiver questionnaire returned for 108 children	Reported the consistency of medicines as a difficulty for children taking antiretroviral medicines grouped with other oral formulation-related barriers.

Of the 'key studies', 2/7 reported problems associated with the texture of specific drug formulations as provided in Table 12 below.

Table 12 Reported problems with the texture of specific drug formulations in the 'key studies.'

Authors	Sample size	Reported problems with the texture of specific drug formulations
Reddington and co-workers (2000)	90 caregivers	'Disliking' the consistency of nelfinavir powder was reported as a reason for difficulty with administration.
Van Dyke and co-workers (2002)	125 children	The texture of nelfinavir powder was described as unusual and challenging for parents.

No frequency data was reported on the impact of texture as a barrier to medicines administration. Reported caregiver data was not revealed in the study by Van Dyke and co-workers (2002), this could be postulation of the authors.

4.4.4.5 Smell

Perceptions regarding the smells of medicines were reported in 4/27 studies (Esteban Gomez *et al.*, 2004, Gibb *et al.*, 2003, Lin *et al.*, 2011, Roberts, 2005).

A quotation describing problems with sensory properties of a medicine was reported by Roberts (2005) and is provided in the 'colour/appearance' themed section, 4.4.4.6.

Esteban Gomez and co-workers (2004) reported problems on an average scaled measure ranging from 0-5 (0= causing no difficulties 5= causing maximum difficulties with adherence). The average smell scores were reported for the liquid: reverse transcriptase inhibitors and protease inhibitors as 0.3 and 2.1 respectively. The study found that the smell of protease inhibitors caused moderate difficulties with adherence.

Of the 7 'key studies', 2 studies discussed reports regarding the smells of antiretroviral drugs. This is detailed in Table 13 below.

Table 13 Reports of unfavourable smells associated with specific drugs in the 'key studies.'

Authors	Sample size	Smell reports associated with specified drug
Gibb and co-workers (2003)	At least one caregiver questionnaire returned for 108 children.	Reports of hating the smell of nelfinavir were provided by caregivers as reasons for difficulty taking antiretrovirals and grouped with other oral formulation-related barriers.
Lin and co-workers (2011)	Chart review of 119 children.	Smell was part of the palatability assessment of the antiretroviral medicines in their study, this was encompassed within the 'dislike taste' category. The independent effect of smell was not reported in this study.

The prevalence of reports of poor acceptance of smell was not provided by the authors.

4.4.4.6 Colour/appearance

Roberts (2005) reported the quotation of a child who perceived the appearance of an unspecified antiretroviral medicine negatively:

“He started having problems taking it, like if he looks at it or smells it, then he’s just coughing and gagging...”

4.4.4.7 The influence of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines

4.4.4.7.1 The influence of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines in the non-key studies (n=20)

The influence of individual oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines was not quantified in 5 of the 20 non-key studies (Hammami *et al.*, 2004, Paranthaman *et al.*, 2009, Plipat *et al.*, 2007, Roberts, 2005, Wrubel *et al.*, 2005). However, the effects of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines were implied through the qualitative-style reports which included subject quotations (see Table 2).

The impact of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines was quantified in 15 of the 20 non-key studies. The outcome measures (acceptance or adherence) were heterogeneous across the studies and could not be compared. Non-adherence was defined across the studies as omitting doses of medicines, delaying administration of doses or changing to an alternative drug formulation in several studies. In studies where the adherence measure was not clearly defined,

reported outcomes included resisting medicines administration and further factors, as reported in Table 2.

4.4.4.7.2 The influence of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines for 'key studies' (n=7)

All of the 7 'key studies' investigated oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines. A summary table of relevant study findings are reported in Table 14 below.

Table 14 Reported oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines across the 7 ‘key studies.’

Authors	Sample size	Reported oral formulation-related barriers to medicines administration	Correlation to child acceptance of or adherence to medicines	Limitations
Bunupuradah and co-workers (2006)	Caregivers of 30 children	Issues experienced with specific antiretroviral medicines prior to taste-masking.	Adherence was unaffected by taste-masking as all participants reported full adherence. 24/30 children said that they liked FLAVORx and wanted to carry on using it. Six children did not want to continue using FLAVORx; caregivers of three children found it too difficult, two children (on orange and strawberry flavours) reported burning sensation on the tongue, and one child had repeated vomiting immediately after taking FLAVORx (strawberry flavour).	
Davies and co-workers (2002)	Caregivers of 122 children	Experience with giving medication: Poor palatability was identified as the most common issue in this study by 21.8% of caregivers, 68% of these attributed to ritonavir.	Experiencing problems (including taste) with antiretroviral medicines did not affect measured or reported adherence in the month in which problems were revealed, however was associated with annual adherence measured by medication return <90% (OR = 3.07; 95% CI: 0.91 – 10.38; p = 0.06).	The prevalence of problems for individual drugs was not quantified.

Authors	Sample size	Reported oral formulation-related barriers to medicines administration	Correlation to child acceptance of or adherence to medicines	Limitations
Gibb and co-workers (2003)	At least one caregiver questionnaire returned for 108 children	Reported 'reasons why a child had difficulty taking medicines' Highlighted the widest variety of oral formulation-related barriers across the studies: comments on taste/flavour/smell, size of tablets, consistency of medicine, causing vomiting/nausea and difficulty in swallowing were grouped and revealed as having the largest number of responses (n=48).	Taking nelfinavir powder was not statistically associated with poorer adherence, yet reported as having a high volume and being hard to dissolve. Nearly 80% of children starting nelfinavir powder switched to tablets, (majority in the first 8 weeks). There was no significant difference reported in adherence between placebo and nelfinavir.	Quantitative results for the influence of independent oral formulation-related barriers on medicines acceptance or adherence were not provided.
Goode and co-workers (2003)	18 parents (12 of which were also treated for HIV on HAART regimens)	Taste (44%), side effects (44%) and procedural factors (28%)-including the mixing and preparation of medicines were responsible for most antiretroviral 'administration difficulties' in this study.	Such difficulties administering antiretroviral medicines accounted for 50% of children taking nelfinavir or ritonavir changing or omitting their medicine.	The prevalence of problems for individual drugs was not quantified.
Lin and co-workers (2011)	119 children	Reasons for medicines refusal for individual drugs were attributed to each key taste issue (dislikes taste, cannot swallow, spits out drugs and vomits). Results reported quantitatively, and directly associated with medicines refusal and drug changes.	Ritonavir was disliked most with 50% of children refusing it because of poor taste, and in 27% of children, ritonavir was changed to an alternative drug.	The prevalence of problems for specific formulations was not reported.

Authors	Sample size	Reported oral formulation-related barriers to medicines administration	Correlation to child acceptance of or adherence to medicines	Limitations
Reddington and co-workers (2000)	90 caregivers	Reasons for difficulty in administration were primarily the size of the nelfinavir tablets, the consistency and taste of nelfinavir powder and the taste of ritonavir liquid and tablets.	Sixty-three percent of respondents (57 of 90) reported that a particular medication was harder to administer. Nelfinavir followed by ritonavir were most difficult to administer. Missing doses was likely to be due to children refusing medicines (reported by 16% of respondents).	Problems with oral formulation-related barriers to medicines administration were reported in a non-quantitative fashion. Further evaluation as to why medicines were refused was not reported.
Van Dyke and co-workers (2002)	Caregivers of 125 children	Taste of ritonavir liquid and nelfinavir (tablets/liquid?)	Difficulty with adherence was more commonly reported for the protease inhibitors than for the reverse transcriptase inhibitors. A common reason for non-adherence was revealed as taste 16%, and 9% for ritonavir liquid and nelfinavir (tablets/liquid?) respectively.	The formulation of nelfinavir was unclear in the study.

In addition, Reddington and co-workers (2000) found that 81% of caregivers rated 'better tasting medicines' as 'very helpful' based on a question using a Likert scale. This was the highest rated intervention, indicating that palatability was a central issue perceived by caregivers.

4.4.4.8 Secondary outcome: Reports on medicines manipulation techniques

The 27 included review studies were examined for descriptions of medicines manipulation techniques used to facilitate the administration of medicines to children (e.g. to improve palatability) or for the purpose of administering a specific dose (e.g. one quarter of a tablet). Medicines manipulation techniques may be used by parents, carers or children on their own accord or sometimes following the instructions of a healthcare professional. Of the 27 included studies, 10 discussed manipulation techniques. Of these 10 studies, Bunupuradah and co-workers (2006) and Lin and co-workers (2011) discussed manipulation techniques instructed by the study teams as opposed to volunteered by parent, carers and children.

Details of manipulation techniques used by parents and carers to administer medicines to children were revealed in 6 of the 10 studies reporting medicines manipulation techniques (see Table 15). For 4/10 studies reporting medicines manipulation, details of the techniques used were not reported. Details on drugs and formulations manipulated were not specified in these studies (see Table 16). Where frequency data was reported this is provided in the Tables.

Table 15 Reported manipulation techniques used to administer medicines.

Authors	Sample size	Reported medicines manipulation techniques
Bunupuradah and co-workers (2006)	Caregivers of 30 children	Discussed FLAVORx addition to antiretroviral medicines in attempt to improve palatability. This study considered a uniform approach to taste-masking antiretrovirals and found that in 80% of children, masking the bitter taste of antiretroviral medicines helped them to take them more easily. Strawberry, orange and grape flavours were the most popular.
Christiansen and co-workers (2008).	55 caregivers	An administration problem encountered by parents included having difficulty crushing tablets and additionally crushing tablets as liquid was not tolerated. Reports of crushing tablets at least once were provided by 24% of parents. Breaking capsules in to ice-cream and crushing tablets on cornflakes were described by two fathers in the study.
Lin and co-workers (2011)	119 children	Authors suggested adding FLAVORx to opened capsules to improve palatability. There was no discussion of administration techniques volunteered by parents/carers or children.
Paranthaman and co-workers (2009)	A convenience sample of 14 caregivers	Quotation of an adherent caregiver: "It was difficult to break the tablets into exact doses. Once they prescribed 1/3 rd of the tablet but it is difficult to give. For this, syrup would have been better. I feel it is difficult because we are unable to break the tablet correctly. I have the feeling that I am not giving the correct dosage."
Roberts (2005)	9 children interviewed with guardians and guardians (alone) of 5 additional children	Some guardians reported giving their children various foods or beverages (e.g., pudding) to make the medications more palatable.
Wrubel and co-workers (2005)	71 caregivers provided one or more accounts	32% of mothers in the study provided examples of how they improve palatability, mixing medicines with some food to disguise the taste, or giving a sweet drink immediately after giving medicines.

Table 16 Reported non-specific medicines manipulation data across the studies.

Authors	Sample size	Non-specific medicines manipulation data
Byrne and co-workers (2002)	Primary caregivers of 42 children	Strategies to improve taste or to omit bad aftertaste were frequently reported (29% and 24%, respectively).
Goode and co-workers (2003)	18 parents (12 of which were also treated for HIV on HAART regimens)	Procedural factors (including the mixing and preparation of medicines) was a difficulty reported by 28% of the respondents.
Hammami and co-workers (2004)	11 primary caregivers of 18 children	Parents offering “nice tasting things” as a reward for taking the medicine.
Marhefka and co-workers (2004)	51 Participants (parents or primary caregivers)	Described difficulties experienced by a caregiver when preparing a solution. No more details were reported.

4.4.5 Quality assessment and risk of bias in review studies

The participants recruited varied across the included studies (i.e. parents/caregivers versus young people). If a child is competent to understand and consent they should be given opportunity to participate in a study. However, fewer than one third ($8/27 = 30\%$) of the studies (Buchanan *et al.*, 2012, Ingerski *et al.*, 2010, Modi and Quittner., 2006, Roberts, 2005, Shemesh *et al.*, 2004, Tucker *et al.*, 2002, Van Dyke *et al.*, 2002, Zelikovsky *et al.*, 2008) reported child involvement. In the majority of the studies the young ages of the children would make assent impossible. Children may only provide assent to participate in a study if they are able to fully understand it.

It is important to remember that responses of caregivers and children may differ. Modi and Quittner (2006) highlighted that swallowing oral enzymes and antibiotics were barriers identified by children with Cystic Fibrosis (CF) in addition to those barriers identified by parents. In the study by Shemesh and co-workers (2004), bad taste was a barrier reported by 4.9% of caregivers of children with liver transplants however problems associated with bad taste were not reported by these children.

In paradox to these discrepancies between the reports of caregivers and children, Buchanan and co-workers (2012) reported significant agreement for the barrier “taste/cannot get it down” ($k=0.44$, $p<0.001$) when comparing child and caregiver responses relating to HIV treatment. As these findings are inconsistent, it seems beneficial to interview child and caregiver independently. When this is not possible a family environment would be preferred and discrepancies reported.

Ethical consideration should be at the forefront of studies involving children. Ethical approval was not discussed in 9 papers (Boni *et al.*, 2000, Buchanan *et al.*, 2012, Byrne *et al.*, 2002, Esteban Gomez *et al.*, 2004, Hammami *et al.*, 2004, Paranthaman *et al.*, 2009, Pontali *et al.*, 2001, Roberts, 2005, Zelikovsky *et al.*, 2008) and informed consent was not mentioned in 5 studies (Christiansen *et al.*, 2008, Goode *et al.*, 2003, Lin *et al.*, 2011, Pontali *et al.*, 2001, Shemesh *et al.*, 2004). As the data was collected differently in 2 studies (Feingold *et al.*, 2000, Lin *et al.*, 2011) the level of ethical approval and consent requirements may have differed, however no information on ethics was reported in the studies.

Studies adopting qualitative methodological approaches are often more time consuming and for this reason lower numbers of participants may be recruited. For 3/12 studies adopting a closed-question approach (i.e. a less qualitative nature) sample sizes were relatively low (n=20) (n=28) and (n=44) (Esteban Gomez *et al.*, 2004, Farley *et al.*, 2003, Pontali *et al.*, 2001) given respectively, thus impacting on the power of these studies. Also, it is possible that recruitment rate is lower in HIV studies as some parents may choose not to participate for fear of disclosing HIV status to their child (Bikaako-Kajura *et al.*, 2006).

Interviewer bias can arise in interviews or when facilitating questionnaires. For 18/27 studies the study personnel are either not disclosed in the text or are recorded as interviewer or researcher and no more information is provided (Boni *et al.*, 2000, Buchanan *et al.*, 2012, Bunupuradah *et al.*, 2006, Christiansen *et al.*, 2008, Gibb *et al.*, 2003, Goode *et al.*, 2003, Ingerski *et al.*, 2010, LePrevost *et al.*, 2006, Marhefka *et al.*, 2004, Modi and Quittner, 2006, Plipat *et al.*, 2007, Reddington *et al.*, 2000, Roberts, 2005, Shemesh *et al.*, 2004, Tucker *et al.*, 2002, Van Dyke *et al.*, 2002, Wrubel *et al.*, 2005, Zelikovsky *et al.*, 2008).

For 3/27 studies, it was implicitly reported that the interviewers were not part of the care team (Byrne *et al.*, 2002, Farley *et al.*, 2003, Hammami *et al.*, 2004). However, in 2/27 studies (Davies *et al.*, 2008, Pontali *et al.*, 2001) the interviewer was known by the participants. In the study by Esteban Gomez and co-workers (2004) a pharmacist dispensing medicines conducted the research, however it was not stated if they were known to the subjects. Paranthaman and co-workers (2009) declared that their interview was conducted by the principal investigator (who had no role in clinical care provided). The study conducted by Bunupuradah and co-workers (2006) was funded by the FLAVORx Company, and therefore the potential risk of bias in this study needs to be highlighted.

To assess the methodological design of a study, the detailed content of the self-report tool is required. For 2/27 studies (Feingold *et al.*, 2000, Lin *et al.*, 2011) reporting data documented by healthcare professionals in medical records, specific methodology on how data was recorded was not revealed in the study reports. In 9/27 studies, themes explored in interviews were discussed although the exact questions were not always reported (Byrne *et al.*, 2002, Christiansen *et al.*, 2008, Gibb *et al.*, 2003, Goode *et al.*, 2003, Hammami *et al.*, 2004, LePrevost *et al.*, 2006, Modi and Quittner, 2006, Paranthaman *et al.*, 2009, Roberts, 2005). In 8/27 studies the questions constituting the self-report tool were reported (Buchanan *et al.*, 2012, Esteban Gomez *et al.*, 2004, Marhefka *et al.*, 2004, Pontali *et al.*, 2001, Reddington *et al.*, 2000, Shemesh *et al.*, 2004, Tucker *et al.*, 2002, Wrubel *et al.*, 2005).

The remaining 8/27 studies referenced an existing self-report tool available in the literature: Boni and co-workers (2000) referenced questions used by Gross and co-workers (Gross *et al.*, 1998), the PACTG tool was referenced by 5 studies (Bunupuradah *et al.*, 2006, Davies *et*

al., 2008, Farley *et al.*, 2003, Plipat *et al.*, 2007, Van Dyke *et al.*, 2002) and the MAM referenced by 2 studies (Ingerski *et al.*, 2010, Zelikovsky *et al.*, 2008).

In several of the studies using a multiple choice closed-question approach, a final option of 'other' was available to enable the interviewee to report an alternative barrier to medicines administration. A risk of using closed questions is the ability to direct the interviewee to an option, reducing accountability of the response. However, when comparing results of these studies to those studies adopting a more qualitative approach, findings were similar.

Assessment of study quality in this review proved difficult. This required assessment of quality of the methodology of interest to the present study (self-report component). The self-report tools varied across the studies (i.e. non-standardised interviews and questionnaires versus data documented by healthcare professionals). For the majority of studies, exploration of oral formulation-related barriers to medicines administration was not the main study focus. Limited studies have extensively explored oral formulation-related barriers, and generally the quality of reporting was sub-optimal. The impact of individual oral formulation-related barriers on specified outcome measures was not reported clearly in the studies.

A systematic literature review titled 'Effects of the Pharmaceutical Technologic Aspects of Oral Pediatric Drugs on Patient-Related Outcomes' (Van Riet-Nales *et al.*, 2010) similarly acknowledged poor quality across study methodologies. They reported that only 2 of their 94 included studies were of good quality based on Jadad scoring (scores 4 or 5).

A heterogeneity of patient outcome measures relevant to the research objective (see section 4.2) existed across the review studies. All 27 studies discussed the influence of oral

formulation-related barriers on medicines administration (i.e. reported the nature and/or prevalence of such barriers to medicines administration) yet few studies reported the individual effects of these barriers on a specific patient outcome. Adherence is multifactorial and there is no accepted standard for its measurement, therefore collating and thus interpreting data across studies is complex. Additionally, optimal adherence levels are higher for some chronic diseases (i.e. HIV adherence is often given a higher adherence cut-off - as discussed in section 2.2.1) and therefore comparing adherence levels across different chronic conditions is not appropriate.

For the purpose of determining the influence of oral formulation-related barriers to medicines administration on child acceptance, it seems credible to evaluate reports of children refusing medicines, as investigated by Lin and co-workers (2011). Reports of refusal, resistance and oppositional behaviours (see Table 2) were identified across the review studies, yet often the reason for this behaviour was not reported. Such patient outcome measures should be fully explored and clearly reported in future studies (i.e. complete refusal of a dose reported independently to reports of child resistance to administration) in order to avoid ambiguous data interpretation.

In 3 studies the impact of individual barriers on medicines administration was not revealed as quantitative data on oral formulation-related barriers to medicines administration was grouped (Buchanan *et al.*, 2012, Gibb *et al.*, 2003, Tucker *et al.*, 2002).

Wrubel and co-workers (2005) quantified the impact of 'side effects' as a barrier for parents when administering medicines, however did not reveal the impact of taste. This impedes the transparency of data reporting and is a criticism of the study.

Reports regarding problems with the quantity of solid dosage forms were unclear across the studies. The barrier, 'too many pills/medicines' created interpretation difficulties. It could not be deciphered whether reference was being made to the number of different solid dosage forms administered (polypharmacy) or the number of units of the same solid dosage form. It is likely that the term 'medicines' was used to refer to liquid formulations.

Similarly, clarification of specific terminology (i.e. 'swallowing issues') and identification of patient groups (e.g. patients with NG or PEG tubes) is needed in order to interpret data on problems with swallowing and the size of solid dosage forms correctly (i.e. to understand whether a child is physically unable to swallow or is averse to/has difficulty swallowing a dosage form). Study reports did not necessarily indicate an issue with the medicine formulation itself (i.e. difficult size or shape), as problems with swallowing could relate to a patient with a physical inability. Clear assumptions cannot be made as this information was not provided in the reports.

Oral formulation-related barriers to medicines administration were not reported for individual drugs in 20/27 studies. Of the 7 'key studies' that did report individual drug data, 2 studies (Davies *et al.*, 2008, Lin *et al.*, 2011) did not specify the actual formulation/s concerned. In order to inform future formulation development, knowledge of specific formulations is vital, thus more detailed data reporting is needed in future studies.

A table summarising quality assessment and risk of bias of the included review studies can be found in Appendix 4.

4.5 Discussion

4.5.1 Summary of evidence and limitations of review studies

The search strategy of this systematic review was designed to be rigorous across the databases used, however applying the strategy to the NeLM data source proved very difficult as a result of its inability to conduct an advanced, detailed search using the refined combination of search strings as in sections 4.3.4.1 - 4.3.4.3. This is a limitation of using the NeLM for data collection. Multiple searches using search terms from the strategic search diagrams were used to retrieve literature in NeLM, see section 4.3.4.4. The NeLM has a strong pharmacy input and therefore in addition to retrieving duplicate articles, retrieved some studies that had not been identified using the other databases. The NeLM data source was used in addition to the other databases in an attempt to minimise the risk of omitting any relevant studies in this review.

This systematic review aimed to explore the influence of oral formulation-related barriers to medicines administration on child acceptance of or adherence to medicines. Included in the review were a total of 27 studies and the majority (79%) of these, reported findings on antiretroviral medicines. Only 7 of the studies ('key studies') associated a named drug with at least one oral formulation-related barrier to medicines administration (some reporting the specific formulation). All of these 7 'key studies' investigated antiretroviral drugs, indicating a clear gap in research across paediatric patients suffering from other chronic conditions.

Several studies were retrieved during the systematic search yet excluded from this review as study methodology was a one-off taste test of paediatric formulations conducted in adults or children. These studies did not focus on problems experienced when administering medicines to children suffering from chronic conditions in a domiciliary, natural environment.

Oral formulation-related barriers to medicines administration were identified and then categorised for purpose of the narrative review under the following thematic sub-headings: Taste, size of solid dosage forms and difficulties with swallowing, volume of powder or liquid and quantity of solid dosage forms, texture, smell and colour/appearance (reported in descending order of acknowledgement across the studies).

Results from the review studies indicate that taste is a key oral formulation-related barrier to medicines administration in children. Taste featured in each of the 27 studies. However where other oral formulation-related barriers (e.g. problems associated with colour, smell, texture) were not offered as a choice (i.e. within studies using a list of barriers) this could underestimate their impact on child acceptance of a medicine.

Observations across the 7 'key studies' revealed that: ritonavir liquid, ritonavir tablets, nelfinavir powder zidovudine syrup, lamivudine syrup, didanosine powder, crushed nevirapine tablets and opened efavirenz capsules were reported to be difficult to administer to children because of poor child acceptance of oral formulation characteristics. According to current PIP guidelines (European Commission, 2008) there is a mandatory requirement to consider palatability when formulating medicines. It is crucial that drug companies are adhering to these guidelines when developing new antiretroviral medicines.

A finding that contrasted to the general trend of taste problems across the studies was reported by Tucker and co-workers (2002). 'Taste/ taste making them feel sick' was not associated with children disliking to take their medicines. The children in the study were taking medicines following renal transplants. Average ages of the African American and European American patients were 12.9 and 15.0 years respectively. As these patients were older, it could be that tablets as opposed to liquid medicines predominated in their regimes, and therefore taste was not perceived as a major barrier to the acceptance of a medicine. This data was not reported so is merely a presumption.

Supporting this finding, Pontali and co-workers (2001) investigating HIV patients reported that children over 10 years of age did not identify taste as a main problem when administering medicines as reported in Table 2. When film or sugar coats (i.e. in tablet formulations) are used, taste is not often perceived to be an issue (EMEA 2006).

Problems associated with the size of solid dosage forms or swallowing them were highlighted in over half (59% 16/27) of the studies. In 2 of these 16 studies, problems with size or difficulties with swallowing solid dosage forms was reported to not be an important barrier to administering medicines (Tucker *et al.*, 2002, Zelikovsky *et al.*, 2008). These studies investigated post renal transplant patients and those requiring a renal transplant. Factors such as the older age of these patients or the size of solid dosage forms prescribed to treat these patients may have influenced this finding. Supporting this finding, Pontali and co-workers (2001) did not report difficulty swallowing tablets as a main problem for children less than 6 years, yet this was reported as a main problem in children 6 years and older (see

Table 2). Nelfinavir in a tablet formulation was reported as ‘too big’ in the study by Gibb and co-workers (2003).

Problems with the volumes of medicines were reported in 3/27 studies. Van Dyke and co-workers (2002) identified an issue with the volume of ‘nelfinavir powder’. It should be acknowledged that child aversion to large volumes of powders and liquids may be influenced by palatability also (EMA, 2006).

Studies investigating solid dosage forms that are small in size (2mm-3mm), recognised as ‘Mini-tabs,’ indicate that such formulations may be accepted by children from the age of 6 months and 2 years respectively (Spomer *et al.*, 2012, Thomson *et al.*, 2009). However, some dosage forms exist as a large volume (i.e. powder/liquid) or size (i.e. tablet/capsule) because of the characteristics of certain drugs (e.g. powder density, volume of drug, dose required). For such dosage forms, improving palatability using standardised manipulation techniques based on a robust scientific evidence base should be considered to improve child acceptance and medicines adherence. This is discussed in the EMA draft guideline (EMA, 2013).

Furthermore, education to help children to learn to swallow solid dosage forms should be introduced to children requiring solid dosage forms as discussed in previous studies (Czyzewski *et al.*, 2000, Garvie *et al.*, 2007).

Problems with the quantity of solid dosage forms were investigated in 6 of the 27 studies. In children aged 6 years and over, the quantity of solid dosage forms was reported as a main problem when administering medicines to HIV patients (Pontali *et al.*, 2001).

Problems with the texture of medicines were revealed in only 4 of the 27 studies. Esteban Gomez and co-workers (2004) commented that texture needs to be improved however did not discuss any supporting study data for this statement. Further examination in to such issues is needed as this has not been at the forefront of pharmaceutical research to date (RCPCH, 2004). In specific patient groups (i.e. those suffering from a learning disability) such organoleptic properties may have a significant impact on medicines acceptance.

Issues with smell and independently colour or appearance of medicines were not as frequently reported across the studies. It might be questioned if barriers perceived by parents and caregivers when administering medicines to children influence child acceptance. Only one of the studies (Roberts, 2005) highlighting such sensory properties mentioned the involvement of children during the interview. Children may associate smell and visual properties of a medicine with taste. Psychology plays a role in how children and their parents and carers perceive medicines. Review findings warrant further research with the help of psychologists to investigate the sensory perceptions of parents and children regarding medicines.

Some children may be more sensitive to the organoleptic properties of medicines than others. The age of a child may influence the problems experienced with medicines and thus the choice of dosage form prescribed. Although dosage form choices may not be dependent on the age of a child, a general trend may exist, and this could be related more closely to age at diagnosis and familiarity with medicines. Factors that may influence dosage form choices of paediatric patients and healthcare professionals need to be investigated in future studies

including: age of child, whether a patient has previous experience of taking liquid or solid dosage forms, gender, age and ethnicity (FormPIC study REC no 13/NE/0020).

Early exposure to different tastes and textures has been reported to affect patterns of food acceptance in children (Harris, 2008). Also, Northstone and co-workers (2001) found that delaying experimentation with lumpy foods at or after 10 months of age increased the likelihood of feeding difficulties and more definite likes and dislikes. Encouraging a child from an earlier age to experiment with various foodstuffs (different flavours and 'mouth feels') may improve child acceptance of medicines.

Owing to the complex, multi-factorial nature of adherence, no accepted, standard measure exists. The heterogeneity and lack of clarity of reported patient outcome measures (acceptance and adherence) across the studies limited the power of data interpretation in this review. Future studies need to improve reporting quality. Patient-related outcome measures should be reported clearly, i.e. reports of medicines refusal resulting in dose omission versus reports of resistance to administration. This will minimise ambiguity and enable data to be compared across studies.

Lin and co-workers (2011) identified oral formulation-related barriers to medicines acceptance for individual drugs and medicines refusal was the reported outcome measure. Reporting was better compared to the other review studies as results of palatability assessments were revealed for all antiretroviral drugs prescribed to the patient population. Lin and co-workers (2011) unveiled important data that should be used to help clinicians when prescribing antiretrovirals in order to maximise medicines adherence.

Reporting the nature and prevalence of medicines manipulation techniques used in a domiciliary environment is important in order to understand the difficulties encountered by parents and carers when administering medicines to children on a daily basis. Medicines manipulation techniques were reported in 10 studies, yet detail on the techniques used was only revealed in 60% of these studies. The medicines concerned and potential risks involved were not explored in the study reports.

The use of medicines manipulation techniques to facilitate medicines administration has the potential to affect drug absorption, bioavailability (through drug-foodstuffs binding) and also cause degradation reactions which can affect drug stability as discussed in section 2.5.3. It would be beneficial for future studies to identify the nature of common medicines manipulation techniques used by parents and carers. This data should direct laboratory formulation work. This would provide a robust scientific evidence base that could be used to inform healthcare professionals and parents, carers and patients on safe and effective medicine manipulations.

It is essential that healthcare professionals involved in prescribing, dispensing and administering medicines are fully aware of potential oral formulation-related barriers to the administration of medicines to children. In addition parents, carers and patients need to be educated on overcoming barriers safely where no alternative therapeutic options are available in view of patient safety and drug efficacy.

4.6 Conclusion

This systematic review has identified that taste is the main oral formulation-related barrier to medicines administration in paediatric patients. The majority of the studies supporting this finding were conducted in children prescribed antiretroviral medicines.

Current research exploring oral formulation-related barriers to medicines administration is limited and has been conducted in narrow patient populations. Future research is required in children suffering from a wide range of chronic conditions and prescribed different medicines. Exploration of barriers to child acceptance of medicines including taste, size, volume of liquid or powder, quantity of solid dosage form, texture, colour, and smell is imperative. Such data should influence future pharmaceutical design. Oral formulation-related barriers are potentially modifiable and overcoming them increases the ability to close a gap in difficulties with administration, thus improve medicines adherence in children.

It is important to remember that adherence is a multi-factorial phenomenon. Adherence cannot be compared equivalently across different chronic conditions as optimal adherence cut-off levels are inconsistent. Overcoming oral formulation-related barriers to medicines administration may reduce the occurrence of paediatric non-adherence through reducing medicine refusals, yet further factors are implicated (including forgetting) that are beyond the aims of this systematic review.

Studies need to report problems with specific medicine formulations to inform future formulation work, thus prioritise drug development. Medicines manipulation techniques adopted by parents, carers and young people to administer medicines in the domiciliary setting need to be identified and potential risks investigated in future pharmaceutical work.

Healthcare professionals, parents, carers and young people need to be educated on safe and effective medicines manipulation techniques. This should be based on robust scientific evidence.

As most of the physical attributes of interest to this study (organoleptic - taste, smell, texture, physical – size/swallowing solid dosage forms) relate commonly to administering oral medicines, the inclusion criterion for this review was designed to include only oral medicines. It would be useful to investigate if such problems influence the administration of inhaled formulations in a future study.

This systematic review informed the overall design of this study. The aim of this review was to identify and evaluate literature investigating oral formulation-related barriers to medicines administration. This systematic review identified that the studies conducted were limited to specific paediatric populations and in the majority of studies, detailed reporting was absent. The present study aimed to report detailed data on oral formulation-related barriers to the administration of medicines in paediatric patients suffering from a wide range of chronic conditions from the perspectives of healthcare professionals (Chapter 5) and parents, carers and children (Chapter 6) to inform future formulation work.

5 EXPLORING PROBLEMS EXPERIENCED WITH ORAL MEDICINES IN PAEDIATRIC PATIENTS FROM THE PERSPECTIVES OF MEDICAL PRACTITIONERS, PHARMACISTS AND NURSES

5.1 Objectives

The primary objective of the focus groups was to inform design of the semi-structured interviews delivered to parents, carers and children (see Chapter 6). The secondary objective of the focus groups was to explore and understand the problems experienced when prescribing, dispensing and administering oral medicines to children from the perspectives of medical practitioners, pharmacists and nurses. The aim of this was to identify common and unique themes across healthcare professional groups regarding problems with oral medicines prescribed to paediatric patients and furthermore to compare their views with those of parents, carers and children.

5.2 Background and setting

Problems with children's medicines may be influenced by many factors. These include issues with prescribing and the supply of medicines, unlicensed medicines and medicines used off-label, difficulties with administering medicines (including manipulation of medicines), behaviour around medicine taking (including influence of family, school and life situation), adverse effects of medicines and medicine adherence problems in specific patient groups (i.e. age groups and chronic conditions).

Barriers to medicines adherence have previously been discussed in Chapters 2 and 4. It is probable that some healthcare professionals may not be aware of the specific barriers and problems that patients and their parents and carers perceive and experience daily when administering medicines. Medicines may be manipulated by parents, carers and young people for which often there is lack of robust scientific evidence (see section 2.5.3). Parents, carers and young people may decide to manipulate medicines of their own accord, unbeknown to the responsible medical practitioner. Alternatively medicines manipulation may be performed following a recommendation from a healthcare professional.

There is a paucity of research investigating healthcare professionals' perceptions of issues with medicines used to treat paediatric patients with chronic conditions. Studies that have been conducted include an exploration of healthcare providers' views on HIV adherence in paediatric patients (Brackis-Cott *et al.*, 2003), an investigation into nurses' knowledge and practice of mixing medicines with foodstuffs (Akram and Mullen, 2012) and those investigating unlicensed medicines use (Mukattash *et al.*, 2011a, Mukattash *et al.*, 2011b). The present study aimed to have a more diverse approach, exploring the perspectives of allied healthcare professionals (medical practitioners, nurses and pharmacists) with regard to problems with oral medicines prescribed to children.

Children suffering from chronic conditions often have regular appointments in the secondary care setting to review their condition and medicines. In the hospital environment different members of the healthcare team are responsible for providing care for patients. This multidisciplinary healthcare team includes medical practitioners, nurses and pharmacists of varying expertise and with different specialist interests.

It was anticipated that the perspectives of medical practitioners, nurses and pharmacists regarding problems with children's medicines would vary owing to their different occupational roles. It would be expected that generally medical practitioners would have more understanding with regard to prescribing medicines than nurses and pharmacists. Pharmacists dispense medicines to patients, and therefore it is probable that they are more aware of the problems associated with the supply of medicines. As nurses administer medicines to children (on paediatric wards and in the community) they may be more knowledgeable on how medicines are administered to children.

This study was conducted with healthcare professionals at UHCW and BCH.

5.3 Methodology

5.3.1 Background work

Medical practitioners at UHCW were emailed study information and invited to respond to the email in order to ascertain if any medical practitioners opposed RV observing clinics. All responses that were received were supportive of the study (see Appendix 5).

Having obtained an honorary contract at UHCW, a variety of paediatric clinics were observed between October and December 2009. These clinics included rheumatology, gastroenterology, HIV, CF, asthma, endocrinology, renal, and diabetes. This preliminary scoping work was used to become familiar with the paediatric clinic environment, the variety of clinics and medical practitioners, to observe the patient-healthcare professional relationship in clinics, and to inform experimental design.

Medical practitioners at UHCW provided case examples of difficulties, highlighted to them by parents when administering multiple formulations to their child. Two of these cases can be found in Appendix 6. Medical practitioners also revealed problems with children's medicines whilst RV observed paediatric outpatient clinics at UHCW (see Appendix 2). The attitude of Medical practitioners at UHCW was positive towards the study.

During the pre-study period a session was arranged with a paediatric pharmacist in the pharmacy department at UHCW to introduce the proposed research. The paediatric pharmacist raised issues with the taste of some liquid medicines and highlighted difficult medicine regimes (see Appendix 2). Examples of manipulations to medicines were revealed and knowledge of risks associated with medicines manipulation was reported. Medicines adherence and also difficulties with unlicensed and Specials medicines were discussed by the paediatric pharmacist.

Attending a 'drug-round' conducted by paediatric nurses on the paediatric wards at UHCW permitted RV to observe nurses administering medicines to children. The pre-study work conducted in paediatric outpatient clinics, the pharmacy department and on the wards at UHCW gave an insight in to existing knowledge on problems with children's medicines and supported the importance of this study, from the perspectives of healthcare professionals at the study setting.

5.3.2 Introduction to the data collection tool

Focus groups collate a plethora of information in a short period of time and explore attitudes, perceptions and feelings. The group setting provides some security for individuals, who might otherwise feel vulnerable to criticism, and encourages them to contribute to the

discussions and their direction, when compared to a more structured agenda (Stewart *et al.*, 2006).

When conducting a focus group between six and eight participants is optimal (Krueger and Casey, 2000). The group should have enough participants to get a wide perspective without being too large, and thus disordered or fragmented, (Rabiee, 2004) and should last 1-2 hours.

Morse and Field (1995) state that using several combined homogenous groups to provide a heterogeneous population enables a wider perception and thus a diversity of views. In addition, scoping and exploring the problems associated with a variety of medicines prescribed to paediatric patients suffering from chronic conditions was intended. It was decided that a more structured research tool (e.g. questionnaire) would not collect the data as effectively as a focus group.

5.3.3 Design of the data collection tool

Focus groups were used to explore the views of healthcare professionals engaged in the care of paediatric patients with chronic conditions. The focus groups were used to develop an in-depth understanding of problems with oral medicines, as perceived by healthcare professionals involved in prescribing, dispensing or administering medicines to children.

The healthcare professionals that were chosen to participate in the focus groups were medical practitioners (specialising in paediatrics), paediatric pharmacists and paediatric nurses. It was intended that three focus groups in total would be conducted (one for each

healthcare profession). The rationale for the chosen focus group populations is reported in Figure 7 below.

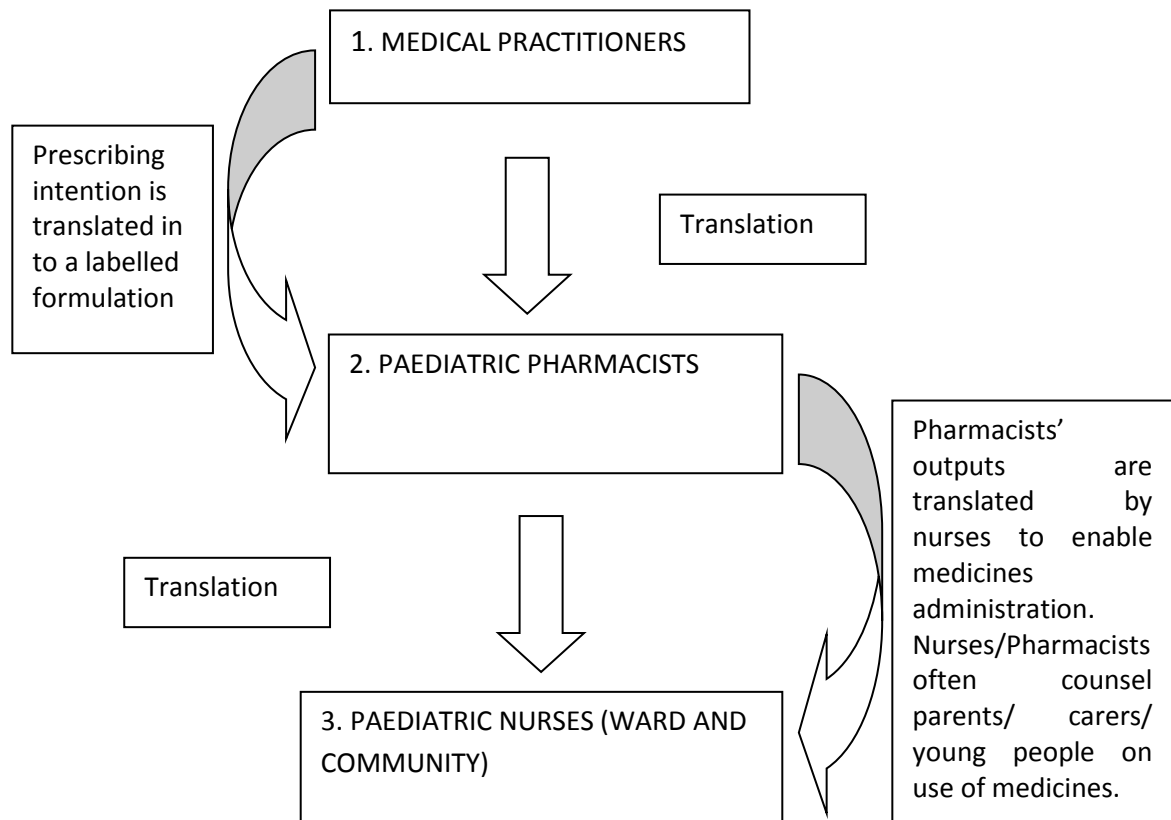


Figure 7 An algorithm displaying the rationale of conducting individual focus groups with medical practitioners, paediatric pharmacists and paediatric nurses.

Figure 7 above shows the relationship and flow of events leading from the prescribing intention of a medical practitioner through to supply of a labelled medicine by a pharmacist and finally administration by a nurse.

Initial ideas generated by RV with the advice of Professor of Clinical Pharmacy and a Consultant Paediatrician were informed by healthcare professionals in pre-study hospital visits (as described earlier in section 5.3.1) and by study objectives (see Chapter 3). Ideas

were used to devise the key topics for exploration in the focus groups. The different professional backgrounds of the individuals involved in study design permitted the collaboration of a clinical and pharmaceutical input.

A template plan of topics to explore was formed. The themes for discussion were consistent across the focus groups.

The focus groups were designed to explore the following themes:

- Problems surrounding prescribing and supply of medicines, highlighting issues around individual or particular groups of medicines
- The use of unlicensed and off-label medicines
- The process of administering medicines (e.g. measurement of dosage, route, organoleptic and physical properties of medicines)
- Manipulation of medicines to improve child acceptability or for purpose of giving a specific dose on wards and in the community (e.g. crushing tablets, mixing with foodstuffs) and the difficulties associated with this
- Behaviour around medicine taking and how this is dealt with
- Adverse effects (e.g. nausea, vomiting)
- Groups of patients or drugs with particular medicines adherence issues
- Factors that affect medicines adherence and how often the regimen is adhered to (timing of medicines, effects on family life, school)
- Patient, parent and carer understanding of medication routine and regimen
- Positive experiences around taking medicines

- Perceptions around the issues of intentional and unintentional non-adherence to medicines
- Ideas for future drug development.

5.3.4 Identification and Recruitment

Healthcare professionals were invited to join a focus group by posters (see Appendix 7) mounted on walls at UHCW (neonatal unit, paediatric wards and paediatric outpatient department).

Healthcare professionals (UHCW paediatricians, paediatric pharmacists, and paediatric ward managers- to disseminate the information to paediatric nurses and community paediatric nursing teams) were contacted via the UHCW email system and invited to respond to register an interest to participate. In addition, targeted emails were sent to paediatric pharmacists in the West Midlands region. An information sheet designed using guidance from the NPSA (2009) was distributed with the invitation email (see Appendix 8).

General Practitioners (GPs) in Coventry and Warwickshire were informed of the study via a study summary article in the clinical pharmacology e-newsletter, (edited by a Professor of Clinical Pharmacology and Therapeutics) routinely disseminated to all GPs in Coventry and Warwickshire. An Invitation to request an information sheet by email or telephone was provided.

It was anticipated that recruitment would not be easy, due to limited free-time during the working hours of healthcare professionals. Outpatient clinic commitments made predicting recruitment for the medical practitioner group most difficult. Owing to relatively few

pharmacists specialising in paediatrics, it was anticipated that the recruitment of paediatric pharmacists would also be difficult.

The dates and times of the focus groups were selected based on the most popular choices that were indicated by respondents wishing to participate. A second pharmacist focus group was arranged for pharmacists at BCH. These pharmacists had generated interest in the study but were unable to attend the UHCW session for logistical reasons.

Verbal and email reminders were provided to interested participants to encourage attendance.

5.3.5 Ethical issues and informed consent

All potential participants were given at least 24 hours from receiving information before consenting to participate in the study. On arrival, focus group participants were asked to sign-in to mark attendance and to provide informed consent for the session to be digitally audio-recorded (see Appendix 9) conforming to Good Clinical Practice (GCP training course 2009 and online 2011 were completed to keep researcher up-to-date).

5.3.6 Conduct of the focus groups

Four focus groups were conducted involving nurses, medical practitioners, pharmacists at UHCW, and a further group of pharmacists at BCH. The four focus groups were conducted between September 2010 and February 2011. It was necessary to create an environment to encourage good engagement of the participants. Private rooms were pre-booked within UHCW and BCH in locations easily and efficiently accessible for staff, to create a suitable and

convenient environment for discussion. Ensuring that participants were relaxed was imperative to prompting exchange of ideas, views and feelings (Rabiee, 2004).

The introduction for each focus group followed the same structure and included a reminder about confidentiality issues delivered at the start. The planning and conducting stages of the focus group sessions were carried out according to procedures suggested by Krueger and Casey (2000).

The four focus groups were facilitated by RV and assisted by Professor of Clinical Pharmacy/Consultant Paediatrician. The groups were digitally audio-recorded using an Olympus digital audio-recording device. Complementary notes were taken by the Consultant Paediatrician during the sessions.

Travel expenses (for those who made a special journey to attend the group) and refreshments were provided.

5.3.7 Transcription of the focus group data

RV transcribed each focus group as soon as was possible after facilitating the group, to ensure the ideas and attitudes discussed were 'fresh in mind'.

The transcription process from digital audio-recording to verbatim transcript is detailed below. This process was followed for all of the four sessions.

1. Verbatim transcripts were produced in Microsoft Office Word 2007 from the digital audio-recordings
2. Numerical coding was used to identify each participant

3. The verbatim text was examined and compared with complementary notes taken during each session
4. Transcription process steps 1 to 3 were repeated to optimise accuracy.

5.3.8 Analysis of the focus group data

The verbatim text was copied in to a commercial data content analysis program (QSR NVivo 8) and thematic content analysis was utilised to analyse the four verbatim files independently. The template plan of topics (see section 5.3.3) was used to explore and identify the themes revealed in each transcript. Following this, common themes revealed across the groups and those unique to each group were identified.

5.3.8.1 Framework analysis approach

A framework analysis approach was adopted as this was deemed to be most appropriate following development of the research question and early theme derivation. This analytical approach is both rigorous and structured and reflects the background work (that is inductive) and develops deductively from study aims and objectives (Pope *et al.*, 2000).

Ritchie and Spencer (1994) defined framework analysis as:

‘An analytical process which involves a number of distinct though highly interconnected stages.’

The five key stages in framework analysis are familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation (Pope *et al.*, 2000). This approach allowed themes that arose in the narratives to be derived. The method was designed to permit triangulation of data with that obtained in semi-structured interviews (Chapter 6) to determine if a paradox existed.

The stages of focus groups data analysis followed guidance from Pope and co-workers (2000) and are listed below:

1. Early ideas that were derived from background work with healthcare professionals at UHCW as discussed in section 5.3.1, formed an initial list of themes
2. The verbatim transcript and complementary notes from each focus group were explored to identify prevalent, emerging themes. These were added to the original list of themes
3. Short-hand text was inserted in to the margins of the transcript and relevant verbatim was highlighted and thematically coded
4. Each theme was identified as a 'node' in QSR NVivo 8
5. Nodes were linked to form relationships and identify the main thematic groups
6. Once thematically grouped the verbatim text was examined
7. Exclusive and overlapping nodes were identified across all focus groups and reported systematically.

5.3.9 Ethical requirements for focus group data

All focus group data was handled ethically and confidentially. Access to the focus group digital audio-recordings and transcribed data was restricted to the direct research team. Digital audio-recordings, notes of paper transcripts and verbatim transcription on password protected spreadsheets were locked securely in a filing cabinet in a secure University office to avoid unauthorised access. The sign-in consent sheets were kept locked in a separate locked filing cabinet in a locked University office.

The focus group data was transcribed on to password protected spreadsheets from the digital audio-recordings, and then analysed confidentially by RV in a secure University office. The encrypted laptop was stored securely in a locked cabinet in a secure room at University when not being used for data input or analysis during the interview and focus group study period.

Digital audio-recordings on the encrypted laptop were securely destroyed following transcription and analysis according to GCP (within twelve months of study completion) using the software program, Eraser 6.0.10.

5.4 Results

Table 17 below reports the number of participants, the professional statuses of participants, dates conducted and locations of the focus groups.

Table 17 Details of the four focus groups conducted to explore healthcare professionals' perspectives of problems with oral medicines in children.

Focus Group	Date conducted	Location	Total no. of participants	Professional statuses of participants
1. Nurses	21 st September 2010	UHCW	5	Neonatal nurse practitioners (2), a nurse with a specialist interest in CF, a community-based nurse and a nurse practice educator
2. Medical practitioners	30 th September 2010	UHCW	8	Paediatric consultants with specialist interests (6), a paediatric registrar, and a GP (with an interest in paediatrics)
3. Pharmacists 1	14 th October 2010	UHCW	2	Paediatric pharmacists
4. Pharmacists 2	1 st February 2011	BCH	4	Paediatric pharmacists

The number of participants across the groups varied. The small population of pharmacists specialising in paediatrics resulted in lower levels of recruitment as predicted. The

pharmacist group conducted at UHCW had a particularly low number of recruits (n=2). This focus group tended to be delivered in a more structured manner (interview style), and represented a nominal group, as inevitably focus groups do not run optimally when the number of participants is low. However, the information gathered from the UHCW focus group in collaboration with that obtained in the BCH pharmacist focus group gave an insight in to the views of pharmacists from the West Midlands region.

The nurse and medical practitioner groups were conducted at lunchtime and the pharmacist groups took place in allocated study time. It was intended that each session would last between 60 and 90 minutes. Groups lasted between 51 and 93 minutes. The exact timings of digital audio-recordings are provided in Table 18 below.

Table 18 The time duration (minutes) of each focus group conducted.

Focus Group	Time duration of group (minutes)
Nurses	58
Medical practitioners	51
Pharmacists 1 (UHCW)	93
Pharmacists 2 (BCH)	57

5.4.1.1 Observations of the dynamics of the focus groups

5.4.1.1.1 Nurse focus group

A total of five participants attended the focus group, CF nurse, children’s community nurse, two advanced neonatal nurse practitioners and a nurse practice educator.

A variety of nurses with differing levels of experience and special interests in caring for children with chronic conditions participated, including neonates and general paediatrics, those working in hospital, post-admission and (follow-up) home environments.

Discussion flowed well across the group.

5.4.1.1.2 Medical practitioner focus group

The medical practitioner focus group had the greatest number of participants across the groups (n=8). One GP attended. She revealed issues and perspectives from a community level with regards to prescribing, Primary Care Trust (PCT) restriction of Specials supply and community follow-up of chronic paediatric conditions. The paediatric registrar attendee had shown much interest and enthusiasm in this study during the pre-study period (personal communication with Consultant Paediatrician). Oncology, HIV, epilepsy, neonatology and general paediatrics were included in the specialist interests of the participants. This range of specialist interests as well as the general paediatric backgrounds of the medical practitioners generated discussion regarding problems with medicines prescribed for different chronic conditions.

Overall, conversation in the group flowed well. Latecomers did not disrupt the flow of the focus group.

5.4.1.1.3 Pharmacist focus group 1

This group had the lowest recruitment (n=2). The session was more directed and structured following the pattern of a nominal group. The scope of ideas and opinions raised during this session were relevant to the research.

5.4.1.1.4 Pharmacist focus group 2

Four pharmacists consented to take part in the focus group at BCH following much interest and enthusiasm for the study.

A breadth of experience and knowledge was apparent, owing to the diversity of interests and experiences of pharmacists in this group.

Discussion flowed well between the group members.

5.4.2 Consent and ethical issues

No feedback or questions regarding issues with consent or ethics were received. Participants all appeared to understand the information and were happy to sign the sign-in consent sheet.

5.4.3 Feedback from focus groups

An email was sent out to all focus group participants to thank them for their time and contributions. Positive feedback was received following the sessions, both verbally and electronically.

5.4.4 Results of the analysis of the focus group data

Following the framework analysis, a structured thematic coding spine (see Table 19 below) was created based on the themes emerging in the focus groups. The coding spine includes themes revealed both independently and across the groups. The results of the analysis are reported systematically, using the code headings and sub-headings listed in Table 19 below.

Table 19 Thematic coding spine detailing code headings and code sub-headings.

Code headings	Code sub-headings 1	Code sub-headings 2
Oral formulation-related barriers to medicines administration	<ul style="list-style-type: none"> • Taste-related problems • Problems with texture • Problems with colour and smell • Problems with size and swallowing • Problems with quantity and volume 	
Future medicines for children	<ul style="list-style-type: none"> • Ideal improvements to medicines • Well-accepted medicines 	
Problems related to medicines administration	<ul style="list-style-type: none"> • Administration problems with specific medicines • Interactions with foodstuffs and sub-optimal drug absorption • Medicines manipulation 	(The knowledge of healthcare professionals regarding physicochemical effects of medicines manipulation, Evidence base for medicines manipulation)
Frequent issues experienced when treating paediatric patients	<ul style="list-style-type: none"> • Specials medicines, unlicensed medicines and off-label administration • Omeprazole formulations • The knowledge and understanding of medical practitioners, pharmacists and parents regarding unlicensed medicine • Extemporaneous dispensing 	(Omeprazole liquid, Losec MUPS- licensed omeprazole formulation)
Parental understanding of medicines	<ul style="list-style-type: none"> • Educating parents and children about medicines • Social problems and language barriers 	
Medicines adherence	<ul style="list-style-type: none"> • The relationship between age of child and dosage form preference • Parental influence on dosage form choice and medicines adherence • The relationship between age of child, disease status, diagnosis, miscellaneous variants and medicines adherence • Polypharmacy 	
Adverse effects of medicines	<ul style="list-style-type: none"> • Excipients • Adverse effects associated with specific medicines 	
The supply of medicines and liquid measuring devices	<ul style="list-style-type: none"> • Problems with the supply of medicines • Problems with the supply of oral syringes and the accuracy of measuring liquid medicines • The parallel importing of medicines 	
Medication errors in pharmacies and GP practices	<ul style="list-style-type: none"> • Standardising the labelling of liquid medicines • Medicine selection errors at GP practices 	
Problems with medicines at school	<ul style="list-style-type: none"> • Problems with medicines at school 	

5.4.4.1 Oral formulation-related barriers to medicines administration

5.4.4.1.1 Taste-related problems

Taste was the most common oral formulation-related obstacle to medicines administration highlighted across the groups. Flucloxacillin solution was reported to be disliked due to taste in all of the focus groups (see Appendix 10 for quotations).

In the BCH pharmacist group, pharmacist 2 described taste problems associated with different flucloxacillin solution brands, stating that children generally prefer taking the higher strength solution so that they take less volume. She discussed the consequences of prescribing alternate second and third-line antibiotics and addressed the potential risks on future antibiotic resistant patterns.

In addition, nurse 4 reported that flucloxacillin solution had interfered with mother-baby bonding in one case and described that parents of children with CF prefer to administer an alternative antibiotic:

“Parents have described feeling like it’s a holiday when administering azithromycin once daily compared to flucloxacillin.” (nurse 4)

The bad taste of prednisolone soluble tablets was highlighted by the medical practitioners and nurses, and described as “really really bitter” (nurse 3) “disgusting” (Medical Practitioner- MP 2) and “vile.” (MP 3)

Chloral hydrate solution was described as “vile” by nurses 1 and 2. The UHCW pharmacist group in addition identified a disliking to the volume and smell in agreement with the nurses “it tastes foul” (UHCW pharmacist 1).

Reports from the medical practitioner and nurse focus groups highlighted the poor palatability of Movicol oral powder.

Table 20 below provides additional reports of medicines recognised to have taste issues by the healthcare professionals.

Table 20 Healthcare professional reports of taste problems with medicines.

Medicines	Reports of healthcare professionals
Gastrografin solution	Nurse 4
Oramorph solution	Nurse 1
Septrin paediatric suspension	Pharmacist 2 UHCW
Rifampicin suspension	Pharmacist 1 UHCW
Kaletra solution	MP 7 describes burning sensation
Nitrofurantoin Special suspension	MP 5
Clarithromycin suspension	MP 2
Generic paracetamol suspension	Nurse 2

5.4.4.1.2 Problems with texture

All of the healthcare professional groups highlighted that children experience problems with the textures of some medicines. The learning disability population were discussed as a problematic patient population across the focus groups when regarding problems with texture.

Specific medicines reported to have problems with texture are listed in Table 21 below.

Table 21 Healthcare professional reports of problems with the texture of medicines.

Medicines	Reports of healthcare professionals
Ciclosporin solution	UHCW pharmacist 1 described as oily
Lactulose solution	MP 1 described as oily
Topiramate sprinkle capsules	MP 1
Calcichew tablets	MP 2
Creon Micro gastro-resistant granules	Nurse 4 described the inconvenience of transporting apple puree to mask the texture

One pharmacist questioned whether there were any problems with textures of medicines (UHCW pharmacist 2).

5.4.4.1.3 Problems with colour and smell

A variety of further organoleptic properties of medicines were identified and most frequently during the focus group with the nurses. These are reported in Table 22 below.

Table 22 Healthcare professional reports of problems with further organoleptic properties (colour and smell) of individual medicines.

Medicines	Reports of healthcare professionals
Rifampicin suspension	Colour described as “off putting” (nurse 1)
Klean-prep oral powder dissolved in liquid	“Smell makes you wretch it’s horrible” (nurse 4)
Abidec multivitamin drops	Bad smell and the colour stains bibs, (nurse 4), yet described as tolerated
Feeds (including nutramigen, the pepti-milks and soya milks)	“Horrendous” (nurse 1) and having a smell that “pervades everything” (nurse 2)

5.4.4.1.4 Problems with size and swallowing

All groups acknowledged that children taking antiretroviral tablets experience problems with their size and also difficulties when swallowing them.

“I know probably the older children have problems swallowing the huge tablets.” (nurse 1)

Medical practitioner 2 in reference to HIV clinic revealed “These little children are expected to swallow these enormous tablets.”

Kaletra tablets are mentioned specifically and medical practitioner 7 describes these as “big bulletry” and “like horse pills.”

Further solid dosage forms identified with problems related to size or swallowing are provided in Table 23 below.

Table 23 Healthcare professional reports of problems with the size or swallowing solid dosage forms.

Solid dosage forms	Reports of healthcare professionals
Slow sodium tablets	“Like an old paracetamol tablet, they’re quite sticky to swallow down” (nurse 4)
Temozolomide capsules (16-21mm)	“I think they’re quite big drugs” (nurse 6)
Ethambutol tablets	Often preferred in multiple small tablets as opposed to a single large tablet according to UHCW pharmacist 2

5.4.4.1.5 Problems with quantity and volume

Problems with the volume of medicines were associated with individual medicines or groups of patients by a member of each healthcare professional group. These are reported in Table 24 below.

Table 24 Healthcare professional reports of problems with the volume of individual medicines or medicines prescribed to specific patient groups.

Medicines	Reports of healthcare professionals
Movicol oral powder dissolved in liquid (each sachet added to 125mls of water)	BCH Pharmacists in agreement
Chloral hydrate solution (dose for 1-12 year olds approximately 5-20mls ‘well diluted with water’)	“Huge” volume (UHCW Pharmacist 1)
Antiretroviral liquids	“Liquid volumes are so high” (MP 7)
Administering considerable volumes of medicines in addition to feeds in neonates	The issue of giving neonates more than their recommended total daily volume of fluids was voiced by nurse 3

Approximate volumes from BNF for Children (2011-2012) provided in brackets.

5.4.4.2 Future medicines for children

5.4.4.2.1 Ideal improvements to medicines

Participants were asked to share their views on key medicine improvements. Improving the taste of flucloxacillin solution was reported by pharmacists, nurses and medical practitioners (BCH pharmacists 2 and 3, nurse 4 and MPs 3, 4 and 5). Additional suggestions to improving medicines were provided in each of the groups. These are reported in Table 25 below.

Table 25 Ideal improvements to medicines as reported by healthcare professionals.

Ideal improvements to medicines	Reports of healthcare professionals
Administering medicines in the smallest volume	Nurses
The use of neutral flavours	Nurse 2
Improving the taste of chloral hydrate solution and using more strawberry and orange flavours	Nurse 1
Using neutral or sweet flavours	Nurse 5
Improving the taste of prednisolone soluble tablets	MP 2, 3 and 4
Improving options available for omeprazole in a liquid formulation	UHCW Pharmacist 1 reported concern that only some manufacturers supply a Certificate of Analysis with Specials medicines
"A licensed melatonin dispersible tablet or liquid would be ideal."	BCH pharmacist 1

UHCW Pharmacist 2 gave a pessimistic response with regard to increasing the availability of liquid medicines "they'd all be easier if they were in.. It's not gonna happen."

5.4.4.2.2 Well-accepted medicines

Calpol suspension was idealised as a formulation in three of the four focus groups (nurse, medical practitioner and pharmacist group at UHCW) and described as "the panacea of the world" by UHCW Pharmacist 1. In addition medical practitioner 6 reported "It's a shame all drugs don't taste like Calpol."

Medical practitioner 3 stated her appreciation of the well-accepted liquid medicine Calpol, and following this discussed concern regarding the risk of Calpol overdoses. Nurse 2 proposed a contrasting argument, and discussed the risk of potential Calpol overdoses resulting from children being too fond of medicine flavours:

“I think that if it’s nice they’ll drink more is not really a valid answer,” and “Doesn’t matter what it is, if it fits with what they want to do they’ll do it.” She also provided the example of children opting to drink bleach out of a cupboard.

When compared to its generic equivalents nurse 2 revealed that children have a unanimous preference for Calpol suspension and described the poor palatability of generic paracetamol suspensions.

5.4.4.3 Problems related to medicines administration

5.4.4.3.1 Administration problems with specific medicines

The groups discussed specific examples of medicines administration issues, these varied between the groups.

Gaviscon for breastfeeding mothers was described as a “challenge” (MP 2).

Frequency of dosing was an issue highlighted by medical practitioner 2. Prescribing amoxicillin three times daily instead of penicillin four times daily was discussed as a way to improve adherence.

5.4.4.3.2 Interactions with foodstuffs and sub-optimal drug absorption

The practicality of giving medicines with feeds was discussed by the nurses. The timing of ciprofloxacin administration in relation to feeds was queried by nurse 1. The ability of phenobarbitone to interact with milk was also highlighted in the nurse group (nurse 5).

The UHCW pharmacist group discussed feed interactions with phenytoin and ciprofloxacin (UHCW pharmacists 1 and 2).

Medical practitioner 5 addressed his concern regarding mixing medicines with bottle feeds resulting in sub-dosing from incomplete dose consumption:

“Yes yes all crushed in to a bottle of milk or something, you know you may get a bit of you know debris in the bottle which never gets taken.”

5.4.4.3.3 Medicines manipulation

The groups were encouraged to reveal parent, carer and child feedback regarding the techniques used to facilitate medicines administration or for purpose of giving a specific dose. Additionally, personal advice given to parents on *ad hoc* manipulation techniques was explored. Manipulation techniques reported across the groups are reported in Table 26.

Table 26 Manipulation techniques used to facilitate medicines administration or for the purpose of giving a specific dose as reported in each focus group.

Nurses	Medical practitioners	UHCW Pharmacists	BCH Pharmacists
Yoghurt with crushed medicines (nurse 1).	What parents told them: Epi granules (epilim chronosphere granules) on jam on toast, have in blackcurrant and orange juice (medical practitioner 1's personal advice, not to mix with coke or fizzy drinks).	Creon Micro gastro-resistant granules with a spoonful of breast milk, apple puree or baby rice (UHCW pharmacist 1).	Losec MUPS with squash and juice (provided an appreciation of mixing and potential acidic issues on the active ingredient when prompted) (BCH Pharmacists 2 and 4).
Creon Micro gastro-resistant granules in apple puree to mask texture (nurse 4).	"They'll sometimes volunteer that they put in milk or they put it in orange juice or blackcurrant juice or they crush it in to jam or yoghurt or something like that" (MP 5).	"Ciclosporin you can mix with stuff" (UHCW pharmacist 1).	Topamax sprinkle on foodstuffs (BCH Pharmacists 1 and 3).
Split doses, e.g. provided with antiretrovirals that were making a child physically sick (nurse 1).	Prednisolone soluble tablets mixed with neat Ribena (MP 4).	Grinding tablets and mixing with yoghurt or dissolving in water (mercaptapurine) (UHCW pharmacists 1 and 2).	Before dispersible tablets came out, recommended opening capsules of melatonin or dispersing them in yoghurt (BCH pharmacist 1).
Use strong flavours to mask bad tastes. Examples given: Gastrografin solution masked with Coke (opposing argument to MP 1) or Ribena.	Give a sweet after flucloxacillin (MP 4).	Liquid paraffin and ice-cream recommended as a technique to numb taste buds (UHCW pharmacist 1).	Movicol oral powder advice.. "in apple puree and stuff." Mixing advice is provided in drug information sheets, but is not referenced (BCH pharmacist 3).
In reference to Movicol: "People hide it in their dinners.. their mash potato.." (nurse 5 - reported on what parents do).	Melatonin "I'll always say yoghurt, the advice I would normally give, put it in yoghurt and do that immediately before you go to bed because it denatures before... and don't use it in hot food" (MP 1).	"Stick in a bit of yogh- put it in a bit of banana or something like that you can A slip things down if you've got something that's a bit harder to take" (UHCW pharmacist 1).	
"The Movicol rep says you can put it in to jellies and things" (nurse 5).	Methotrexate and mercaptopurine tablets "I'm sure they must get crushed up those" (MP 4).		

The medical practitioners and nurses revealed more information on the nature of manipulation techniques used by parents to administer medicines to children. When asked if specific foodstuffs were mixed with particular medicines, the answers provided by nurses 5 and 1 were:

“Not x goes with y, just try whatever the child likes.” (nurse 5)

“Whatever the child likes.” (repeated by nurse 1)

In relation to antiretrovirals and mixing with foodstuffs medical practitioner 7 questioned:

“Would you mix them at all?” and added “I think it’s difficult to mix those HIV ones ‘cos the liquid volumes are so high and so disgusting that there’s not much you could mix it with and they’re not small tablets that you could hide in yoghurt or something like that.”

5.4.4.3.3.1 The knowledge of healthcare professionals regarding physicochemical effects of medicines manipulation

Awareness of potentially altering the stability of a drug when using administration techniques was acknowledged across the groups.

Concerns regarding pharmacokinetic effects of a drug following medicines manipulation were most evident in the UHCW pharmacist group.

UHCW pharmacist 1 gave her view on mixing with Ribena as an example:

“You might test it against Ribena but most of the mothers would then actually go and buy Asda’s.. .” and “or you know you buy some cheap one that’s just.. whatever flavour and then the pHs may be different..”

Nurses 1 and 2 discussed their concerns of not knowing what they can safely mix with medicines. The instruction of a pharmacist not to mix omeprazole soluble tablets with hot water as it could risk altering drug pharmacokinetics was revealed by nurse 1.

Medical practitioner 1 discussed that melatonin may denature when mixed in to yoghurt and left for a period of time.

5.4.4.3.3.2 Evidence base for medicines manipulation

The paucity of robust scientific evidence supporting medicines manipulation was revealed by a UHCW pharmacist and a medical practitioner.

UHCW pharmacist 1 discussed the lack of evidence when such manipulation techniques are used. She argued that if there is not a known interaction with food, the drug will inevitably mix with stomach contents anyway and her attitude was to get the medication down in any way possible. Additionally she stated that manipulating medicines prescribed commonly to children would not be recommended.

Medical practitioner 1 acknowledged the lack of evidence for manipulating medicines and discussed advising others of medicines manipulation techniques that had been provided to her.

5.4.4.4 Frequent issues experienced when treating paediatric patients

5.4.4.4.1 Specials medicines, unlicensed medicines and off-label administration

The issues associated with Specials and unlicensed medicines were discussed in all focus groups. The Specials medicines that were discussed are provided in Table 27 below.

Table 27 Specials medicines identified by healthcare professionals.

Specials medicine	Reports of healthcare professionals
Spironolactone liquid	Short expiry highlighted in the nurse group.
Nitrofurantoin suspension, hydroxycarbamide (hydroxyurea) liquid and Albright's solution	MP 4
Phenobarbital liquid	MP 3
Clobazam suspension	MP 1
Tacrolimus liquid	"Heart sink drug" by BCH pharmacist 2. Problems with maintaining continuity of supply and drug bioavailability.
Captopril liquid, furosemide liquid	Various strengths and the risk of inconsistency between formulations from different Specials manufacturers (BCH pharmacist 3). BCH pharmacists 2 and 4 described such risks generally across Specials medicines.

Common issues attributed to the Specials medicines identified by the medical practitioners in Table 27 above were related to medicines supply (e.g. waiting for medicines, GPs unwilling to prescribe), the variety of strengths availability to order, shortened expiry dates and palatability.

5.4.4.4.2 Omeprazole formulations

5.4.4.4.2.1 Omeprazole liquid

Omeprazole liquid Special was mentioned often across the groups. Frequently, the nurses described problems associated with omeprazole including those related to cost (nurse 2 and 3), medicines wastage (nurse 2), medicines supply (nurse 1 and 4) and GPs' unwilling to prescribe (e.g. prescribing often restricted to a named-patient basis) (nurse 5).

The UHCW pharmacist group discussed Specials issues in more depth and revealed shortened expiries and wastage problems. The unavailability of Certificate of Analyses (suggesting limited stability evidence) from some suppliers was discussed by UHCW and BCH pharmacists. The inconsistency of storage conditions of omeprazole liquid was described by the BCH pharmacists.

5.4.4.4.2 Losec MUPS (licensed omeprazole formulation)

Losec MUPS blocking feeding tubes (resulting in feeding tube replacements) and the poor solubility of the granules in sodium bicarbonate were reported (nurse 1, 2, 4 and 5). Such problems were highlighted across the groups (medical practitioner 1, BCH pharmacist 4 and UHCW pharmacist 1).

UHCW pharmacist 1 and BCH pharmacist 2 additionally described the inconvenience of administering the Losec MUPS formulation (i.e. the time taken for the granules to dissolve). Concerns regarding the high bicarbonate load (UHCW pharmacist 1) and risk of administration errors (BCH pharmacist 2) were reported.

5.4.4.4.3 The knowledge and understanding of medical practitioners, pharmacists and parents regarding unlicensed medicines

UHCW pharmacists described how both medical practitioners and parents often lack understanding about Specials medicines, and specifically how medical practitioners do not understand the importance of continuity of supply. The BCH pharmacist group shared similar views on this topic. However, BCH pharmacist 2 gave an opposing argument that sometimes parents are too informed when given a Specials information letter to help their community pharmacist to order the Special. An example was provided, where a parent became obsessed with maintaining a specific Specials brand of ergocalciferol liquid, which was not vital in the professional opinion of BCH pharmacist 2 who discussed the unnecessary difficulties with supply that were encountered.

It was suggested that some community pharmacists “aren’t using their logic” (BCH pharmacist 2) when receiving prescriptions for Specials. BCH Pharmacist 4 agreed with this

and in addition hypothesised that GPs may be fearful and unwilling to change things prescribed by specialists.

In the medical practitioner focus group, the GP participant (MP 3) described first-hand how GPs are advised by PCTs to cut Specials in relation to their budget. Similarly UHCW Pharmacist 1 addressed the influence of money shortages from PCT level on the prescribing of Specials by GPs. In addition she queried whether pharmacists are acting assertively and supplying the readily available licensed products first as often medical practitioners do not specify dosage forms. The lack of consistency between Specials, costing reliant on source, lack of guidance and GP cost issues (influenced by the drug budget from the local PCT) were discussed by the BCH pharmacist group. BCH Pharmacist 3 voiced that multinationals are often unwilling to source beyond their Specials supplier.

As predicted the pharmacists had a strong focus on the problems surrounding Specials medicines, and showed particular concern towards risks of error and inaccurate dosing. Both pharmacist groups discussed the lack of PILs supplied with Specials medicines (UHCW pharmacist 1 and BCH pharmacists 2, 3, and 4). In addition, parental confusion and lack of mathematical skills was given as a potential cause of overdosing in paediatric patients (BCH Pharmacist 1).

Licensing problems with medicines administration via feeding tubes and the associated accuracy and safety issues were discussed frequently by the BCH pharmacists.

5.4.4.4 Extemporaneous dispensing

On the topic of extemporaneous dispensing, UHCW pharmacists compared the more rigorous approach used in hospital pharmacy to that used in community pharmacy. They

perceived that some community pharmacy premises were unsuitable environments for dispensing extemporaneously. The influence of economic issues on staffing levels in hospitals was highlighted. UHCW pharmacist 1 stated “pressure in the hospitals has turned” and revealed that less extemporaneous dispensing is performed in hospital pharmacies.

The BCH pharmacy group revealed a negative attitude towards extemporaneous dispensing in community pharmacies. The view of BCH Pharmacist 3 was that “enough preparations are out there without extemp.” Problems addressed by the group included the preparation work involved and the lack of quality of ingredients (BCH pharmacist 3). BCH Pharmacist 1 discussed that a shortage of time and unsuitable work conditions could be detrimental and thus increases the risk of errors. Deskilling of the workforce across hospital and community pharmacy was identified as a problem by BCH pharmacist 2. BCH Pharmacist 4 spoke about the increased prevalence of extemporaneous dispensing in an allied European country, and compared the higher level of quality control that is implemented.

The nurses recognised problems with the supply of extemporaneously dispensed solutions. These are reported in Table 28 below.

Table 28 Healthcare professional reports of extemporaneously dispensed solutions.

Extemporaneously dispensed medicines	Reports of healthcare professionals
Sodium phosphate solution	Nurses 2, 3, and 5 discussed short expiry resulting in inconvenient and frequent hospital journeys.
Sodium chloride solution	“The solution has no preservative in it” and “you have to keep ordering it every day. Keeping on top of those prescriptions for parents is quite a struggle.” (nurse 4)

5.4.4.5 Parental understanding of medicines

All groups discussed concerns regarding parental understanding. The paucity of information provided on Specials medicines, parents not reading labels on medicines, the lack of

consistency between strengths of formulations ordered from community pharmacies and thus the associated risk of error were reported by the focus group participants. Specific examples were highlighted, parents not understanding the difference between strengths of drugs (UHCW pharmacist 1) and problems with “parents’ mathematical skills” (BCH pharmacist 1).

Examples were revealed suggesting that some parents are unaware that two different medicines can both contain paracetamol:

“I mean parents don’t even know Calpol is paracetamol” (nurse 5)

Nurse 2 added “or they give Medised and that’s got paracetamol in it as well.”

5.4.4.5.1 Educating parents and children about medicines

In the nurse group, the need for parental education was discussed by nurse 1. Additionally Medical practitioner 4 and BCH Pharmacists reinforced the importance of counselling and communicating with parents to improve medicines adherence.

Training and aids used to help children to swallow solid dosage forms were discussed in the nurse and pharmacist groups. BCH Pharmacist 2 discussed the “pill-glide administration aid” used in some epileptic patients following a ketogenic diet. BCH Pharmacist 3 queried if this compliance aid has a placebo effect, and BCH pharmacist 2 agreed, and additionally compared the “pill-glide” cost implication versus the cost of Specials. BCH Pharmacist 1 described pill-swallowing techniques used for HIV patients by a fellow pharmacist:

“She gets sweets of the different sizes of ascending order and it’s basically I’ll swallow this if you swallow that you know they go up in size, so you start off with a tic-tac or something then you sort of go up in size..”

BCH Pharmacist 2 identified a “gap” in the care of patients as they are often not trained to take medicines orally, and BCH Pharmacist 1 agreed.

UHCW pharmacist 1 admitted being unaware of who teaches children to swallow tablets, and then described her knowledge of training used:

“I’ve seen you know.. various training aids to teach children how to swallow tablets on..I can’t remember whether it was the CF trust or what now.. oncology sites.. or the HIV..”

Nurse 4 demonstrated her awareness of the training requirements for swallowing solid dosage forms in Australia:

“Well in Australia they all have to go to a swallowing clinic so they can all swallow their tablets by the time they start school.”

5.4.4.5.2 Social problems and language barriers

UHCW Pharmacist 1 recognised “the disorganisational social problems” and children in “dreadful circumstances” reporting the example of refugee children. She identified that medicines may not be their priority.

Language was a barrier highlighted in the BCH pharmacist group. BCH Pharmacist 2 acknowledged that translators are rarely booked at patient discharge to discuss management at home.

5.4.4.6 Medicines adherence

5.4.4.6.1 The relationship between age of child and dosage form preference

Pharmacists, medical practitioners and nurses reported that dosage form preference is influenced by individual patient choice.

BCH pharmacist 2 revealed that dosage form preference (liquid versus capsules) varies between individual patients taking itraconazole and this should not be predicted. Similarly UHCW pharmacists discussed the variation in dosage form preference across patients, providing the example of a child wanting solid dosage forms (UHCW pharmacist 1) and a 16 year who will only take liquid medicines (UHCW pharmacist 2).

Medical practitioners 4 and 5 also discussed how dosage form preference is unrelated to the age of a child:

“I’ve got a 17 year old who doesn’t like tablets” and “other children who’d much prefer to have a crushed up tablet in some jam than to take any of the syrups” and “it’s really.. patients’ difference. I never guess anymore now, I just ask.” (MP 4)

“It’s not age related really.. a lot of children say they want tablets rather than medicines.” (MP 5)

Medical practitioner 7 discussed the difficulties in administering medicines to HIV positive children and particularly getting them to swallow multiple tablets from the age of three.

5.4.4.6.2 Parental influence on dosage form choice and medicines adherence

The groups contended that parents can influence dosage form choice and medicines adherence in paediatric patients. Reports of parents and carers influencing child adherence were frequently addressed in all groups. This included parents not allowing young people empowerment and also parents not supporting medicines adherence.

Examples given in the medical practitioner group included parents concealing the medicines of an eleven year old oncology patient in a cupboard (MP 4 and 5), and parents being “overprotective,” insisting that a young person still requires liquids, thus demanding a specific Specials formulation (MP 2).

UHCW pharmacist 1 gave her disapproving view on parents handing medicine responsibility to their eleven year old son “he’s just not old enough to do that.”

Examples of parents altering doses of medication uninstructed were provided in the nurse focus group “Yeah parents stop omeprazole I know parents just stop giving it” (nurse 5). Nurse 2 revealed how a mother declared that she would stop administering medicines to her baby following hospital discharge.

The BCH pharmacists discussed parents altering doses if they believe that the medicines are not working, “they even increase it scary” (BCH pharmacist 4). BCH pharmacist 3 reported that a mother with strong opinions regarding her son’s treatment influenced doctors to prescribe a different antibiotic drug.

UHCW pharmacist 1 suggested that adherence may be better when nurses administer medicines owing to the child recognising a different relationship with a nurse compared to their parent or carer. Her response when questioned about demanding parents was that if parents are persistent they get what they want.

5.4.4.6.3 The relationship between age of child, disease status, diagnosis, miscellaneous variants and medicines adherence

BCH pharmacists discussed the effects that age of child, parental influence, perceived severity of chronic condition and an association with perceived disease improvement may have on medicines adherence. BCH pharmacist 2 addressed medicines responsibility at different ages, “toddlers” relying upon parents and “teenagers” having increased responsibility and empowerment for the use of their medicines. She also commented that some children with chronic diseases (reporting patients with CF as an example) discontinue

medicines administration to see what happens even though they understand the importance of taking them. She came to a decision that medicines adherence is likely to be related to the treatment goal of the condition being treated.

BCH pharmacist 4 proposed that non-adherent “teenagers” may be rebelling against “normal life.” She anticipated that if an immediate improvement in condition is seen by a patient that they are more likely to take medicines. However she ended her view with uncertainty on this matter, “I don’t really know.”

Regarding medicines adherence patterns across paediatric oncology patients, UHCW pharmacist 2 perceived that little difference in medicines adherence exists between “teenagers” and parents responsible for administering medicines.

Medical practitioner 4 discussed medicines adherence patterns of different paediatric patients, indicating that “toddlers and teenagers” [negative tone] were deemed to be problematic.

Nurse 4 compared drug naïve and CF patients and thus related adherence to acute versus chronic patients:

“Depends how often child takes medication, for example CF as opposed to a child who comes in with a pneumonia- they won’t be used to medicines at all whereas our children are used to medicines and see the advantages to swallowing a pill rather than having syrup to take.” (nurse 4)

UHCW pharmacist 1 hypothesised that an interesting relationship exists between what children are familiarised with taking and their adherence to medicines. She gave the example of Calpol suspension which may be seen as a “rub and a kiss” by children and

implied that when drug-naïve children are prescribed medicines, they experience different flavours that they are not used to and this can affect medicines adherence.

5.4.4.6.4 Polypharmacy

BCH pharmacist 2 described her views on polypharmacy and rationalising prescribing:

“I think the other thing you end up with chronic conditions as well is people or children with lots of multiple conditions where you get lots of prescribers involved all adding in their own individual bit they all want added in prescribed for different conditions so the poor child then walks away with massive bag-fulls of drugs and sometimes there’s no rationalisation actually could we remove the odd few things to actually encourage them to take it.” (pharmacist 2 BCH)

Medical practitioner 5 proposed that “polypharmacy” patients should be considered. The example group of patients reported was CF patients.

5.4.4.7 Adverse effects of medicines

5.4.4.7.1 Excipients

BCH pharmacist 4 addressed concerns regarding liquid medicines as many are adult medicines that contain certain excipients which are unsuitable for children. Table 29 below details excipients in medicines, identified as problematic by healthcare professionals

Table 29 Problems with excipients in medicines as reported by healthcare professionals.

Excipients	Reports of healthcare professionals
Propylene glycol	BCH pharmacist 4
Sorbitol	BCH pharmacist 4 described the osmotic effect of sorbitol, causing diarrhoea in patients administered medicines through enteral feeding tubes.
Sugars	Causing tooth decay.
Alcohol	Phenobarbital liquid preparation listed in BNFC.

5.4.4.7.2 Adverse effects associated with specific medicines

In the nurse group, ciprofloxacin was associated with “terrible diarrhoea” and azithromycin with behavioural issues.

In the medical practitioner group both Movicol oral powder and nitrofurantoin suspension were reported to cause nausea. Additionally, vomiting was an adverse effect highlighted following consumption of antiretroviral medicines, similarly reflux or vomiting after taking multivitamins.

5.4.4.8 The supply of medicines and liquid measuring devices

5.4.4.8.1 Problems with the supply of medicines

The medical practitioners addressed specific Specials medicines when asked about problems with the supply of medicines (as reported in Table 27). Problems with the supply of additional medicines are reported in Table 30 below.

Table 30 Problems with the supply of medicines reported by healthcare professionals.

Medicines	Reports of healthcare professionals
Antituberculosis medicines and Gastrografin solution	Nurse 4 (Gastrografin solution specified to be difficult to order in community pharmacies).
Reconstituted erythromycin suspension	MP 4

5.4.4.8.2 Problems with the supply of oral syringes and the accuracy of measuring liquid medicines

The nurse focus group highlighted difficulties with obtaining oral syringes for children who were not enterally fed. Nurse 5 reported the reluctance of supply by pharmacists, inferring that this is a financial problem and additionally discussed her concern of numbers being erased from oral syringes as they are frequently re-sterilised. UHCW pharmacist 1 also reported that re-sterilising oral syringes is concerning, and acknowledged the associated risk of inaccurate dosing. She spoke about the lack of oral syringe sizes available in the Drug Tariff “It would be useful if you could get different size syringes on the Drug Tariff though.”

This confirmed her awareness that oral syringes of a specific volume can be prescribed on an NHS prescription.

Medical practitioner 3 addressed the disallowance of prescribing oral syringes on an FP10 prescription and reported her uncertainty as to whether pharmacists are allowed to freely provide oral syringes or if it is out of their own goodwill. Nurse 1 also demonstrated awareness of the problems with obtaining oral syringes, stating that they have to be purchased by parents.

The risk of inaccurate dosing when using a teaspoon to measure liquid medicines was described by UHCW pharmacist 1:

“If you’ve lost your medicine spoon and use a teaspoon that can vary from 3mls to 8mls couldn’t it.”

5.4.4.8.3 The parallel importing of medicines

The pharmacist focus groups discussed parallel imported medicines. Reports provided by pharmacists can be found in Table 31 below.

Table 31 Parallel imported medicines reported by pharmacists.

Medicines	Reports of healthcare professionals
Cephatoxin	BCH pharmacists 1 and 2-(American, although manufactured in India) UHCW pharmacist 1-(imported from Australia).
Clindamycin	BCH Pharmacist 2-(German) UHCW pharmacist 1-(imported from Germany).

Both Pharmacist groups acknowledged protocols for handling parallel imported medicines which detailed the need for translation of the PIL.

5.4.4.9 Medication errors in pharmacies and GP practices

5.4.4.9.1 Standardising the labelling of liquid medicines

The UHCW pharmacist group emphasised the importance of standardising the labelling of liquid medicines:

“It would all be easier if they could formulate it so the calculations were easier so they were always 10milligrams in 5ml... 100milligrams in 5ml or something” “and if they were all labelled in 5mls or in a ml.” (UHCW pharmacist 1)

UHCW pharmacist 2 agreed with this suggestion.

5.4.4.9.2 Medicine selection errors at GP practices

The risk of medication errors at GP practices associated with untrained staff selecting incorrect medicines information on computer systems was addressed by BCH pharmacist 3.

5.4.4.10 Problems with medicines at school

Reports of how medicines are dealt with in the school environment were similar across the focus groups. Reports are provided in Table 32 below.

Table 32 Healthcare professional reports of how medicines are dealt with in the school environment.

Comments provided on how medicines are dealt with at school	Reporting healthcare professionals
Medicines should be prescribed where possible to be administered outside of the school day.	UHCW pharmacist 1 and MP 5
School policy regarding medicines depends on the school concerned (i.e. varies between institutions).	MP 3 and MP 4
Some schools have refused to allow medicines on the premises.	Nurse 2
Children taking chronic medication would not be denied of their medicines at school. Prescribed medicines can be administered during school hours if they are labelled and added that schools often expect parents to administer medicines during the school day.	UHCW pharmacist 1
Schools are not allowed to deny children their medicines and the acceptance of medicines is improving in schools.	Nurse 4

UHCW pharmacist 1 queried whether teachers have time to give children medicines and also questioned whether children requiring antibiotics at regular intervals should attend school.

5.5 Discussion

5.5.1 Oral formulation-related barriers to medicines administration

Commonly reported oral formulation-related barriers to the acceptance of medicines in children across the four focus groups included taste, texture, size of solid dosage form, and volume. Taste was the most prevalent oral formulation-related problem highlighted across the groups. Flucloxacillin solution was perceived by all healthcare professional groups to be disliked by children due to its taste. Baguley and co-workers (2012) similarly reported that oral flucloxacillin is often considered unpalatable by children and suggested conducting a taste-test with an individual child prior to prescribing flucloxacillin solution.

Chloral hydrate solution, prednisolone soluble tablets and Movicol oral powder were all highlighted with respect to taste in two of the focus groups. Similar findings were reported in studies by Chung and co-workers (2000) (oral chloral hydrate), and Lucas-Bouwman and co-workers (2001) (taste of prednisolone oral solution superior to crushed tablets). However, a study conducted by Pashankar and co-workers (2003) found that Movicol oral powder was preferred by children when compared to alternative treatments for chronic constipation.

Gastrografin solution, Oramorph solution, Septrin paediatric suspension, rifampicin suspension, Kaletra solution, nitrofurantoin Special suspension, clarithromycin suspension and generic paracetamol suspension were all associated with taste problems in an individual focus group. Powers (1996) similarly acknowledged the poor palatability of clarithromycin

suspension. All medicines reported with taste problems in the focus groups were perceived by participants to cause problems with adherence.

All healthcare professional groups reported texture as a barrier to medicines administration; particularly amongst children with learning disabilities. Field and co-workers (2003) defined five feeding problems (including one related to the texture of foodstuffs) and explored pre-disposing factors to these problems. Over one quarter of children suffering from Down's syndrome, autism or cerebral palsy refused to eat food textures that were considered to be developmentally appropriate (Field *et al.*, 2003). Feeding problems (including those related to texture) should be considered carefully by prescribers prior to making prescribing decisions to treat such patients as the consistency of some medicines (including those reported in Table 21) may be difficult to ingest.

The nurses reported the widest variety of oral formulation-related barriers to medicines administration including those that affect sensory perceptions (colour and smell). They shared an in-depth knowledge on oral formulation-related barriers to medicines administration that the medical practitioners and pharmacists did not discuss, highlighting the importance of conducting focus groups with different healthcare professionals. This plethora of knowledge mirrors the 'hands-on' experience that nurses have on administering medicines to children. Limited studies have revealed the impact that the appearance and/or smell of a medicine may have on medicines acceptance in children as discussed in Chapter 4.

Across the focus groups, the large sizes of antiretroviral tablets were associated with swallowing problems in children. Several studies investigating children suffering from HIV support these findings and have reported the negative attitudes of children regarding the

size of antiretroviral tablets (Czyzewski *et al.*, 2000, Garvie *et al.*, 2007, Gibb *et al.*, 2003, Marhefka *et al.*, 2004, Paranthaman *et al.*, 2009, Reddington *et al.*, 2000, Roberts, 2005). Additionally, large dose volumes were perceived to be a barrier to medicines administration and examples of formulations with large dose volumes were volunteered across the groups.

Owing to the paucity of research investigating the variety of oral formulation-related barriers to medicines administration, further studies are warranted to explore the perspectives of healthcare professionals, parents, carers and children (see Chapter 6).

5.5.2 Future medicines for children

Reports of issues with bad-tasting medicines were ubiquitous when probing the participants for their views on ideal medicine improvements. Improving the taste of flucloxacillin solution was considered important in all of the groups. This finding was anticipated, owing to the negative attitudes regarding the taste of flucloxacillin solution in this study and reported in literature (as revealed earlier in section 5.5.1).

The nurses and medical practitioners prioritised the improvement of a variety of bad-tasting medicines as reported in section 5.4.4.2.1. However, the pharmacists perceived that an improvement to Specials medicines would be ideal. Pharmacists felt that providing Certificates of Analyses to assure the safety and stability of Specials medicines and also licensing some medicines not commercially available in child appropriate formulations should be considered in order to improve medicines for children. Improving Specials medicines was not reported as an ideal medicine improvement by the nurses or medical practitioners, suggesting that this problem is not such a concern for them. Supporting these findings, Elkins-Daukes and co-workers (2005) investigated the opinions of GPs regarding off-

label prescribing and found that less than 15% of GPs admitted to specific concerns when prescribing off-label, including the risk of adverse effects and unevaluated efficacy.

Calpol suspension was described positively across all groups. Pharmaceutical companies should be fully aware of medicines that are generally well-accepted by the paediatric population. Although the excipients used to procure Calpol suspension are not suitable for taste-masking all drugs, where similar flavourings are appropriate these should be taste-tested for use in the paediatric population. Alternatively, pharmaceutical companies should provide information on safe and effective manipulation techniques (as discussed earlier) based on flavours preferred by the general paediatric population when applying to license medicines, as is set out in the PIP (European Commission, 2008).

5.5.3 Problems related to medicines administration

All groups discussed *ad hoc* manipulation techniques that had been reported to them by parents and carers and also those that they recommend to parents and carers to facilitate the administration of medicines to children (see Table 26). Manipulation techniques were discussed in detail by the nurses. The nurses gave examples of medicines manipulation on wards and also highlighted how parents administer medicines at home.

The medical practitioners also volunteered information on manipulation techniques. The examples were provided by the medical practitioner with a role in the community, responsible for children who suffer from delayed learning and physical development. This finding suggests that medical practitioners caring for children with delayed learning and physical development are more aware of the difficulties associated with administering

medicines to this patient population and are more likely to recommend medicine manipulation techniques.

Pharmacists reported the advice that they provide to parents when supplying medicines. Often hospital pharmacists will not see follow-up patients as continuation of therapeutic treatment is often supplied by community pharmacies. Inevitably, these pharmacists were less aware of how parents manipulate medicines to aid medicines administration in a domiciliary environment.

Pharmacists showed more concern with regard to the risks of *ad hoc* medicines manipulation (e.g. mixing medicines with foodstuffs) compared to nurses and medical practitioners who demonstrated some awareness of the possible effects of reducing the stability of a medicine. Pharmacists demonstrated a better level of understanding than the other groups with regard to the risks of medicines manipulation. The potential pharmacokinetic effects of manipulating medicines were discussed and examples were provided, including the effects of mixing medicines with foodstuffs of differing acidities (i.e. Ribena versus supermarkets own equivalent). Although the medical practitioners provided less knowledge of the risks of manipulating medicines, the risk of incomplete consumption of a dose of medicine when mixed with milk feeds was highlighted.

Focus group findings indicate that paediatric pharmacists' knowledge on risks of medicines manipulation was better than that of the allied healthcare professionals in this study. This suggests that the knowledge of paediatric pharmacists should be used to guide and educate healthcare professionals when prescribing or administering medicines in paediatric patients. To support this, the knowledge and education of paediatric pharmacists should be addressed

to ensure that they have optimal understanding of key scientific properties that may affect the dissolution and disintegration of a dosage form, properties including the fat and dairy-protein content, pH and solubility of foodstuffs (Akram and Mullen, 2012). Such factors, in addition to food affecting gastric emptying rate, risk altering the bioavailability of a drug (Bowles *et al.*, 2010).

Findings of the focus groups indicate that the participating healthcare professionals were unaware of the level of evidence supporting various *ad hoc* manipulation techniques (see section 5.4.4.3.3.2). Laboratory work is warranted to provide a robust scientific evidence base to support safe and effective medicines manipulation. This should be used to inform guidelines detailing suitable manipulation techniques for parents and healthcare professionals administering medicines to children. User-friendly manipulation guidance based on this evidence would be a useful addition to formulation monographs in the BNFC.

A study by Akram and Mullen (2012) used questionnaires and interviews to explore the knowledge and understanding of nurses regarding mixing medicines with foodstuffs. Similar to the present study, Akram and Mullen (2012) observed that the majority of nurses were unaware of potential drug stability and degradation issues when performing *ad hoc* administration techniques and additionally some nurses were not conscious of a possible impact upon clinical outcome. Akram and Mullen (2012) highlighted that further studies are needed to investigate the knowledge of healthcare professionals involved in the medical care of children.

The risks of medicines interacting (through binding) with nutritional feeds and the potential effects on drug absorption were discussed by the pharmacists and nurses. Nurses declared

their uncertainty regarding how and when to administer the calcium binding drug ciprofloxacin, highlighting that advice is needed when administering medicines and nutritional feeds to optimise therapy. More scientific evidence, based on laboratory work investigating interactions between medicines and nutritional feeds (i.e. identifying potential insoluble complex formation) should be used to direct and standardise pharmaceutical advice. It would be useful to translate this scientific evidence in to appropriate sources for nurses and parents and carers to guide the order and timing of administration of medicines to children with complex regimens to optimise the therapeutic effects of medicines.

5.5.4 Frequent issues experienced when treating paediatric patients, the supply of medicines and liquid measuring devices

The problems with Specials medicines and unlicensed medicines were discussed in all groups and extensively amongst the pharmacists. Omeprazole liquid Special was frequently discussed with regard to several issues including cost. This finding was supported by a BBC news article revealing a variety of costs for omeprazole liquid (see section 2.4.5). Additionally, with regards to Specials prescribing, cost was mentioned by the nurses, pharmacists and the GP with respect to prescribing influence of the PCT. The wide ranging costs of Specials medicines have been a major issue. The recent procurement of the new Specials Tariff should help to reduce such problems although not all Specials formulations are included in this as discussed in introduction chapter, see section 2.4.5.

Losec MUPS is an omeprazole formulation that is often prescribed instead of omeprazole Specials liquid. Reports of Losec MUPS granules blocking NG tubes were highlighted at least once in each focus group. This is an issue that needs to be addressed as NG/PEG tube

blockages may lead to patient discomfort and additionally, replacements which are costly. The prevalence of reported problems with Losec MUPS indicates that an alternative, suitable paediatric formulation is required. This finding should direct and prioritise future laboratory work in identifying a formulation (i.e. an alternative proton pump inhibitor) that is appropriate for administering to children and also those with more complex medical needs (e.g. children fitted with an NG or PEG tube).

Problems with Specials medicines were a main focus of the pharmacist groups. Pharmacists demonstrated their increased knowledge, awareness and enthusiasm regarding Specials medicines. They discussed a variety of problems surrounding Specials which they frequently experienced first-hand (e.g. unpredictable bioequivalence between different Specials medicines) compared to the medical practitioners and nurses. The medical practitioners seemed to have the least understanding and knowledge of the depth of issues with Specials and tended to identify Specials medicines and issues with supply. The medical practitioner group suggested that some pharmacists may not be aware that certain medicines can be ordered and query whether pharmacists remind patients about the shortened expiries of Specials medicines and the need to frequently re-order. The nurses expressed their concern towards extemporaneously dispensed products and the inconvenience of frequent journeys to hospital pharmacy.

Several studies have identified differences in the knowledge on Specials medicines between allied healthcare professionals. A study at UHCW investigating the Specials knowledge of medical practitioners, nurses and hospital pharmacists found that pharmacists had a better understanding of Specials terminology than nurses and medical practitioners (Venables *et*

al., 2012b). There was a particularly poor understanding of the term 'Special'. In total, 50% of paediatric consultants were able to define it adequately but no doctor in training was able to (see Appendix 11 for published abstract of presented conference poster, reporting key study findings).

Similarly, Mukattash and co-workers (2011a) reported a significant difference between healthcare professionals regarding familiarity with unlicensed medicines/prescribing off-label. Community pharmacists were most familiar with the term unlicensed medicines (93.0%) whilst consultant paediatricians were most familiar with the term off-label (83.3%). A further study conducted with hospital-based paediatricians demonstrated that although over 69% of respondents understood the term off-label, only 28% actually knew when they were prescribing off-label (Mukattash *et al.*, 2011b).

Further investigation is necessary to address the education and support that is needed to improve knowledge of unlicensed medicines, Specials and off-label prescribing amongst healthcare professionals. Educating doctors and allied healthcare professionals on the appropriate use of Specials medicines at degree or equivalent level is fundamental to improving their understanding of unlicensed medicines and optimising safe and cost-effective prescribing practices. Implementing e-learning for healthcare professionals could be a useful approach to addressing education and understanding. It is necessary to ensure that pharmacists are knowledgeable of all licensed alternatives to Specials medicines and are able to support prescribers and reinforce excellent prescribing practice and protocols. Additionally, educating healthcare professionals should improve counselling advice provided to parents, carers and young people.

Regarding Specials medicines, a better understanding of the alternative formulations readily available, costing, supply, stability, and accuracy of dosing is required. It is also important that the continuity of supply of Specials medicines is monitored as medicines sourced from different Specials manufacturers may not be bioequivalent (see section 2.4.4).

Additionally, the supply of non-Specials medicines needs to be considered and effective communication between healthcare professional groups should improve awareness of problems that are experienced with the supply of medicines from pharmaceutical companies. Feedback to medical practitioners should be delivered in a standardised manner by pharmacists and patients should be well-informed of possible delays with medicines supply. Results from this study suggest that pharmacists have a greater knowledge on the extent of supply problems (including the parallel importing of medicines) compared to allied healthcare professionals, therefore increasing the understanding of medical practitioners and nurses on the extent of supply problems may be useful to improve medicines supply, thus optimise patient care.

Difficulty in freely obtaining oral syringes on the NHS was highlighted by all of the healthcare professional populations. Study findings indicate that the Government should address NHS funding in this area. Pharmacists highlighted the risks of using inaccurate measuring devices. Household teaspoons can vary between 2ml and 10ml and thus using a teaspoon could result in a significant underdose or overdose (McKenzie, 1981). Pharmacists should be ensuring that the correct dosing instrument is supplied to all patients and that counselling is provided to parents and carers to assure accurate measurement of a dose.

5.5.5 Parental understanding of medicines

Parental influence on medicines adherence and also limited parental understanding of medicines featured in all groups. The nurses emphasised the need for parental education, whilst the BCH pharmacist group acknowledged the limited time available to counsel patients effectively, resulting in their reliance upon nursing staff. Incorporating appropriate information in to clinic appointments for parents, carers and children could improve the safety and effectiveness of medicines use and also reduce medicines non-adherence.

Improving time organisation to permit pharmacists to counsel patients effectively could help to minimise problems that result from poor parental understanding. Pharmacists identified that staff shortages were a barrier to counselling patients. Government funding bodies need to consider this when calculating financial budgets available to the NHS. Parental education may be valuable in improving general medicines knowledge in order to prevent harm (e.g. educating parents on medicines containing paracetamol to minimise paracetamol overdose risk). This was discussed by nurses in this study and also identified by the RPS in a recent report (RPS, 2012).

‘Pill-swallowing training’ for groups of patients with specific chronic conditions was discussed by the nurses and pharmacists. Mandatory ‘Pill-swallowing training’ for all children of a specific age was reported to be implemented in Australia. Several studies investigating solid dosage form training have found improvements in swallowing abilities amongst children diagnosed with HIV (Czyzewski *et al.*, 2000, Garvie *et al.*, 2007).

Further investigation is needed to determine if such training may be of significant benefit to children suffering from other chronic conditions. This may help to reduce difficulties with

tablet size that have been highlighted (e.g. antiretroviral tablets). Additionally, training to teach children how to swallow solid dosage forms may support the use of novel formulations, (e.g. mini-tabs (Spomer *et al.*, 2012, Thomson *et al.*, 2009)) in paediatric patients that would not generally be prescribed a solid dosage form until they are older.

The UHCW pharmacist group highlighted the plethora of social issues that prevail in the domiciliary setting, implying that medicines adherence is not always prioritised in some social circumstances. Similarly, studies have found that family circumstances can influence medicines adherence in children (see section 2.2).

5.5.6 Medicines adherence

Findings from the focus groups suggest that dosage form preference is not correlated to the age of a patient, yet based on an individual's choice. The EMA (EMA, 2006) reports a matrix of general acceptability of different routes and dosage forms in relation to child age, yet acknowledges that children of the same age may prefer different dosage forms. Dosage form choice of an individual child may be based on several factors including properties of the formulation, child's illness, child's mood, the influence of their caregivers, cultural and/or regional habits (EMA, 2006). The influence of these factors on choice of dosage form requires further investigation.

Examples of parents influencing medicines adherence were reported across the focus groups. These included some parents not allowing young people empowerment over their medicines and others not supporting medicines adherence.

Study reports of the medical practitioners and pharmacists indicate that within the paediatric age spectrum young patients and “teenagers” tend to be less adherent to medicines. Several studies have concluded that adolescents are more likely to be non-adherent than younger children when prescribed medicines to treat HIV, immunosuppression (post-transplant), CF and oncology (Beck *et al.*, 1980, Brownbridge and Fielding, 1994, Elise *et al.*, 2005, Feinstein *et al.*, 2005, Gudas *et al.*, 1991, Patterson, 1985, Reddington *et al.*, 2000, Serrano-Ikkos *et al.*, 1998, S.D. Smith *et al.*, 1979, Tebbi *et al.*, 1986).

Suggestions that drug naïve patients may be less likely to adhere to medicines than patients with chronic conditions were commonly reported across the focus groups. A proposition was made by the BCH pharmacist group that if an improvement in a child’s condition is perceived, medicines adherence is more likely. The pharmacists voiced their views, implying that adherence to medicines may depend upon the specific condition being treated. The balance of treatment benefit versus risk on medicines adherence has been similarly acknowledged in a study conducted in adults with chronic conditions, including cancer and asthma (Horne and Weinman, 1999).

The value of rationalising medicines in children who are prescribed multiple medicines (polypharmacy) was proposed by a medical practitioner and BCH pharmacist. Polypharmacy was investigated further in the semi-structured interviews conducted with parents, carers and young people in section 6.7.5.

To improve childrens’ understanding of chronic conditions and the importance of adhering to medicines regularly, encouraging and promoting the participation of children at groups such as the YPG at BCH may be useful. The BCH YPG encourages young people to interact

and learn about medicines and chronic conditions. Participation in the group gives young people the opportunity to ask questions about medicines they are taking and what adverse effects they may experience.

The importance of medicines adherence should be thoroughly explained to parents and children especially in circumstances where an improvement of a chronic condition is not apparent. This may help to discourage parents, carers and young people from discontinuing medicines without consulting healthcare professionals and through this improve medicines adherence. A cross-sectional survey of parents of 622 children with asthma found an association between parental beliefs about medicines and adherence, thus supports the need for parental education to promote adherence (Conn *et al.*, 2007).

5.5.7 Adverse effects of medicines

The medical practitioners and nurses identified key adverse effects of medicines with which they were familiar. Future work should investigate whether incorporating education for parents, carers and young people within clinic sessions, on common and minor adverse effects of medicines to support patients and manage their expectations of medicines has the potential to improve adherence.

Concerns regarding the safety of excipients were at the forefront of the BCH pharmacist session, with specific reference to propylene glycol, alcohol, sweeteners and sugars. The draft guideline on pharmaceutical development of medicines for paediatric use (EMA, 2013) reinforced the requirement for pharmaceutical companies to carefully select excipients when formulating medicines for children. The final decision to include an excipient should be evaluated using a benefit to risk ratio of the end pharmaceutical product (GRIP, 2013).

Often, the concentrations of excipients included in a medicine are not explicitly provided by pharmaceutical companies. Several studies have investigated the risks of using propylene glycol in intravenous formulations administered to neonates, but there is a paucity of research on the potential risks that flavouring agents (containing excipients such as propylene glycol) added to oral medicines may have on paediatric patients (GRIP, 2013).

Protocols should be in place to alert healthcare professionals to excipients that could be harmful to the paediatric population when consumed in large quantities. This should additionally highlight medicines containing excipients that are inappropriate for regular administration to children and also direct healthcare professionals to alternative, safer choices. Where such alternative options are not currently available for a specific drug, pharmaceutical companies should prioritise the development of novel, age-appropriate formulations or provide robust evidence supporting mixing medicines with foodstuffs as discussed in the EMA (2013) draft guideline.

5.5.8 Medication errors in pharmacies and GP practices

The UHCW pharmacists perceived that the labelling of liquid medicines should be standardised, for example, labelling all liquid medicines as the weight of drug in the same volume (i.e. Xmg in 1ml). Both healthcare professionals and parents can become confused when different strengths are printed on medicine labels and examples of this were provided by the UHCW pharmacists. Through standardising the labelling of liquid medicines it may be possible to minimise some dosing errors. Studies are required to investigate if standardising the labelling of liquid medicines could significantly improve patient safety. It is prudent that

medicines labelling guidance provided to pharmaceutical companies when applying for a Marketing Authorisation is addressed imminently.

The risk of medication selection errors at GP practices was identified in the UHCW pharmacist focus group. This finding suggests that safeguarding measures and staff training need to be addressed across GP practices.

5.5.9 Problems with medicines at school

Problems with medicines at school were reported across the groups. Unanimous reports suggested that medicines should be prescribed to be administered outside of the school day (where this is possible). Reports of some schools refusing to accept responsibility for medicines suggests that medicines policies are not adopted uniformly across schools. The National Service Framework for Children, Young People and Maternity Services 2004 (DOH, 2004) reinforced the need to support children requiring medicines in schools. The requirement for school staff to receive adequate support, advice and training regarding medicines was reported. Additionally the framework emphasised the need for policies to guide safe storage, supply and administration of medicines in schools (DOH, 2004).

Several studies have investigated medicine policies in schools. A survey of London primary school head teachers by Wong and co-workers (2004) found that 95% of participants reported having a medication policy for young people in school. However an earlier study by Pugh and co-workers (1995) reported that only 40% of primary schools and all secondary schools had a policy in place for asthma treatment.

Medicines adherence during school hours may be sub-optimal if schools do not support medicines administration. Omitting doses of medicines during the school day could have a significant impact on clinical outcome, therefore it is critical that medicines administration is addressed correctly in schools. This is especially important for paediatric patients suffering with chronic conditions and those requiring vital acute medicines.

5.5.10 Discussion of limitations

Recruitment to focus groups was conducted in a structured manner. Logistics created the greatest problem when recruiting participants. Time constraints resulting from staff shortages restricted the availability of healthcare professionals and affected study recruitment. A weakness of the focus group study was the low recruitment rate in the UHCW pharmacist group, as inevitably a focus group does not run correctly when only two participants are present. This focus group represented more a nominal group. However the information gathered from the UHCW pharmacist focus group in collaboration with the BCH pharmacist group widened the scope of pharmacist views in this study. Pharmacists from these institutions are required to meet the same standards with regards to training and it was not anticipated that the practice of pharmacy would differ significantly between BCH and UHCW.

Although latecomers have the potential to disrupt the flow of a focus group, this did not cause a problem in this study as discussion was not interrupted. Supplementary data was collected from those attending late because of clinic commitments.

The perspectives of healthcare professionals with experience in community and hospital settings were explored across the focus groups. It was necessary to investigate the issues

encountered in domiciliary and hospital environments in order to understand the scope of problems that present when prescribing, dispensing and administering medicines to paediatric patients. It would be useful in future studies to explore the perspectives of further hospital doctors, nurses and pharmacists and additionally those working solely in the community sector to gather a wider perspective. This would increase the validity of views across the healthcare sectors.

The varied specialist interests and level of expertise of healthcare professionals in each group was advantageous to this study and permitted the collaboration of both common and unique data within and between the groups. The study aimed to investigate problems with oral medicines prescribed for many different chronic conditions, thus the variety of specialist interests of participating healthcare professionals was pertinent to this study.

Inevitably some healthcare professionals participating from the same institution were known to each other. This could be seen as a potential limitation as it is thought that participants may be more inclined to speak in a 'socially accepted' manner (i.e. less honestly) (Rabiee, 2004). As the nature of this focus group study was not perceived to be threatening, it is unlikely that participants would have contributed in this way.

The study was conducted at two sites in the West Midlands, therefore it cannot be generalised and viewed as a nationwide perspective. The focus groups were used to scope the research and inform design of the semi-structured interviews with parents, carers and young people (Chapter 6).

5.6 Conclusion

In summary, this focus group study has identified a large number of issues perceived by some healthcare professionals to cause problems when administering oral medicines to children that are not always considered when using medicines in children.

Some of the problems highlighted with children's medicines had been anticipated, including those surrounding poor palatability, however some problems were more novel. These included the limited awareness of medical practitioners with regard to risks associated with medicines manipulation (e.g. mixing medicines with foodstuffs) and issues surrounding Specials medicines.

Collaboration between doctors, nurses and pharmacists is essential to optimise patient care. Communication is crucial and each healthcare professional group should be utilised for the wealth of their knowledge, for example it may be beneficial for medical practitioners and nurses to seek advice from hospital pharmacists on drug-foodstuff incompatibilities as findings suggest that their knowledge is greater. However, the findings of this study suggest that a paucity of scientific evidence is available to support the many *ad hoc* manipulation techniques regularly used. Review of medicines manipulation data available in literature confirmed that a robust scientific evidence base is lacking.

It is evident that medical practitioners require more information when prescribing medicines to ensure supply, clinical effectiveness and to maximise cost efficiency. This information should include guidance on Specials prescribing, supported by a small-scale study on knowledge of Specials at UHCW which found that in particular, the existing knowledge of junior doctors regarding Specials medicines requires attention (Venables *et al.*, 2012b).

Addressing the education of healthcare professionals involved in prescribing, dispensing and administering oral medicines to children and additionally counselling provided to parents, carers and paediatric patients will be invaluable to improving the therapeutic treatment of paediatric patients. Protocols detailing best practice guidance need to be developed based on the problems identified in this study.

An understanding of problems with oral medicines from the perspectives of key healthcare professionals involved in the supply and administration of medicines to children was required prior to exploring problems perceived by parents, carers and children to inform interview design. It was anticipated that the focus groups would reveal if a paradox exists between problems with oral medicines reported by healthcare professionals, and parents, carers and young people. The views of parents, carers and children are reported in the consecutive Chapter, 6.

6 DETERMINING BARRIERS TO ADMINISTERING ORAL MEDICINES TO PAEDIATRIC PATIENTS FROM THE PERSPECTIVES OF PARENTS, CARERS AND PATIENTS

6.1 Objectives

The primary aims of this study were to identify the prevalence and nature of oral formulation-related barriers to medicines administration and in addition, *ad hoc* manipulation techniques used to administer medicines to children in the domiciliary setting. The primary outcomes of this study were to identify medicines commonly associated with reports of oral formulation-related barriers to administration and to establish if correlations exist between oral formulation-related barriers to medicines administration and child refusal of medicines.

6.2 Background

Structured discussions through West Midlands Medicines for Children Research Network (WM-MCRN) activities with parents and carers of children of differing social and ethnic backgrounds and suffering from chronic conditions, generated positive feedback regarding the importance of examining problems with medicines (see Appendix 1).

Chapter 4 identified that limited studies have investigated oral formulation-related barriers to medicines administration across chronic conditions in paediatric patients. Systematic review included studies that were conducted in children prescribed a narrow spectrum of medications. The methodological tools used across these studies included the Medical

Adherence Measure (MAM) adherence interview (Ingerski *et al.*, 2010, Zelikovsky *et al.*, 2008), Treatment Interview Protocol (TIP) (Marhefka *et al.*, 2004), and Pediatric Acquired immuno-deficiency syndrome Clinical Trials Group (PACTG) questionnaire (NIAID). Detailed reporting of results of oral-formulation related barriers to medicines adherence in the included review studies was generally limited.

The focus groups with healthcare professionals (see Chapter 5) highlighted obstacles to medicines administration and adherence in children. This warranted further exploration in to these problems from the perspectives of children and their parents/carers.

Manipulation techniques used by nurses to administer medicines to children have been investigated as discussed earlier in section 2.5.2 (Akram and Mullen, 2012, Richey *et al.*, 2011, Skwierczynski and Conroy, 2008). However, studies have not explored the prevalence of manipulation of medicines performed by parents, carers and young people in the domiciliary environment.

6.3 Setting

UHCW was the chosen study setting for conducting this research. UHCW is a large teaching hospital offering a wide range of secondary and tertiary paediatric services. The hospital covers a child population of 66000, with approximately 3866 new paediatric patients seen in paediatric clinics each year and 8035 paediatric patients having ongoing follow-up in paediatric outpatient clinics (statistics based on 2011-2012 data). The catchment area covers inner city Coventry and rural Warwickshire, thus a diverse ethnic and socio-economic patient group attends the hospital.

6.4 Data collection technique

Malim and Birch (1996) state that the balance and compromise for research is to maximise information gained with ease of analysis. A semi-structured interview tool was selected for this study to obtain the appropriate balance in data collection and subsequent analysis.

A semi-structured interview approach allows the interviewer to initially define the area to be explored, and then diversify to pursue a response in more detail if necessary (Pope and Mays, 1999). The sequence of questions can be changed as required, whilst facilitating data collection in a reproducible fashion. Both quantitative and qualitative data can be collected within semi-structured interviews.

During a semi-structured interview, the interviewer is able to show empathy and alter phrasing of questions in order to elicit detailed and considered responses from participants. These benefits have been previously shown to provide more detailed outputs (Gillham, 2000) and an increased response rate (Chambers, 2000) compared to paper-based questionnaires. A criticism of using an interview as a collection tool is the phenomenon of patients telling the interviewer what they want to hear, i.e. what they think would be socially acceptable as a response and hence there is risk of collection of 'false' data (Butz, 2006).

Successful interviewing techniques were reviewed. Techniques included listening and not asking too many questions else the interviewee may expect the interviewer to take lead, not asking more than one question at once (to avoid confusion), not to be nervous, to wait for a response (give time) and not to interrupt or teach (Morse and Field, 1995). In addition it was

important to conduct the research in a safe setting and to obtain a good interaction with interviewee to maximise interview effectiveness (Chirban, 1996).

Green and Thorogood (2004) suggest an order for the interview: introduce interviewer by name, discuss the aims of the interview, provide a reminder that interviewee can stop at any point without penalty and offer an opportunity to ask any questions. Special care and consideration is required when collecting more sensitive (i.e. background and ethics) data to avoid recording information not required for analysis. It was deemed most appropriate to ask sensitive questions towards the end of the interview, proceeding questions that could be answered more easily (Pope and Mays, 1999).

Inviting a wide variety of participants with different backgrounds is vital to minimise bias. Interviewer bias also requires consideration as the social and ethnic characteristics of the interviewer could affect responses (Chambers, 2000).

6.5 Methods

Semi-structured face-to-face interviews with parents/carers and young people were designed to explore oral formulation-related barriers to medicines administration, and identify the influence of barriers on child acceptance of paediatric medicines, thus adherence.

6.5.1 Design of semi-structured interview

The aims and objectives of this study (see Chapter 3) were used to inform template design of the interview questions to provide the relevant output. A copy of the semi-structured

interview prompt sheet for parent/guardian can be found in Appendix 12. These were modified appropriately for young people.

6.5.1.1 Barriers to medicines administration

The study questions were designed based on methodological tools used in previous studies: MAM (Ingerski *et al.*, 2010, Zelikovsky *et al.*, 2008), TIP (Marhefka *et al.*, 2004) and PACTG (NIAID) to identify the oral formulation-related barriers to medicines administration.

The medication module in the MAM adherence interview explored ‘obstacles that could result in non-adherence (e.g. forgetting, refuse, hard to swallow, etc.)’ This methodology was used in a study of 56 young people aged between 11 and 18 years on a renal transplant list (Zelikovsky *et al.*, 2008) and also in a study by Ingerski and co-workers (2010) conducted in 74 young people aged between 13 and 17 years diagnosed with either Crohn’s disease or ulcerative colitis and their carers. Marhefka and co-workers (2004) designed the TIP to identify regimen knowledge, potential adherence barriers and adherence problems. The TIP was completed by 51 primary carers of HIV-infected children aged between 2 and 12 years.

The National Institute of Allergy and Infectious diseases (NIAID) PACTG developed a structured questionnaire exploring general barriers to adherence to antiretroviral regimens, adapted for different age groups. In the PACTG questionnaire a Likert scale was used to provide a greater range of options than a simple yes or no response. For example, 0= never a problem 1= hardly ever a problem (1 - 2x a month) 2= frequent problem (1 - 2x a week) 3= almost always a problem (more than 3x a week). The PACTG tool has been used in several studies (Bunupuradah *et al.*, 2006, Davies *et al.*, 2008, Farley *et al.*, 2003, Pliapat *et al.*, 2007, Van Dyke *et al.*, 2002) as reported in Table 2.

The MAM adherence interview (Ingerski *et al.*, 2010, Zelikovsky *et al.*, 2008) and TIP (Marhefka *et al.*, 2004) elicit qualitative responses, whilst the PACTG questionnaire (NIAID) is more structured and includes a checklist of barriers. A limitation of asking open-ended questions revolves around phrasing of the questions on barriers to adherence. In the methodology of the TIP (Marhefka *et al.*, 2004), example barriers are provided to the interviewee when delivering the question, this could influence bias. Such methodological tools have only been used in narrow patient populations (transplant patients and HIV-infected patients) and not across different chronic conditions.

Methodological tools used to collect data on the obstacles to medicines administration (MAM (Ingerski *et al.*, 2010, Zelikovsky *et al.*, 2008), TIP (Marhefka *et al.*, 2004) and PACTG (NIAID)) informed design of the explorative, open-ended questions within the interview of the present study. Questions were asked for each medicine to detect oral formulation-related issues. This approach to data collection enabled detailed information about barriers to medicines administration to be determined.

In addition to determining barriers to medicines administration, in order to understand non-adherence behaviours it was decided that an estimation of respondents revealing full adherence and also intentional versus unintentional non-adherence behaviours would be calculated. Paediatric adherence studies have utilised modified adult adherence measures that have not been validated for use in children. Morisky and co-workers (1986) validated a structured four-item self-reported adherence measure of blood pressure control in adults which they concluded can be easily included in clinic visits; this was developed further to an eight item scale with improved sensitivity (Morisky *et al.*, 2008).

The Morisky questions (Morisky *et al.*, 2008, Morisky *et al.*, 1986) were designed to be asked generally across a group of medicines (i.e. patients taking blood pressure medicines) and to give a composite score. In isolation, these closed questions were insufficient to meet the aims of the present study as they do not explore the obstacles to medicines administration. For example, Morisky and co-workers (1986) did not ask about the refusal of specific medicines, but used the question, 'Are you careless at times about taking your medicine?' this question would not provide sufficient information within this study. However, adaptation of the Morisky questions directed the design of the questions on adherence.

Questions (1 - 5) used to detect barriers to medicines adherence in this study are reported below. The questions were designed to be delivered to parents and carers (and were re-worded appropriately when delivered to 12-18 year olds):

1. Have you ever forgotten to give this medicine? Yes/No
2. Has the child in your care ever refused (chosen not) to take the medicine? Yes/No
3. When the child in your care is feeling better do you stop giving this medicine? Yes/No
4. If the child in your care is feeling worse do you stop giving the medicine? Yes/No
5. Is there any other reason that your child is unable to take this medicine? Yes/No (a positive response led to the question, for what reason/s?).

In a self-reported adherence study conducted in 260 HIV infected adults, Pratt and co-workers (2001) found that self-reporting accuracy improved when reporting missed doses as opposed to doses taken and also when patients were asked about time periods of less than one month. A further study conducted in 34 HIV infected adults found that the number of doses omitted in the preceding three days (self-reported) was correlated to missed doses

measured by electronic medication monitoring and pill-count (Bangsberg *et al.*, 2000). Doses omitted in the preceding three days (Van Dyke *et al.*, 2002) and up to three weeks (Goode *et al.*, 2003) have been used in paediatric studies investigating oral formulation-related barriers to medicines administration.

The present study interview was designed to record if doses were missed in the week prior to interview. This time period was chosen as it was decided to be sufficient to detect if a once weekly medication was missed with the intention of also maintaining accurate memory recall. Appropriate questions were designed to collect this information, and further questions investigating when a medicine was last missed were also used (see sections 6.5.1.1.3 and 6.5.1.1.5).

Although general adherence behaviour was explored, reports of children refusing a dose of medicine were of primary importance in scope of the present project aims. Forgetting to administer a dose of medicine (leading to dose omission) and other reasons for missing medicines were considered, but were secondary outcomes of this study.

Open-ended questions were placed between the closed questions on adherence when designing the interview prompt sheets (see Appendix 12) to make the participants feel at ease, in order to optimise the accuracy of information collected.

The interview prompt sheets were used as a guide to elicit data on medicines administered to a child, name, formulation type, route, dose, frequency, problems with interrupting daily lives, forgetting, any manipulations made to the medicine to facilitate medicines administration or for purpose of dosing, problems with acceptance attributed to the

properties of oral formulations, how happily the child takes the medicine and medicines refusal, any adverse effects experienced, further barriers to adherence, problems with the supply of medicines and with PILs. In addition, general problems with medicines at school and techniques used for reminding to administer medicines were investigated.

The questions delivered to parents and carers are provided within the themed sections reported below. These questions were re-worded appropriately for young people (12-18 years) participating in the study. Questions using Likert scales were also designed based on those within the PACTG module 2 questionnaire (NIAID) so that parents/carers/young people could rate their responses to some questions.

6.5.1.1.1 Oral formulation-related barriers to medicines administration

The open-ended questions listed below were designed to identify obstacles to the administration of oral medicines to children (including unfavourable organoleptic and physical properties):

- If you could change one thing about this medicine, or how child takes it what would this be?

A prompt was delivered to participant:

- How would you like it (the medicine) to be changed if you could decide?

Where children were too young to verbally describe problems i.e. with the taste, parental judgement was used. Behavioural descriptions including wry face, shrugging shoulders, vomiting or spitting the medicine out, were used as indicators of unfavourable organoleptic properties (EMEA 2006).

6.5.1.1.2 Medicines Manipulation

The *ad hoc* manipulation of a medicine was defined by consensus of RV with a Professor of Clinical Pharmacy and a Consultant Paediatrician. Relevant definitions for terminology used to design the interview tool are listed below.

- Gold standard = medicine delivered to the route of administration without manipulation
- Manipulation of a medicine = medicine physically adapted to facilitate medicines administration or for the purpose of giving a specific dose.

The study defined terminology related to gold standard administration and the manipulation of medicines were not explained to study participants as it was anticipated that this may reduce reporting accuracy and underestimate the prevalence of medicines manipulation across the study population.

The questions on manipulation of a medicine are reported below:

- Do you give medicine in a different way? Prompt used, mix with food or juice, Crush or cut tablet or open capsule or dilute medication? Yes/No
- Prompt used: how do you get the child in your care to take this once you get it home? Prompt used, exactly like it is or does it need to be dissolved?
- If yes, how often? 1= Always 2= most of the time 3= not sure 4= rarely

6.5.1.1.3 Medicines Refusal

It was necessary to investigate medicines refusal to determine if oral formulation-related barriers influenced medicines refusal by children.

Refusal of a medicine was defined for the purpose of this study as complete omission of a dose by intent on at least one occasion, including spitting the dose back out, and/or closing the mouth. The questions asked:

- Has the child in your care ever refused (chosen not) to take the medicine? Yes/No
- If yes, how many times in last week? 1 2 3 4 5 6 7
- When was the last time they refused to take the medicine?

Resisting the administration of a medicine was not considered to be refusal. Disliking a medicine as a result of oral formulation properties (i.e. organoleptic or physical) may not necessarily cause refusal, but instead poor acceptability and may result in child resistance. This often requires increased parent or carer persuasion and persistence in order to prevent dose omissions. Interruption of a dosing schedule may result from child resistance. Dosing at precise time intervals may be crucial for some regimens and delaying doses may have significant implications on the clinical response of a drug.

6.5.1.1.4 Child acceptance of medicines

An indication of how well children accept medicines was explored based on a Likert scale assessment:

- How often is child happy to take this medicine? 1= Always 2= most of the time 3= not sure 4= rarely 5= never.

6.5.1.1.5 Forgetting to administer medicines

Forgetting to administer a medicine was defined as complete omission of a dose on at least one occasion, resulting from unintentional memory lapse at the time of administration. The questions designed are listed below:

- Have you ever forgotten to give this medicine? Yes/No
- If yes, how many times in last week? 1 2 3 4 5 6 7
- When was the last time you forgot? Yesterday, 2 days ago, 3 days ago etc.

Forgetting to administer a dose of a medicine resulting in delayed administration was not considered a missed dose for the purpose of this study, providing that the delayed dose was administered before the next dose was due to be administered.

6.5.1.1.6 Reminding systems for administering medicines

Reminding techniques are often useful to help parents/carers and young people to administer medicines regularly and also at the correct dosing times. The following question was designed to prompt participants to report techniques used to remember to administer medicines:

- How do you remember to administer medicines?

Prompt was delivered:

- What reminding system do you use?

6.5.1.1.7 Intentional discontinuation of medicines

Parents, carers or children may choose to discontinue the administration of medicines unilaterally (i.e. without the advice of a healthcare professional). Medicines may be discontinued when a child is feeling better or worse, or when parents or carers perceive this.

The questions that were used are listed below:

- When the child in your care is feeling better do you stop giving the medicine? Yes/No
- If the child in your care is feeling worse do you stop giving the medicine? Yes/No.

6.5.1.1.8 Adverse effects and treatment effectiveness of medicines

Adverse effects of medicines may contribute to treatment discontinuation. A question was designed to determine the prevalence and nature of adverse effects of medicines experienced by children:

- Does/has the child in your care experienced side effects? Yes/No.
- Can you please describe to me.. Prompt with sickness, headache, pain, rash?

A further question with a Likert scale response was designed to evaluate the perceptions of parents, carers regarding treatment effectiveness of medicines.

- How often do you feel that the medicine makes the child in your care better?
1= Always 2=most of the time 3=not sure 4=rarely 5=never.

6.5.1.1.9 Additional barriers to medicines adherence and medicines adherence status

Barriers to medicines adherence were defined as reasons for omitting doses of medicines.

To identify barriers to medicines adherence in addition to refusing, forgetting and discontinuing medicines, the following question was used:

- Is there any other reason that your child is unable to take this medicine? Yes/No
- If yes, for what reason/s?

An indication of participants reporting unintentional and intentional barriers to adherence was determined from reports of refusing, forgetting, discontinuing and additional reasons for omitting doses of medicines.

6.5.1.1.10 Issues surrounding the supply of medicines

It was necessary to explore any problems experienced by parents, carers and young people when obtaining medicines in order to develop a detailed understanding of the range and extent of problems encountered. The questions that were delivered are reported below:

- Do you have any problems getting this medicine in hospital/community pharmacies?

Yes/No

- If yes, what problems?

6.5.1.1.11 Problems with PILs

The information provided in PILs corresponds to the licensed use of a medicine. A question was designed to investigate how well parents, carers and young people use and understand

PILs:

- Do you feel that the information you get is in plain English and clear/easy to understand? Yes/No

Appropriate terminology was used to obtain participant understanding. Prompts to the “leaflet in the medicine box” were provided by RV. It was anticipated that participants may report on other sources of information (e.g. information provided by healthcare professionals).

6.5.1.1.12 Problems with medicines at school

In order to explore how well medicines are accepted in schools, the following questions were asked:

- Do you have any problems with medicines at school? Yes/No

- Prompt used, are teachers happy to store medicines safely and give out medicines?

A further question to evaluate if participants perceived that teachers and social staff require more information on medicines was asked:

- Do you think that teachers and other school staff should be given more information on medicines? Yes/No.

6.5.2 Ethical approval to conduct semi-structured interviews with patients and their parents

Once the initial design was complete, information sheets, consent forms, posters and supporting documents were produced (including a detailed research protocol and simplified flowchart - see Appendix 13).

The development of all study information sheets involved active consultation with the UHCW Youth Council with representation from age-appropriate individuals and parents and carers. The assent and consent forms were designed using template examples provided in NPSA (2009) guidance and ethically approved MCRN trials.

An application was made to the Research Ethics Committee (REC) through the Integrated Research Application System (IRAS). The submission to the South Birmingham REC was completed on the 14th May 2010. An appointment was allocated by the South Birmingham REC on the 15th June 2010 to review the study application. Ethical approval was granted on the 8th July 2010 (REC no 10/H1207/47), see Appendix 14.

6.5.3 Delivery of the semi-structured interview

It was necessary to ensure that questions were delivered using a layman approach, (Gillham, 2000) thus collaboration with the consumer liaison team was crucial in the early design stages. The YPG at BCH provided positive, constructive feedback when asked to review the drafted interview questions in a pilot session using qualitative focus groups on the 14th November 2009. During the session the children were split in to small groups according to age range (under 9 years, 9-12 years and over 12 years), and asked questions from the age-appropriate drafted template in order to gather their views on this study. Their views and feedback were incorporated in to the final study documents.

Empathy from the interviewer was an important aspect within this study to provide reassurance to parents, carers and patients that their responses would not affect their clinical care. Statements to reassure participants that they could answer honestly without fear of blame were delivered by RV during the interview. Such statements included that RV would not “report back to doctors that medicines have not been taken as instructed” and also “everyone is human and humans sometimes forget.” However, study participants were informed that if a dangerous practice was identified that could put someone at harm this would be reported confidentially to the medical practitioner responsible for treating the child.

6.5.3.1 Study populations

Interview strategies were developed for :

1. Parents and carers of children taking long-term medication for a chronic condition

2. Young people aged between 12-18 years taking long-term medication for a chronic condition.

Study interviews were conducted with parents or carers (if legal guardians) of children or young people. The opportunity to assent and participate alone was given to 12-16 year olds providing parent or carer consent was also obtained. Young people over 16 years of age were permitted to consent alone and encouraged to discuss the study with a parent or legal guardian before providing consent.

6.5.4 Identification and recruitment to participate in semi-structured interviews

Target recruitment was 300 children taking long-term medicines for a chronic condition. The aim was to sample approximately 100 parents or carers of children or young people in each age group (0-4 years, 5-11 years, and 12-18 years) in order to examine how results vary in relation to age of a child. As no other study has investigated oral formulation-related barriers to medicines administration in a paediatric population suffering from various chronic conditions, this sample size was calculated based on detecting the difference in medicines adherence between the three age groups. The study was powered to detect a difference of 20 percentage points between the three age groups with alpha of 5% and power of 80% (see Appendix 15 for statistical advice from Research Design Service - RDS). For the purpose of the power calculation it was assumed that similar power would be achieved for the other outcomes and factors in this study.

It was intended that the children would have a variety of chronic conditions (e.g. epilepsy, CF, neoplasms, cardiac disorders, endocrine disorders, tuberculosis, HIV, renal diseases,

rheumatological diseases and survivors of neonatal intensive care). It was anticipated that some of the children would have specific problems related to their route of medicines administration e.g. fitted with an NG or PEG tube.

Many of the children were attending specialist paediatric outpatient clinics at UHCW. There was a scheduled approach to accessing patients at these clinics on a rotating basis to ensure wide coverage of the target patient population. Inpatients with chronic conditions were also recruited to this study to minimise the risk of missing patients who were hospitalised during the study period.

Attendance at UHCW outpatient sessions was planned at least two weeks in advance. Lists of follow-up patients due to attend identified clinics were retrieved using the hospital patient booking information system in order to identify all patients potentially eligible for study inclusion. A letter of invitation (see Appendix 16) to participate in the study was posted out to potential participants, to arrive at least 24 hours prior to their outpatient appointment, (generally one week before). The invitation letter also contained age-appropriate information sheets (see Appendix 16 for parent/guardian version) explaining the present study. On arrival at outpatient department, families were asked if they had received the study information and whether they would be interested in participating.

Inpatient participants were identified on the morning after being admitted on to a paediatric ward, providing that they met the defined inclusion criteria (see Table 33). Appropriate information sheets were provided and a minimum of 24 hours was allowed for the potential participants to decide whether they wished to participate.

Following agreement to participate and checks to ensure that the study inclusion criteria were met, the consent and assent forms (see Appendix 17) were completed as defined in GCP. Written consent was witnessed by RV.

Following a positive consent/assent process, the interview was conducted by RV. The responses were recorded on the data recording template sheets (see Appendix 18 for parent/guardian version). The data recording template sheets included patient hospital numbers and were held confidentially and securely at UHCW. Hospital numbers were added to a database in order to reduce the risk of duplicating interviews at UHCW.

Interviews conducted with inpatients were identical to those conducted in the outpatient department. All Interviews took a maximum of 45 minutes to complete and were conducted in a private room in the paediatric outpatient department or behind a curtained bay on the wards, to maximise participant confidentiality and create a comfortable environment. Outpatient interviews were conducted either before or after outpatient appointments, ensuring minimal disruption to the running of clinics. The option to arrange a mutually agreeable alternative date was offered to families for whom participating at outpatient appointment was inconvenient.

6.5.4.1 Inclusion and exclusion criteria for recruiting participants

Studies included in Chapter 4 investigated patients prescribed a narrow spectrum of medicines. The inclusion criteria for this study (as provided in Table 33 below) included a more widened target population as children were not recruited based on a specific chronic condition.

Table 33 Inclusion and exclusion criteria for recruiting participants to the study.

Inclusion	Exclusion
0-<18years (pre-term to young person)	≥18 years
Parents/carers of children ranging from pre-term up to 18 years	Parent/carer unable or unwilling to give consent
If 12-17 years must also agree to take part. Must read and sign assent form once read and understood information	Young person unable or unwilling to give consent (unless unable to consent and parent/carer provides consent)
Chronic condition classed as any state requiring long term (study defined as > 1 month) therapy with medicines	Had chronic condition likely to be long term for < 1 month
Diagnosed with condition at least one month previous to inclusion	A short completed illness lasting less than one month
Receiving at least one medicinal product	Where not receiving at least one medicinal product (e.g. just having physiotherapy but not taking medicines)
Outpatients and Inpatients	Patients who do not have follow-up appointments in a secondary care environment, and only utilise the primary care service
Main carer/ parent/young person (whichever may be completing) needs to read and understand and speak English or have someone with them to translate (Generally, patients/parents/carers requiring a translator are booked one for whilst at outpatient clinic or during hospitalisation, we would endeavour to utilise this translator).	Where main carer/parent/young person does not read and understand and speak English and has no-one with them to translate.

Where carer is reported, s/he must have legal guardian status.

6.5.5 Data analysis

6.5.5.1 Introduction to data analysis and software

The collated quantitative data was analysed using a statistical program (IBM SPSS 20). All data was analysed confidentially, and the outcomes of the analyses reported anonymously. Qualitative data arising from the interviews was coded and analysed thematically with the aid of QSR NVivo 8, applying the same strategy used to analyse the Focus Groups (see section 5.3.8).

6.5.5.2 Qualitative data analysis

Utilising a simple frame-work analysis approach, themes were defined and formed a coding spine analogous to that described in section 5.3.8.1.

This frame-work analysis approach was used to code the qualitative responses retrieved from open-ended questions investigating oral formulation-related barriers to medicines administration (including unfavourable properties of oral formulations), other formulation and administration-related problems, *ad hoc* manipulation techniques used to administer medicines and also for reports of additional barriers to medicines adherence.

6.5.5.3 Statistical data analysis

Review of the initial aims and objectives of this study (see Chapter 3) identified five key binary outcomes:

- Reporting manipulation of a medicine
- Reporting refusal of a dose of medicine on at least one occasion
- Reporting refusal of a dose of medicine within 6 months prior to interview
- Reporting forgetting to administer a dose of medicine on at least one occasion
- Reporting forgetting to administer a dose of medicine within 6 months prior to interview

Quantitative analysis based on these five key binary outcomes for medicines administered by the participants in the study was proposed. The methods of data analysis used required that, for each category of a factor under consideration, there was at least one positive, and one negative outcome. For example, when considering the effect of gender on forgetting

doses, there needed to be at least one male patient who had reported forgetting a dose, and one who had not. Where this was not the case, then it was not possible to calculate odds ratios, and any statistical models produced would not converge, resulting in unreliable results. For this reason, the reports of forgetting and refusing doses of medicines in the week prior to interview were not included in the statistical analysis, due to the small frequency at which they were recorded.

Results of forgetting and refusing to administer doses of medicines in the previous six months were derived from the open-ended questions enquiring when a medicine was last forgotten or refused (see sections 6.5.1.1.3 and 6.5.1.1.5). An assumption was made that a six month period would not alter the age range in which the patient was stratified at the time of interview.

All data was entered in to IBM SPSS 20 so that both patient and medicine-specific variables could be converted into categorical variables. Patient data was stratified according to the patient and participant variables and medicine-specific variables listed in Tables 34 and 35 below.

Table 34 Stratification of patient and participant variables into categories.

Patient and participant variables	Categories
Age band of patient at time of interview	0-4y, 5-11y, 12-18y, split according to pre-school, primary school and secondary school age ranges.
Type of patient	Inpatient or Outpatient
Gender	Male or Female
Health-related need of guardian (included medical conditions, problems with eyesight, hearing)	yes, no, not applicable (n/a) (n/a category was excluded for this analysis)
English first language	yes, no
Additional Educational needs of child	yes, no, n/a (n/a category was excluded for this analysis)
Attendance at mainstream school	yes, no, n/a (n/a category was excluded for this analysis)
Ethnicity	Regrouped and coded into two categories, white and any other ethnic group
Age band at diagnosis	Regrouped according to BNFC recognised prescribing age bands, less than 1 month, 1 month- 2 years, 2 years -12 years, 12 years -18 years
Number of current prescribed oral medicines	1, 2, ≥ 3
Multiple health conditions	yes, no
Other health-related need of patient (additional to medical condition including feeding problems, problems with eyesight, physical/mental impairment)	yes, no
Patient had PEG/NG tube fitted	yes, no
Who is responsible for administering medicines	Recoded into groups with individual responsibility and shared responsibility: child, child plus parent/guardian/other, parent/guardian/other
The Index of Multiple Deprivation (IMD) score 2010	Variable grouped based on the quartiles in the data: <11.5, 11.5-19.8, 19.9-31.9, 32+

Logistic models require at least one positive and negative response within each categorical variable otherwise it is not possible to fit such a model. As a result of this, variables were grouped and recoded accordingly. Re-grouping was also used for variables with too many categorical groups of uneven proportions.

The Index of Multiple Deprivation 2010 (IMD 2010) score is a measure of multiple deprivation. This value encompasses 38 indicators that cover a range of economic, social and housing issues, giving a single deprivation score for each lower super output area (LSOA) in England. Each area can be related to another according to deprivation score (Lad, 2011). The higher the IMD 2010 score, the greater the deprivation.

Table 35 Stratification of medicine-specific variables into categories.

Medicine-specific variables	Categories
Formulation type of medicine	Regrouped to liquid, tablet or capsule, and other-granules, powders, soluble tabs and melts as too many categories with small numbers were present for analysis to run correctly.
BNFC Chapter	Chapters 1-6, 8, 9, omitting chapter 7, 10 and medicines not featuring in any of the BNFC chapters as small samples would not permit model to run. For BNFC chapters (see Appendix 19).
Specials medicine	yes/no.
Oral formulation-related barriers to medicines administration: Taste (taste, aftertaste/lack of taste) Size of solid dosage form or aversion to/difficulty swallowing Texture (texture, consistency, thickness) Volume or quantity Colour/appearance Smell Other formulation and administration problems	yes/no.
Frequency of dosing	Regrouped to less than once daily- i.e. monthly/weekly/alternate daily, once daily, twice daily, three times or more daily (omitting 'when required' medicines).

Logistic models require at least one positive and negative response within each categorical variable otherwise it is not possible to fit such a model. As a result of this, variables were grouped and recoded accordingly. Re-grouping was also used for variables with too many categorical groups of uneven proportions.

Binary logistic models were employed with each of the five key binary outcomes reported earlier in this section. These were set as dependent variables. Data analysis was performed on an individual medicine level, thus allowed for each medicine taken by a patient to be analysed separately, rather than just considering their response to medicines as a whole. It also allowed comparisons to be made between medicine-specific variables (e.g. different medicine groups and forms), which are not possible on a patient level. However, it also raised the issue of non-independence in the data, since there were likely to be inter-correlations between the responses to medicines taken by an individual patient (i.e. if they refuse one medicine, then they are more likely to refuse another).

In order to account for this, univariable generalised estimating equations were used. These are statistical models which adjust for inter-correlation within outcomes from the same subject. The univariable analysis did not control for potential relationships between variable factors, therefore multivariable analysis was conducted using the combination of variable factors found to be significant ($p < 0.05$) for the five key binary outcomes in the univariable models. The variables used to form the multivariable logistic regression are highlighted in Appendix 20.

Throughout the results section, the multivariable analysis results are reported. Some variables had to be recoded to enable some multivariable models to run as analysis is only possible if there is at least one positive and one negative outcome for each category of an independent variable. Where recoding was necessary this information is provided in the appropriate results sections.

6.5.5.3.1 Spearman's correlation test

It was hypothesised that properties of oral formulations including taste, texture, volume or quantity colour and smell could be interrelated. A Spearman's correlation test was used to identify relationships between these properties based on the interview reports.

6.5.6 Ethical requirements of semi-structured interview data

6.5.6.1 Ethical storage of semi-structured interview data

Access to consent forms, assent forms and paper-based data recording templates were restricted to the immediate research team at all times and stored in designated locked filing cabinets in a locked MCRN office at UHCW. Consent and assent forms were stored

separately to paper-based data recording template sheets in a separate, locked filing cabinet.

All information transferred on to the designated study encrypted laptop had restricted password protected access and was only available to the immediate research team. Data transfer on to the study laptop was completed in a secure office at UHCW. The data was analysed by RV at University on the same encrypted laptop on which the data was recorded. The laptop was retained securely in a locked office, within a locked cabinet at University when not in use. The key was kept securely by RV.

6.5.6.2 Confidentiality and ethical issues

All information was held confidentially by the research team. It was hypothesised that the interview would not be disturbing or contentious, but participants were reminded to put forward any questions or concerns before or after the interview. Participants were able to freely withdraw from the study at any point in time, and were advised before opting to consent that a decision to withdraw from the study would not affect their care.

6.6 Results of semi-structured interviews

6.6.1 Identification and recruitment to semi-structured interviews

A total of 1559 study invitation letters were sent out by post (1448/1559) or handed out on the paediatric wards (111/1559) to potential recruits during the study period, between November 2010 and February 2012. Table 36 below reports the frequency of clinics targeted for this study (n=191).

Table 36 Frequency of clinics targeted during November 2010 and February 2012.

Clinic	Frequency of clinics targeted during study period
Allergy	1
Asthma/ respiratory	13
Cardiology	4
Cystic Fibrosis	9
Diabetes	5
Endocrinology	14
Epilepsy	12
Gastroenterology	18
HIV	4
Oncology	10
General paediatrics	48
Neonatal	32
Orthopaedic	3
Renal	7
Rheumatology	9
Sickle cell anaemia	2

In total, 280 participants consented to the study. There were 483 patients that did not meet study criteria (majority not prescribed medicines for at least one month) and 47 subjects declined to participate in the study. Reasons for choosing not to participate included a parent who did not want to fill out personal information on the consent form, a family with social issues, difficulty with an autistic young person in clinic and a parent who could not read or write in English so had not understood the study information sheet. The majority of participants opting not to participate in the study did not provide a reason and were mostly young people.

The remaining 749 patients included:

- Patients that 'did not attend' (DNA) clinic
- Parents who had phoned before clinic appointment to cancel a patient's appointment and classed as 'unable to attend' (UTA) clinic
- Patients that were missed whilst interviewing other subjects or restricted by time

- Those requiring more time to read study information properly and decide (postal mail was delayed in some cases).

Two planned clinic days were missed due to unforeseen circumstances.

Of the 280 subjects that consented to this study, 278/280 participants (211 parents/carers and 67 adolescents) completed the study. One young person decided to discontinue participation in the study and one parent did not complete any questions on medicines administration. Of the medicines currently prescribed at the time of interview, 79% (542/682) were oral medicines, and 8% (41/542) of these were identified as Specials medicines.

The information collected on currently prescribed oral medicines was most valuable and relevant to the present study as formulation-related barriers pertinent to this study were those associated with oral medicines. For 91% (252/278) of children in this study, an orally-ingestible medicine was prescribed. The remaining 26 patients were not prescribed any orally-ingestible medicines. Data collected from these 26 patients has been excluded from subsequent analyses.

In the results and discussion sections of this chapter, young people, parents and carers answering each question are reported as respondents.

6.6.2 Demographic results of 252 children

6.6.2.1 Participant response rates for patient data

Figure 8 below shows participant response rates for patient data.

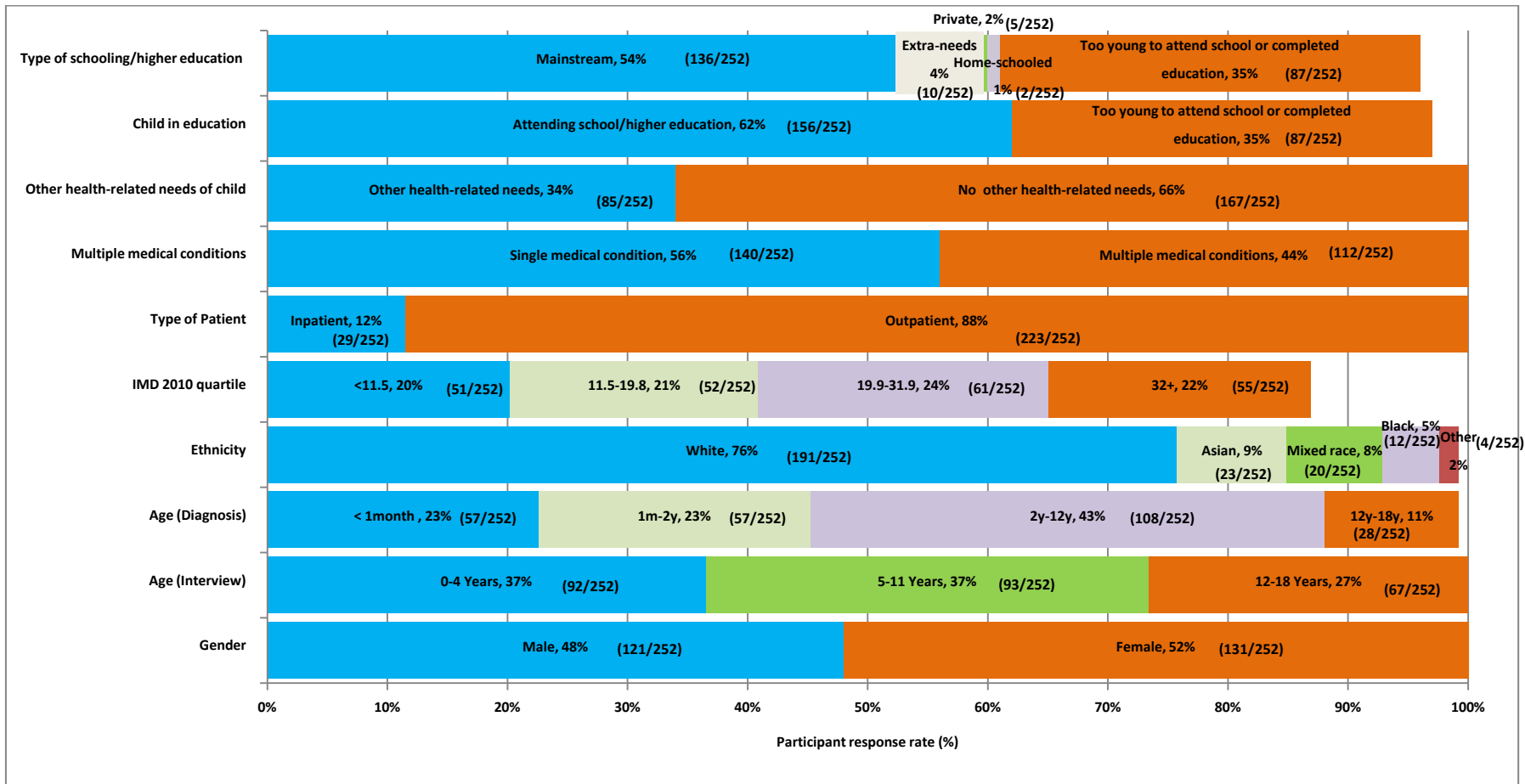


Figure 8 A histogram displaying participant response rates for patient data.

Uncoloured sections of bars represent missing data.

6.6.2.1.1 Patients with NG or PEG tubes

Nine patients utilised NG tubes (either for feeds or medicines) and five patients had PEG tubes fitted at the time of study participation.

6.6.2.2 Main chronic condition

The frequency of children with each main condition is provided in Table 37 below.

Table 37 The frequency of children diagnosed with the main chronic conditions listed.

Main chronic condition	Frequency of children
Gastro-intestinal disorder (chronic constipation, Crohn's, celiac disease, colitis, vomiting)	44
Neoplasm (sarcomas, lymphomas, metastatic disease)	15
Epilepsy	43
Cerebral palsy	3
Chronic allergies	8
Oesophageal Reflux	10
Cystic Fibrosis	13
Systemic Lupus Erythematosus (SLE) and uveitis	14
HIV	4
Growth problems	5
Thyroid condition	19
Blood related disorder	18
Other genetic disorders	2
Asthma	15
Renal disease	27
Cardiac	4
Diabetes Type 1	1
Chronic fatigue Syndrome	2
Chronic migraine	2
Other (autism, scleroderma, chronic dermatological condition).	3

6.6.2.3 Participant response rates for participant data

Figure 9 below displays participant response rates to questions regarding participant data.

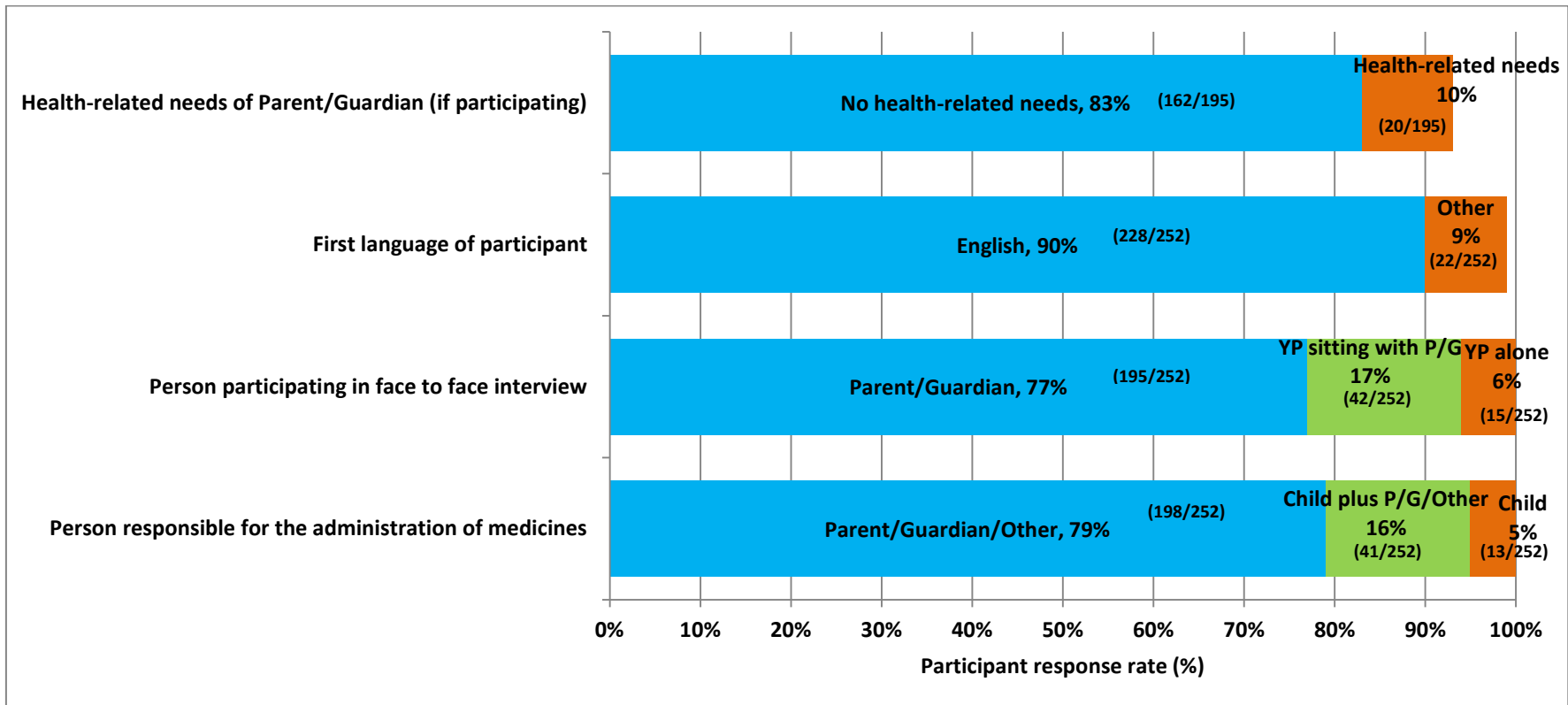


Figure 9 A histogram displaying participant response rates for participant data.

Uncoloured sections of bars represent missing data.

6.6.3 Medicines data for 252 children

The frequency of medicines prescribed and purchased (i.e. over the counter – OTC medicines, herbal medicines, vitamins, minerals and dietary supplements) were identified and then stratified according to age range of child at interview. The total number of medicines taken by the 252 patients was calculated. The results are reported in Table 38 below.

Table 38 The frequency of medicines prescribed and purchased stratified by child age range (0-4, 5-11 and 12-18 years).

Age group	0-4y (n=92)	5-11y (n=93)	12-18y (n=67)	Total in 252 patients
Total number of currently prescribed medicines (including feeds, thickening agents, vitamins etc)	228	236	174	638
Total number of OTC medicines administered	75	77	46	198
Total number of vitamins, minerals and supplements purchased	9	16	7	32
Total number of herbal medicines purchased	1	0	1	2
Total number of dietary supplements purchased	0	1	0	1
Total number of medicines, vitamins, minerals and supplements taken	313	330	228	871

Of the medicines currently prescribed, 85% (542/638) were oral medicines. The frequency of oral formulation types prescribed across child age ranges at interview is provided in Table 39 below.

Table 39 The frequency of oral formulation types prescribed across child age ranges (0-4y, 5-11y, 12-18y).

Age group	0-4y (n=92)	5-11y (n=93)	12-18y (n=67)	Total in 252 patients
Liquids	130	86	36	252
Tablets or capsules	20	61	96	177
Other (granules, powders, soluble tablets and melts)	49	47	17	113
Totals	199	194	149	542

6.6.3.1 Response rates for interview questions

Owing to the nature of the semi-structured flexible design and also restricted time to interview participants in the clinic environment, not all study questions were delivered to all participants or asked for all oral medicines prescribed to each patient (see Figures 10 and 11 below for missing data, represented by uncoloured sections of bars). This applies throughout the results, analysis and discussion sections of this chapter.

Response rates for questions are reported appropriately (i.e. on a participant/individual medicine level or both) according to the nature of the question. Question response rates for participants and medicines are reported in Figures 10 and 11 below. The narrative that follows, discusses the response rates shown in these Figures.

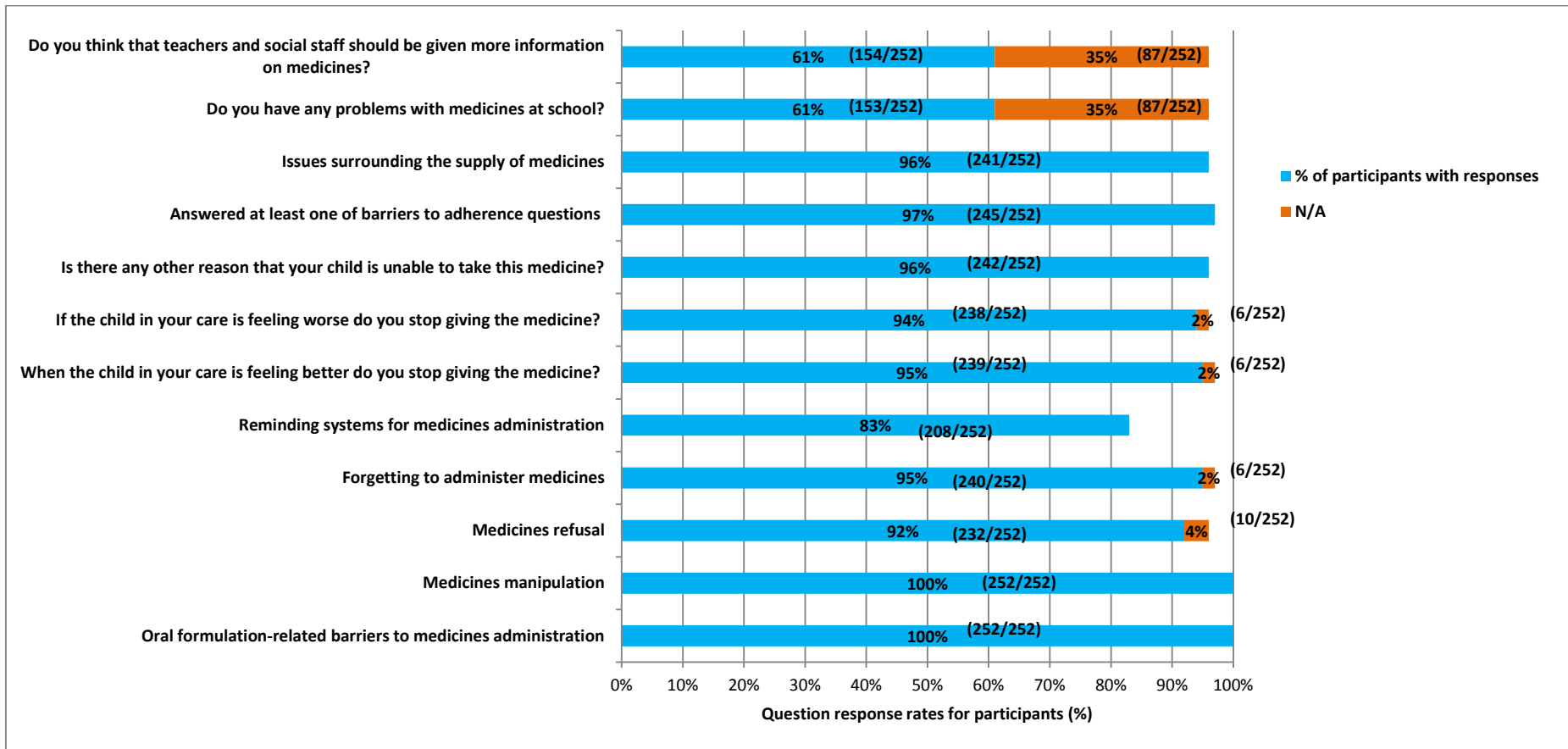


Figure 10 Question response rates for participants.

Uncoloured sections of bars represent missing data.

N/A= where question is not applicable, see narrative that follows for discussion of this.

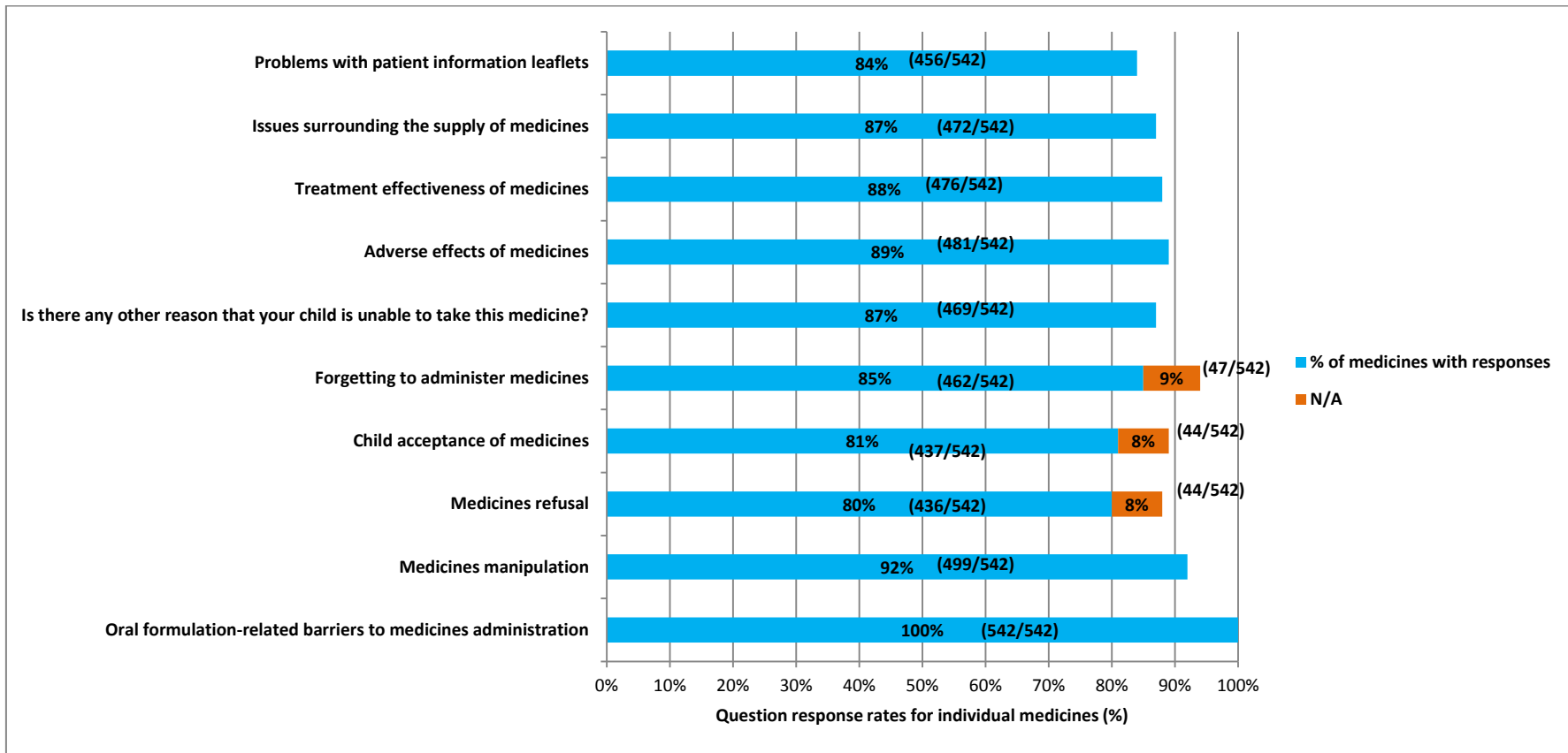


Figure 11 Question response rates for individual medicines.

Uncoloured sections of bars represent missing data.

N/A= where question is not applicable, see narrative that follows for discussion of this.

6.6.3.1.1 Oral formulation-related barriers to medicines administration

All 252 participants answered this question for all 542 medicines prescribed.

6.6.3.1.2 Medicines manipulation

All 252 participants answered the question regarding how exactly medicines are administered for the majority (499/542) of medicines prescribed.

6.6.3.1.3 Medicines refusal

The majority (232/252) of participants answered the question regarding the refusal of medicines, this resulted in data concerning 436/542 of medicines.

For 10/252 of patients taking a total of 42 medicines this question did not apply as these patients were administered medicines only via NG or PEG tubes and formulations could not be refused via the current route of administration. For a further patient administered 2 medicines via an NG tube the refusal question was asked as one medicine was administered orally. In total, 8% (44/542) of medicines were administered via NG or PEG tubes and medicine refusal was not possible. Data on medicine refusals was absent for these 44 medicines.

6.6.3.1.4 Child acceptance of medicines

The question used to understand child acceptance of medicines was asked for 437/542 of the medicines prescribed. For 44/542 medicines this question was not applicable as they were administered via NG or PEG tubes.

6.6.3.1.5 Forgetting to administer medicines

The majority (240/252) of participants answered questions on forgetting medicines for at least one medicine, this resulted in data regarding 462/542 of medicines.

Questions on forgetting medicines were not applicable for 6/252 participants. The medicines prescribed for these children were instructed to be taken 'when required,' and according to disease symptoms. In total, 47/542 of medicines were administered on a 'when required' basis and therefore questions on forgetting were not applicable.

6.6.3.1.6 Reminding systems for administering medicines

A total of 208/252 participants answered the question regarding reminding systems used to remember to administer medicines.

6.6.3.1.7 Intentional discontinuation of medicines

Of the participants, the majority, 238/252 and 239/252 answered the question regarding stopping medicines unilaterally (i.e. without the advice of a healthcare professional) if a child was feeling worse or better respectively.

For 6 children these questions were not applicable as medicines were prescribed to be taken on a 'when required basis'.

6.6.3.1.8 Adverse effects and treatment effectiveness of medicines

For 481/542 of the medicines, a question was asked to investigate if adverse effects had been experienced.

For 476/542 of the medicines, a question was delivered to ascertain whether they were perceived by respondents to be effective.

6.6.3.1.9 Additional barriers to medicines adherence and medicines adherence status

The question exploring additional barriers to adherence was delivered to the majority (242/252) of participants, resulting in data for 469/542 of the medicines prescribed.

Of the participants, 245/252 provided a valid response for at least one of the barriers to adherence questions (see sections 6.5.1.1.3, 6.5.1.1.5, 6.5.1.1.7 and 6.5.1.1.9 for questions on refusing, forgetting, discontinuing and additional reasons).

6.6.3.1.10 Issues surrounding the supply of medicines

In total, 241/252 of participants answered this question, resulting in data for 472/542 of medicines, of which 8% (38/472) were Specials medicines.

6.6.3.1.11 Problems with PILs

Data on problems with PILs was collected for 456/542 of medicines.

6.6.3.1.12 Problems with medicines at school

In total, 153/252 of participants responded to the question: Do you have any problems with medicines at school? This question was not applicable for 87/252 of children as it was reported that they were not receiving education (were either below school age or had completed education).

In total, 154/252 of participants responded to the question: Do you think that teachers and social staff should be given more information on medicines? For 87/252 participants this question was not applicable as it was reported that they were not receiving education (were either below school age or had completed education).

6.6.4 Results of semi-structured interviews with parents, carers and young people

6.6.4.1 Oral formulation-related barriers to medicines administration

Study participants were asked to report barriers to administering medicines, as detailed in section 6.5.1.1.1.

Reported obstacles to medicines administration were grouped into oral formulation-related barriers, derived using thematic analysis (guided by Pope and co-workers (2000), and detailed in section 5.3.8.1): taste-related (taste, lack of taste, aftertaste), texture-related (texture, thickness or consistency), quantity or volume (of solid dosage forms or liquid/powder), size or aversion to/difficulty swallowing (size of solid dosage form or solid dosage form described as difficult to swallow), smell and colour/appearance. A further group 'other formulation and administration problems' was created which encompassed problems not directly related to oral formulations (e.g. storage of medicine and frequency of dosing).

Oral formulation-related problems identified with individual medicines in this study are reported in relation to:

- Prescribing frequency of individual medicines
- Prescribing frequency across different drug therapeutic classes (based on BNFC chapter classification, see Appendix 19). An additional category 'other' was used to categorise medicines that did not feature in the main BNFC chapters.

Following data observation, a cut-off prescribing frequency of n=6 was used for fair representation of the data on individual medicines. Individual medicines are reported

generically, yet include their proprietary equivalents. An exception is paracetamol liquid, this includes Parapaed and generic versions, yet excludes Medinol and Calpol as no oral formulation-related barriers were reported for these formulations.

6.6.4.1.1 Taste-related problems

For 35% (188/542) of the medicines prescribed, taste-related problems were reported (see Appendix 21 for quotations). Frequencies of taste-related problems associated with individual medicines and across drug therapeutic classes are shown in Figures 12 and 13 below.

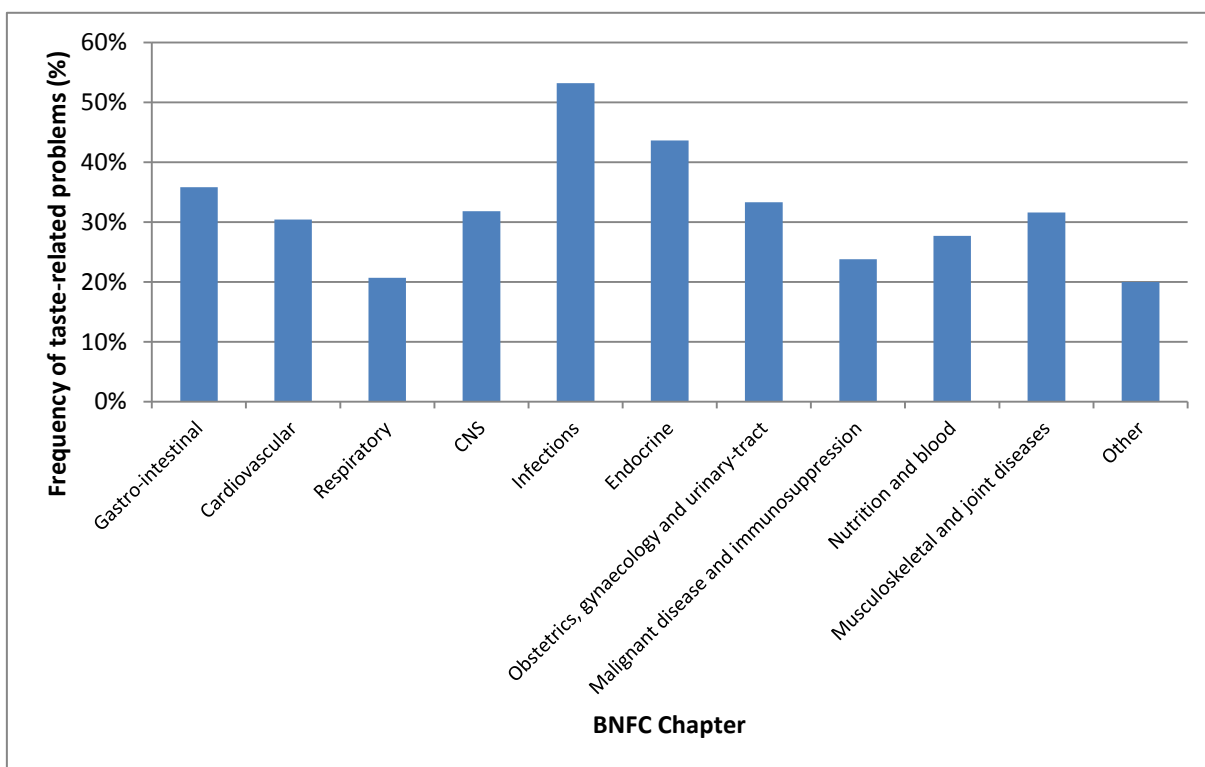


Figure 12 A histogram displaying the frequency of taste-related problems reported across drug therapeutic classes (based on BNFC chapter classification).

CNS = Central Nervous System.

Taste-related barriers to medicines administration were reported for at least 20% of medicines prescribed from each BNFC chapter (see Figure 12).

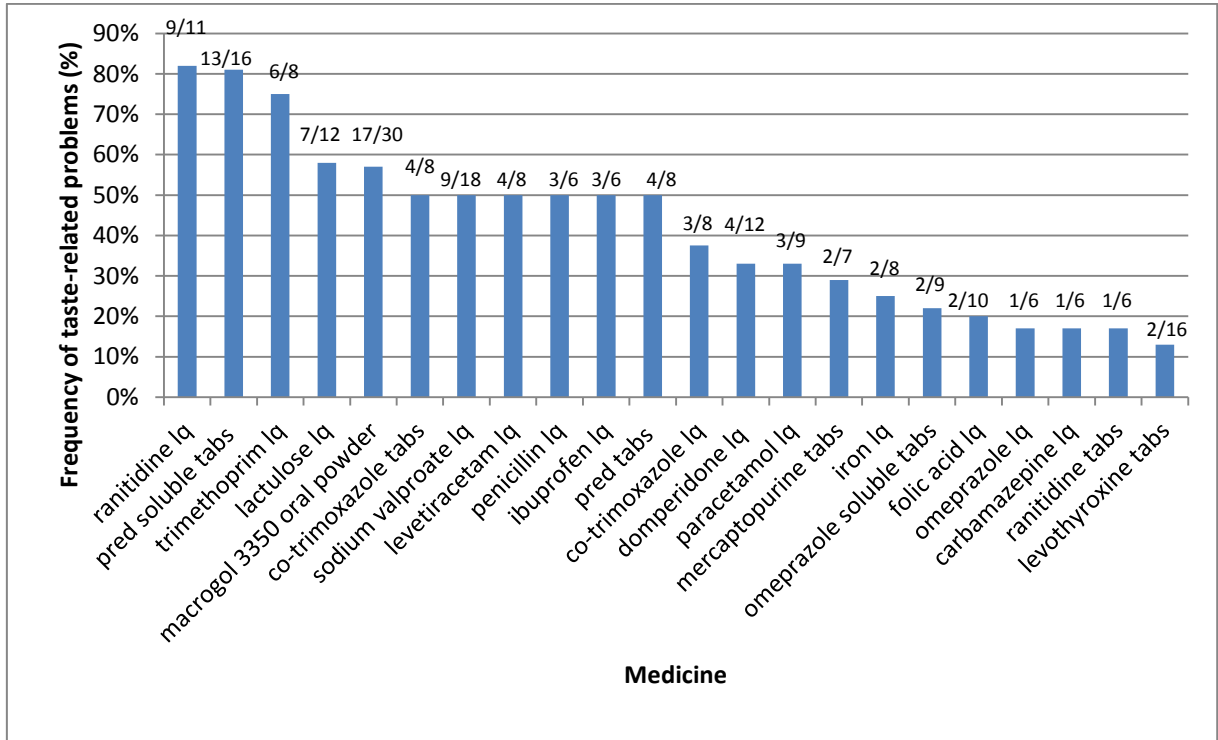


Figure 13 A histogram displaying the frequency of taste-related problems reported for individual medicines (prescribing frequency cut-off of n=6).

pred = prednisolone, lq = liquid, tabs = tablets.

Figure 13 above shows that ranitidine liquid (82%), prednisolone soluble tablets (81%) and trimethoprim liquid (75%) were most commonly reported to have taste problems.

6.6.4.1.2 Texture problems

Of the medicines prescribed, 8% (42/542) were reported to have an unfavourable texture (see Appendix 21 for quotations). Figures 14 and 15 below show the prevalence of problems with texture associated with medicines in different drug therapeutic classes and amongst individual medicines.

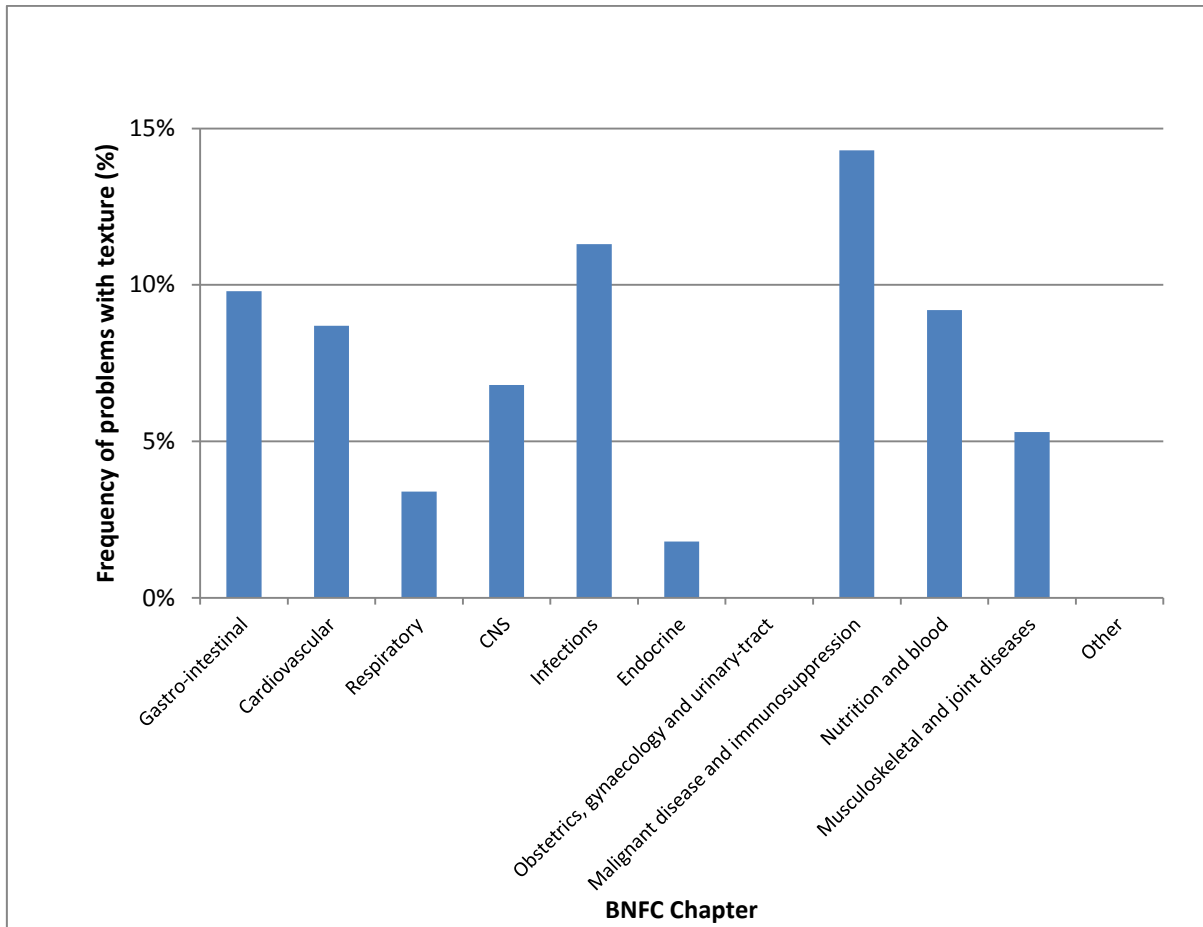


Figure 14 A histogram displaying the frequency of problems related to texture reported across drug therapeutic classes (based on BNFC chapter classification).

CNS = Central Nervous System.

The highest frequency of texture problems (14%) were reported for medicines prescribed from chapter 8 of BNFC (i.e. drugs used to treat malignant diseases and immunosuppressants) as shown above in Figure 14.

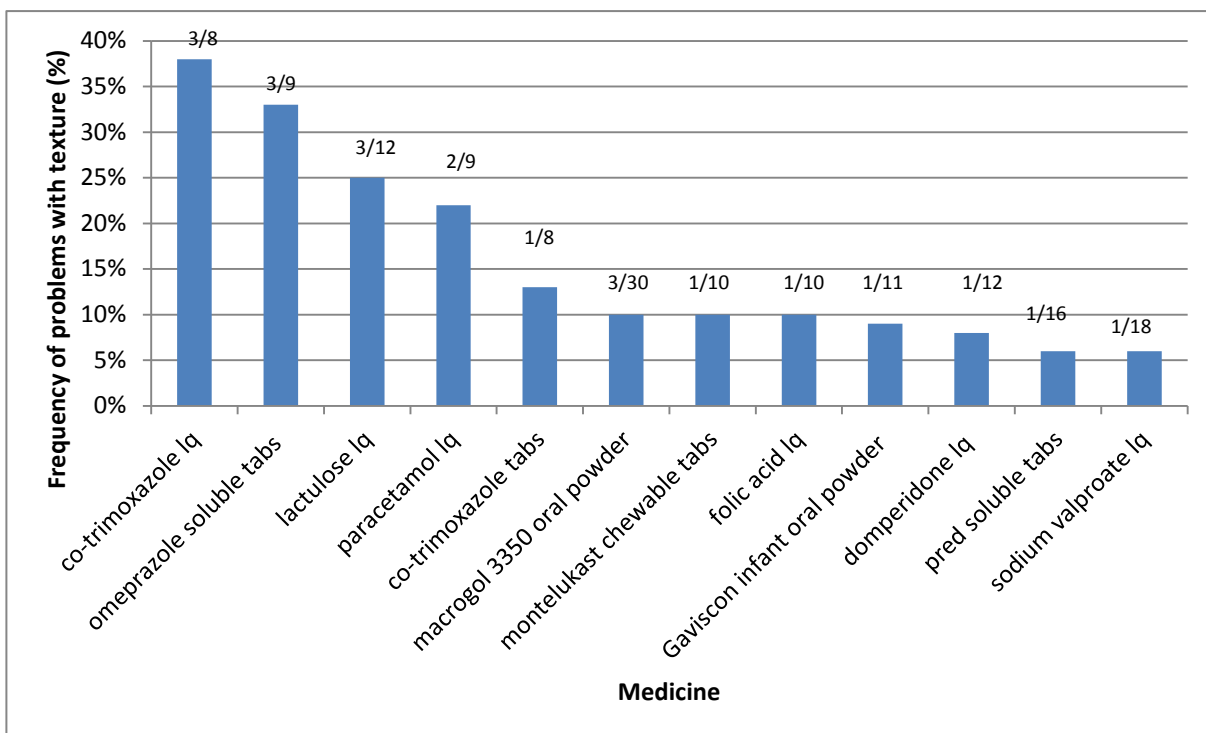


Figure 15 A histogram displaying the frequency of problems related to texture reported for individual medicines (prescribing frequency cut-off n=6).

pred = prednisolone lq = liquid, tabs = tablets.

Co-trimoxazole liquid (38%), omeprazole soluble tablets (33%) and lactulose liquid (25%) were most commonly reported to have texture-related problems (see Figure 15 above).

6.6.4.1.3 Quantity and volume problems

Of the medicines prescribed, 5% (29/542) were reported to have 'too large' a volume or 'too many' solid dosage units to be administered at one dosing interval (see Appendix 21 for quotations). The frequency of reported problems associated with quantity and volume are displayed in relation to drug therapeutic class and individual medicines in Figure 16 and Table 40 below.

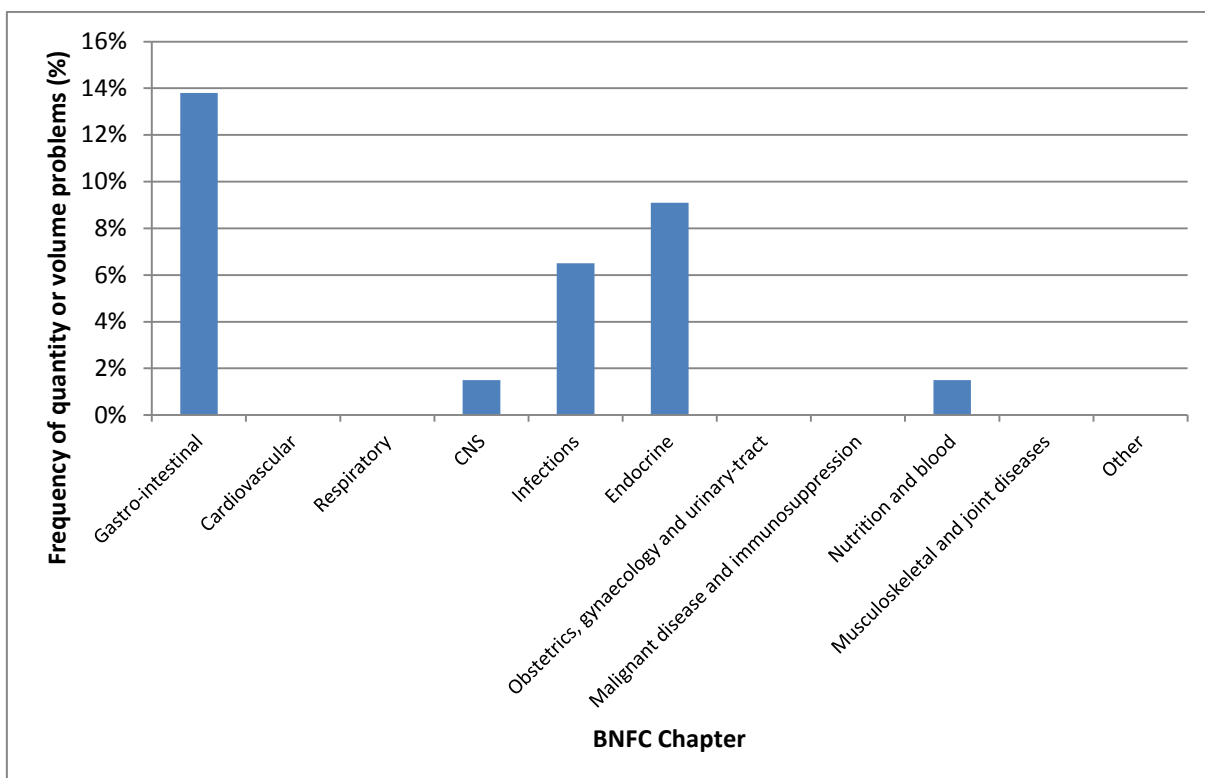


Figure 16 A histogram displaying the frequency of reported problems associated with quantity or volume across drug therapeutic classes (based on BNFC chapter classification).

CNS = Central Nervous System.

Problems associated with quantities or volumes of medicines were most commonly reported for medicines featuring in the gastro-intestinal chapter of BNFC (BNFC chapter 1) as shown in Figure 16 above.

Table 40 The frequency of reported problems associated with the volume or quantity of individual medicines (prescribing frequency cut-off n=6).

Medicines most commonly reported with quantity or volume problems	Frequency of quantity or volume reports (prescribing frequency cut-off n=6)
Pancrealipase capsules	(5/8)= 63%
Macrogol 3350 oral powder	(12/30)= 40%
Prednisolone soluble tablets	(3/16)=19%

Almost two thirds of patients prescribed pancrealipase capsules reported problems with too many unit doses at one dosing interval (see Table 40 above).

6.6.4.1.4 Problems with size and aversion to or difficulty with swallowing

Problems related to i) the size of a solid dosage form or ii) aversion to or difficulty swallowing a solid dosage form was associated with 5% (28/542) of the total medicines prescribed (16% if only solid dosage forms considered), see Appendix 21 for quotations.

For 16% (28/177) of solid dosage forms prescribed to patients, problems experienced either with the size of a solid dosage form or where children were averse to/reported difficulties swallowing a dosage form were reported. Problems specifically related to the sizes of particular solid dosage forms were reported for 68% (19/28) of these medicines, and aversion to, or difficulty swallowing solid dosage forms was reported for the remaining 32% (9/28) of medicines (see Figure 17 below). It should be noted that these patients were not physically unable to swallow (i.e. not patients fitted with an NG or PEG tube).

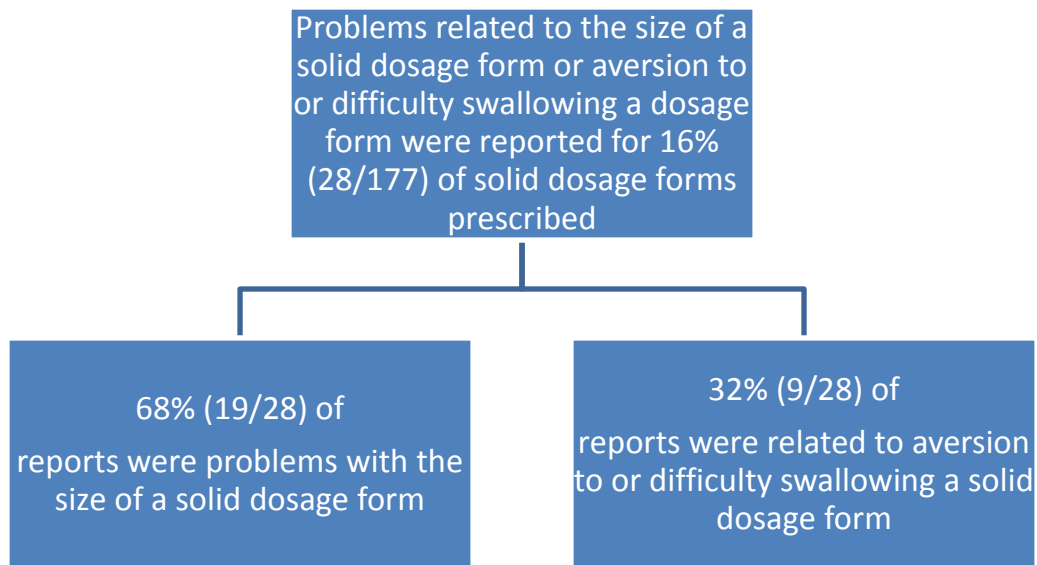


Figure 17 A diagram displaying the proportion of reports regarding problems with the size of a solid dosage form and aversion to or difficulty swallowing a solid dosage form.

Problems reported with the size of a solid dosage form and aversion to or difficulty swallowing, were grouped for the purpose of statistical analyses. Figure 18 below shows the proportion of medicines from each therapeutic class identified with a problem related to the size of a solid dosage form or aversion to or difficulty swallowing a solid dosage form.

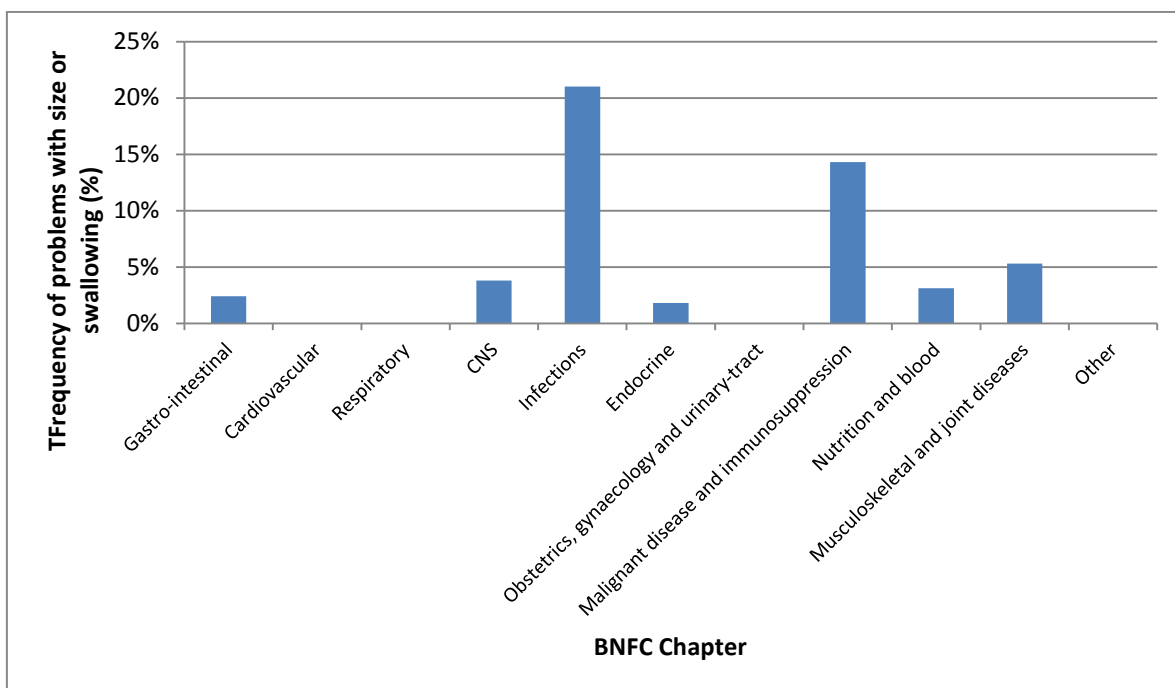


Figure 18 A histogram displaying the frequency of problems reported with the size of, aversion to or difficulty swallowing solid dosage forms across drug therapeutic classes (based on BNFC chapter classification).

CNS = Central Nervous System.

Over 20% of medicines prescribed from BNFC chapter 5 - infections (antibiotics, antivirals and antifungals) were reported to be too big or difficult to swallow.

The most commonly reported medicine with regard to size or aversion to/difficulty swallowing was the tablet formulation of co-trimoxazole. The majority (7/8= 88%) of patients prescribed co-trimoxazole tablets reported a problem with their size or difficulty swallowing them.

6.6.4.1.5 Colour/appearance and smell problems

An unfavourable colour/appearance was associated with 2% (11/542) of medicines prescribed (see Appendix 21 for quotations).

For 11% (2/18) of children prescribed sodium valproate liquid its 'alarming colour' was highlighted. Similarly, 11% (1/9) of patients prescribed paracetamol liquid described its unappealing colour.

In addition, 2% (11/542) of medicines prescribed were identified as having 'off-putting' smells (see Appendix 21 for quotations).

For 25% (2/8) of children prescribed trimethoprim liquid, an unfavourable smell was described.

6.6.4.1.6 Spearman's correlation statistical test

Spearman's correlation coefficients were calculated to test for correlations between the organoleptic and physical properties of medicines. The results are reported in Table 41.

Table 41 A table displaying the results of a Spearman's correlation test investigating the correlation between organoleptic and physical properties of medicines.

	Taste	Texture	Volume or quantity	Size or aversion to/difficulty swallowing	Smell	Colour
Taste		0.151 (P<0.001)	0.102 (P=0.017)	-0.030 (P=0.486)	0.143 (P=0.001)	0.033 (P=0.449)
Texture	0.151 (P<0.001)		0.054 (P=0.212)	-0.005 (P=0.992)	0.007 (P=0.867)	0.007 (P=0.867)
Volume or quantity	0.102 (P=0.017)	0.054 (P=0.212)		0.019 (P=0.666)	-0.034 (P=0.427)	-0.034 (P=0.427)
Size or aversion to/ difficulty swallowing	-0.030 (P=0.486)	-0.005 (P=0.992)	0.019 (P=0.666)		-0.034 (P=0.435)	-0.034 (P=0.435)
Smell	0.143 (P=0.001)	0.007 (P=0.867)	-0.034 (P=0.427)	-0.034 (P=0.435)		0.072 (P=0.094)
Colour	0.033 (P=0.449)	0.007 (P=0.867)	-0.034 (P=0.427)	-0.034 (P=0.435)	0.072 (P=0.094)	

Results are based on a 2-tailed Spearman's correlation test. For significant results, Spearman's correlation coefficients and associated p values are reported in bold font.

The Spearman's statistical test found a weak, yet significant positive correlation between reported taste-related issues and texture, smell and volume/quantity, with correlation coefficients 0.151 (p<0.001), 0.143 (p=0.001) and 0.102 (p=0.017) respectively.

6.6.4.1.7 Other formulation and administration problems

Of the medicines prescribed, 12% (63/542) were associated with ‘other formulation or administration problems’ (i.e. those not associated directly with oral formulations). Problems reported in this study included frequency of dosing, difficulty with or dislike of the route of medicine administration, children fearing syringes, medicines blocking NG and PEG tubes, difficult storage conditions and short expiries.

6.6.4.1.8 Well-accepted medicines

The positive attributes of some medicines were reported in the present study (see Table 42 below).

Table 42 The frequency of medicines identified with positive oral formulation properties.

Oral formulation properties reported in a positive manner	The frequency of medicines associated with positive reports regarding oral formulation properties
Taste	4% (24/542)
Texture	<1% (3/542)
Smell	<1% (1/542)
Size	<1% (1/542)

6.6.4.2 Medicines manipulation

For this study ‘Gold standard’ administration of a medicine was defined as: ‘a medicine delivered to the route of administration without manipulation’.

A medicine manipulation was defined as: ‘a medicine physically adapted to facilitate medicines administration or for the purpose of giving a specific dose’.

Responses to questions on how medicines were administered to/taken by children were analysed using a thematic approach (see section 6.5.5.2).

All 252 study participants were asked to describe the process of medicines administration for at least one of their medicines.

Although not classed as medicine manipulations, some dosage forms were reported to be administered at the same time as various foodstuffs (e.g. with a drink other than water, followed or preceded by biscuits or sweets). In addition, 8% (38/499) of medicines were administered via NG or PEG tubes in their existing form. Patients who were administered medicines via NG or PEG tubes are discussed as a subgroup of the population in section 6.6.4.2.1.

A total of 71% (178/252) of respondents reported administering medicines in a 'gold standard' manner accounting for the administration of 82% (405/499) of medicines.

Almost one third of respondents 29% (74/252) reported manipulating medicines.

In total, 19% (94/499) of medicines were manipulated. Of these, 87/94 medicines were reported to be manipulated always (i.e. prior to every dose administration), 4/94 most of the time, 1/94 rarely. For the remaining 2/94 medicines, an 'unsure' response was provided regarding the frequency of medicines manipulation.

Thematic analysis of the reported data derived two thematic groups:

- Medicines manipulated for the purpose of administering a specific dose
- Medicines manipulated to facilitate administration.

Manipulation techniques that were reported in the study interviews were used to generate thematic sub-groups. A coding spine was developed based on the thematic groups and sub-groups (see Table 43 below).

Table 43 Thematic coding spine for medicines manipulation.

Medicines manipulation thematic groups	Medicines manipulation thematic sub-groups
For the purpose of administering a specific dose	<ul style="list-style-type: none"> • Measuring part volumes of solution following dissolving a soluble tablet/crushing a tablet • Segmenting tablets and splitting sachets of powder or granules.
To facilitate medicines administration	<ul style="list-style-type: none"> • Mixing sachets/soluble tablets/ liquids with foodstuffs (including dairy products, acidic juices, warm drinks, breakfast cereal) • Mixing non-soluble tablets with diluents • Opening capsules and mixing powder or granules with foodstuffs • Crushing/segmenting tablets.

The proportion of medicines classified into each thematic group is reported in Figure 19. Four medicines were manipulated for both reasons (e.g. tablet crushed, and then added to orange juice). Such physical adaptations were categorised into both thematic groups and is the reason for percentages exceeding 100% in Figure 19 below.

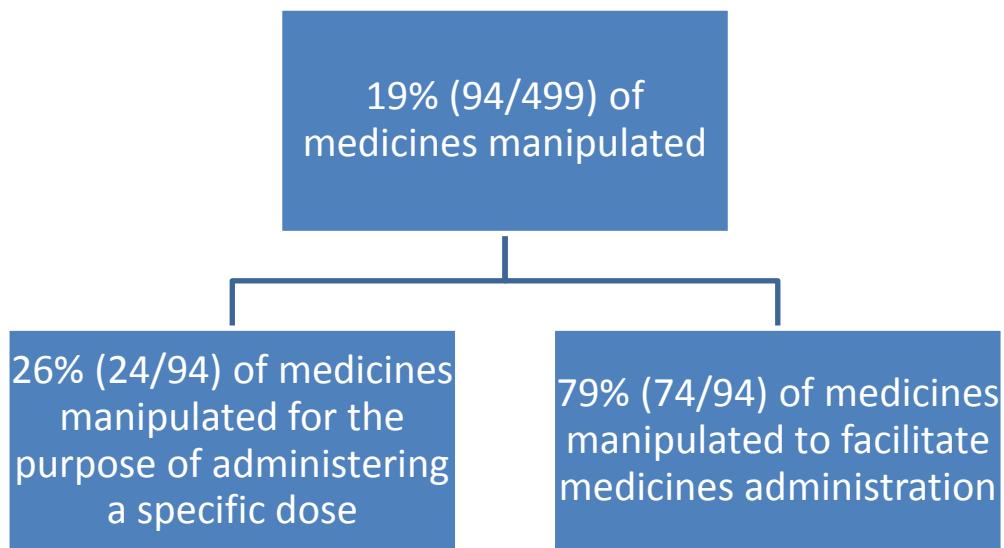


Figure 19 A diagram displaying the proportion of medicines manipulated for the purpose of administering a specific dose, to facilitate medicines administration and for both reasons.

Reports of physical adaptations of medicines for the purpose of administering a specific dose and to facilitate medicines administration are reported in Tables 44 and 45 below respectively.

Table 44 Medicines manipulated for the purpose of administering a specific dose.

Medicine	BNFC chapter	Medicine Manipulation
Amlodipine tablets	2	Mixed with xmls of water and xmls measured
Aspirin soluble tablets (n=2)	10	Mixed with xmls of water and xmls measured
Azathioprine tablets*	8	Halved, mixed with water and swirled
Co-trimoxazole tablets	5	Quartered
Gaviscon infant oral powder	1	Quartered
Hydrocortisone tablets	6	Crushed, mixed with water and xmls measured
Lansoprazole soluble tablets	1	Dissolved in xmls of water and xmls measured
Macrogol 3350 oral powder (n=2)	1	Halved/dissolved in xmls of water and xmls measured
Mercaptopurine tablets	8	Halved
Mycophenolate mofetil tablets*	8	Halved
Nifedipine tablets	2	Halved
Omeprazole soluble tablets *(n=5)	1	Halved/dissolved in xmls of water and xmls measured
Ondansetron melts	4	Halved
Piroxicam tablets	10	Cut one quarter out
Prednisolone tablets	6	Halved
Prednisolone soluble tablets	6	Dissolved in xmls of water and xmls measured
Ranitidine tablets	1	Halved
Tranexamic acid tablets*	2	Crushed and mixed with squash/water and xmls measured

*Identifies medicines manipulated for both reasons. n=1 unless otherwise stated.

Table 45 Medicines manipulated to facilitate medicines administration.

Medicine	BNFC chapter	Medicine Manipulation
Azathioprine tablets*	8	Halved then added to water and swirled
Calcium liquid (n=2)	9	Added to yoghurt/hot chocolate
Co-codamol soluble tablets	4	Mixed with blackcurrant squash
Co-trimoxazole tablets (n=3)	5	Administered in two halves/administered in three segments
Fludrocortisone tablets	8	Crushed and mixed with water
Hydroxychloroquine tablets	10	Crushed
Lactulose liquid	1	Added to bottle of milk
Levetiracetam liquid	4	Added to breakfast cereal
Lamotrigine soluble tablets	4	Crushed and added to meals
Levothyroxine tablets (n=5)	6	Segmented before administration/added to pureed fruit/crushed and added to water
Loperamide capsules	1	Opened and contents mixed with water

Medicine	BNFC Chapter	Medicine Manipulation
Macrogol 3350 oral powder (n=20)	1	Added to orange juice/blackcurrant juice/pure apple juice/pure orange juice/apple and blackcurrant juice/warm hot chocolate/cup of tea/milk/breakfast cereal/warm water
Melatonin capsules (n=2)	4	Opened, contents added to lemonade and stirred/ yoghurt
Mercaptopurine tablets (n=2)	8	Mixed with water/crunched prior to swallowing
Metformin liquid	6	Added to orange or blackcurrant squash
Methotrexate tablets (n=2)	8	Crushed prior to swallowing/added to blackcurrant juice
Montelukast sodium granules	3	Mixed with yoghurt
Mycophenolate mofetil tablets*	8	Administered in two halves in squash
Omeprazole capsules	1	Contents added to squash
Omeprazole soluble tablets* (n=3)	1	Mixed with apple juice and xmls measured/pineapple juice/mixed with breakfast cereal
Ondansetron liquid	4	Added to yoghurt
Pancrealipase Micro gastro-resistant granules (n=3)	1	Added to bottle of milk/fruit puree
Prednisolone soluble tablets (n=5)	6	Added to orange juice/strawberry squash or summer fruits squash/blackcurrant squash n=2/Ribena
Procarbazine capsules	8	Contents added to yoghurt
Rifinamide tablets	5	Crushed and added to meals
Setraline tablets	4	Administered in two halves
Sodium chloride liquid (n=3)	9	Added to bottle of milk/squash and 'everything'
Sodium valproate liquid (n=2)	4	Added to breakfast cereal/glass of milk
Topirimate capsules	4	Contents added to every meal as didn't mask taste in juices
Tranexamic acid tablets*	2	Crushed and mixed with squash/water and xmls measured
Trimethoprim liquid	5	Added to bottle of milk
Zinc soluble tablets (n=3)	9	Added to warm water (dissolves quicker)/blackcurrant squash/squash

*Identifies medicines manipulated for both reasons. n=1 unless other otherwise stated.

For medicines with a prescribing frequency of n=6, rates of medicines manipulation were calculated to determine which medicines were most commonly reported to be manipulated (see Figure 20 below).

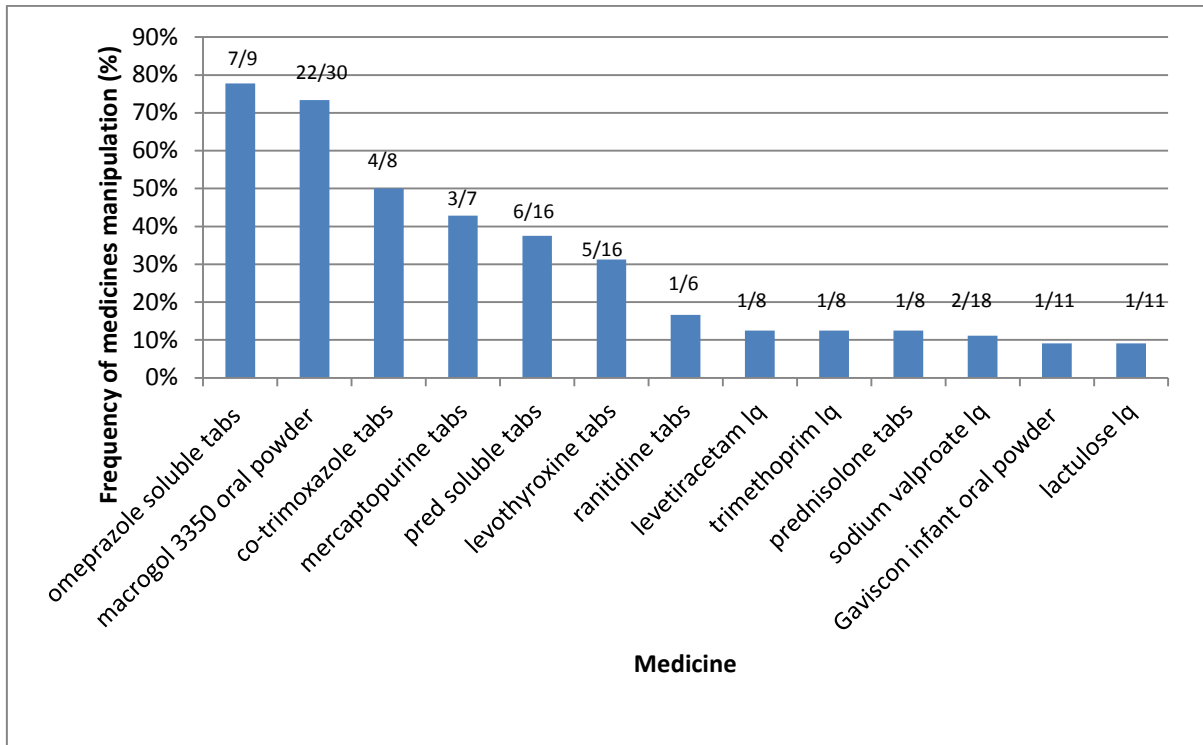


Figure 20 A histogram displaying the frequency of individual medicines reported to be manipulated (prescribing frequency cut-off n=6).

pred = prednisolone, lq = liquid, tabs = tablets.

Omeprazole soluble tablets (7/9 78%), macrogol 3350 oral powder (22/30 73%) and co-trimoxazole tablets (4/8 50%) were most commonly reported to be manipulated by respondents, as shown in Figure 20 above.

6.6.4.2.1 Patients with NG/PEG tubes

In total, 8% (44/542) of orally ingestible medicines were administered non-orally to 79% (11/14) of children with NG or PEG tubes. The remaining 3 patients with NG or PEG tubes fitted did not have any medicines administered via this route.

Over one third (36% (4/11)) of participants administering medicines via the NG/PEG tube route had to manipulate at least one medicine prior to administration. Figure 21 below

shows the breakdown of children with NG/PEG tubes requiring medicines to be manipulated.

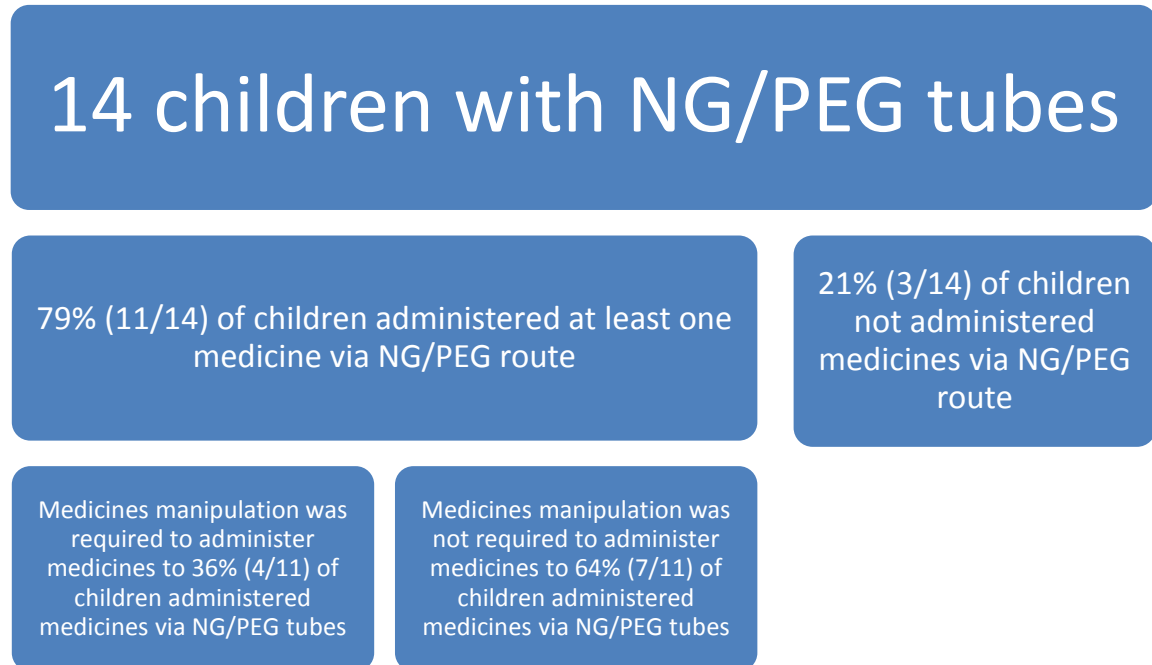


Figure 21 A diagram displaying medicines administration and manipulation in children fitted with NG or PEG tubes.

In total, 14% (6/44) of medicines administered via NG or PEG tubes were manipulated and are included in the multivariable analysis. The remaining 38/44 medicines were administered unadulterated.

Over one quarter (26%) of medicines prescribed for patients fitted with NG or PEG tubes were Specials medicines, compared to only 5% of medicines prescribed to patients without NG or PEG tubes fitted.

6.6.4.2.2 Multivariable analysis

To identify which factors significantly influenced the manipulation of medicines, binary logistic regression using multivariable models was used to analyse the data as discussed in section 6.5.5.3. Variable factors that required adjustment for the statistical model to converge are reported in Appendix 22. The results of the multivariable analysis are reported in Table 46 below. Odds ratios with 95% confidence intervals and associated p values are reported for the variables used in the analysis.

Table 46 Multivariable analysis results: Reports of medicines manipulation.

	Odds Ratio (95% CI)	P Value
Age of child at Interview		0.005*
0-4 years	1	
5-11 years	0.29 (0.13-0.67)	0.004*
12-18 years	0.18 (0.06-0.59)	0.005*
Is English first language of participant		0.085
Yes	1	
No	0.26 (0.06-1.20)	0.085
Formulation type		<0.001*
Liquid	1	
Tablets and Capsules	9.66 (3.48-26.87)	<0.001*
Other	23.97 (9.14-62.84)	<0.001*
Problem with size of dosage form or aversion to/difficulty swallowing dosage form		0.013*
No	1	
Yes	4.52 (1.37-14.90)	0.013*
Problem with texture		0.006*
No	1	
Yes	3.15 (1.39-7.14)	0.006*
Problem related to other formulation and administration problems		0.206
No	1	
Yes	1.89 (0.70-5.08)	0.206

BNFC Chapter in which medicine is classified			0.075
	1	1	
	2	0.85 (0.14-5.06)	0.855
	3	0.07 (0.01-0.51)	0.008
	4	0.79 (0.27-2.26)	0.656
	5	0.42 (0.15-1.17)	0.097
	6	1.07 (0.38-3.02)	0.895
	8	2.04 (0.65-6.38)	0.222
	9	0.54 (0.16-1.87)	0.335
	Other	0.76 (0.25-2.29)	0.625
Who is responsible for medicines administration			0.049*
	Parent/Guardian	1	
	Child plus Parent/Guardian	0.28 (0.10-0.81)	0.019*
	Child	0.22 (0.02-1.94)	0.171
Problem with volume or quantity			0.157
	No	1	
	Yes	2.17 (0.74-6.35)	0.157
Frequency of dosing			0.404
	1x daily	1	
	2x daily	0.70 (0.34-1.45)	0.345
	≥3x daily	0.20 (0.03-1.46)	0.113
	<1x daily (not including medicines prescribed on a 'when required' basis)	0.76 (0.23-2.46)	0.647

p values marked with * identify statistically significant results ($p < 0.05$).

The 'other' group includes medicines from chapters 7, 10 and those medicines not featuring in BNFC.

6.6.4.3 Medicines refusal

Refusal of a medicine was defined in this study as: 'complete omission of a dose by intent on at least one occasion, including spitting the dose back out, and/or closing the mouth'.

Questions on refusal are reported in 6.5.1.1.3.

Almost one third 31% (71/232) of respondents reported medicines refusal on at least one occasion, 9% (20/232) of respondents reported medicines refusal in the six months prior to interview and 6% (15/232) of respondents reported medicines refusal in the week prior to interview.

The frequency of medicines reported to be refused on at least one occasion, within one week and six months prior to interview are displayed in Figure 22 below.

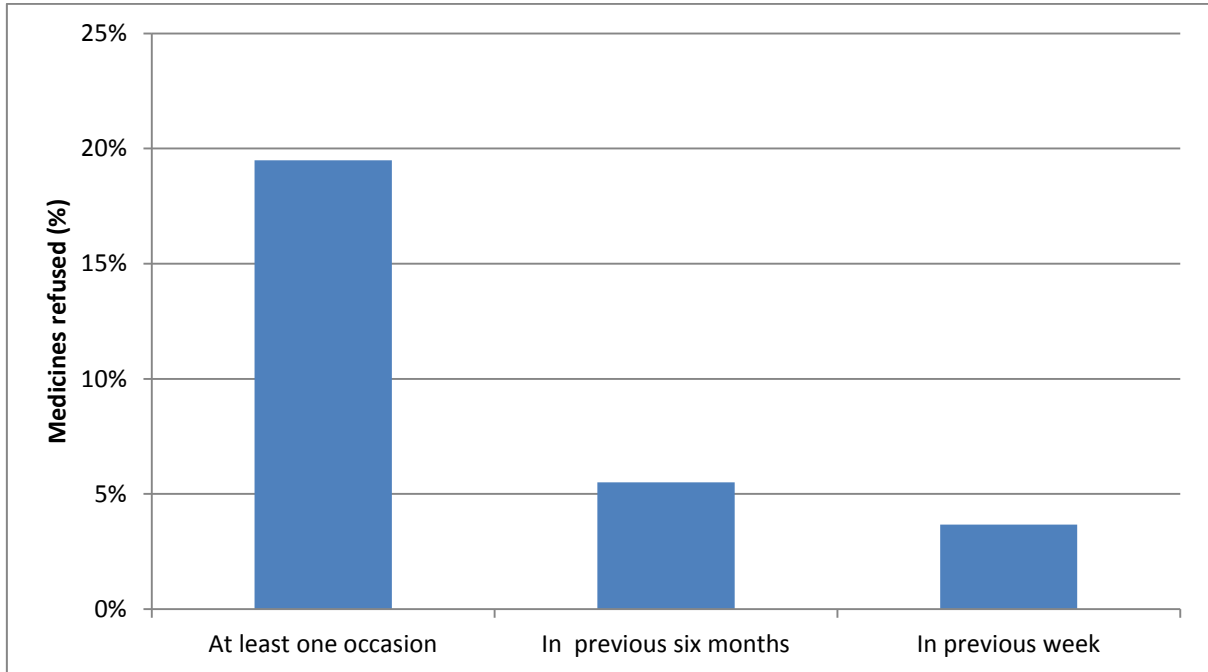


Figure 22 A histogram displaying the reported frequency of medicines refusal on at least one occasion, within one week and six months prior to interview.

Refusing a medicine on at least one occasion was reported for 19% (85/436) of medicines in total. In the six months prior to interview, 6% (24/436) of medicines were reported to be refused and in the week prior to interview, 4% (16/436) of medicines.

6.6.4.3.1 Patients with NG or PEG tubes

Children who were administered all oral medicines non-orally (via an NG or PEG tube) were treated as a sub-group of the population, as medicines could not be refused via the current route of administration. These are reported as N/A in Figure 10.

Over half (52% (23/44)) of the medicines administered via these routes at the time of interview were reported to have been refused orally prior to changing to PEG or NG tube administration.

6.6.4.3.2 Multivariable analysis

Binary logistic regression using multivariable models was used to analyse reported medicines refusal on at least one occasion and in the six months prior to interview, as discussed in section 6.5.5.3. The multivariable analysis results for reporting medicines refusal are provided in Tables 47 and 48 below. Odds ratios with 95% confidence intervals and associated p values are reported for the variables used in the analysis.

Table 47 Multivariable analysis results: Reports of medicines refusal on at least one occasion.

	Odds Ratio (95% CI)	p Value
Age of child at Interview		
		0.016*
0-4 years	1	
5-11 years	0.42 (0.19 - 0.89)	0.024*
12-18 years	1.31 (0.54 - 3.20)	0.554
IMD 2010 score		
		0.002*
<11.5	1	
11.5-19.8	1.32 (0.49-3.51)	0.584
19.9-31.9	3.19 (1.37-7.43)	0.007*
32+	4.75 (2.02-11.18)	<0.001*
Formulation type		
		0.336
Liquid	1	
Capsules and Tablets	0.59 (0.27-1.30)	0.193
Other	0.64 (0.30-1.38)	0.254
Problem with taste		
		<0.001*
No	1	
Yes	3.82 (2.11-6.92)	<0.001*
Problem with texture		
		0.017*
No	1	
Yes	3.38 (1.24-9.22)	0.017*
Problem with volume or quantity		
		<0.001*
No	1	
Yes	12.79 (4.41-37.12)	<0.001*
Problem with smell		
		0.776
No	1	
Yes	1.24 (0.28-5.46)	0.776

p values marked with * identify statistically significant results (p<0.05).

Table 48 Multivariable analysis results: Reports of medicines refusal during the six months prior to interview.

	Odds Ratio (95% CI)	p Value
Age of child at Interview		0.017*
0-4 years	1	
5-11 years	0.06 (0.01-0.48)	0.009*
12-18 years	0.35 (0.07-1.69)	0.191
Age of child at diagnosis		0.030*
<1m	1	
1m-2y	0.91 (0.23-3.56)	0.890
2-12y	0.46 (0.11-1.98)	0.300
12-18y	5.37 (0.74-39.03)	0.097
Problem with taste		0.021*
No	1	
Yes	2.66 (1.16-6.07)	0.021*
Problem with texture		0.021*
No	1	
Yes	3.34 (1.20-9.32)	0.021*
Problem with volume or quantity		0.043*
No	1	
Yes	4.44 (1.05-18.82)	0.043*

p values marked with * identify statistically significant results (p<0.05).

6.6.4.4 Child acceptance of medicines

Descriptions of children being rarely or never happy to take a medicine were reported for 51% (43/85) of medicines reported to be refused on at least one occasion.

For 35% (30/85) of medicines claimed to be refused on at least one occasion, children were reported to be 'never happy to take'.

6.6.4.5 Forgetting to administer medicines

Forgetting a medicine was defined in this study as: ‘complete omission of a dose on at least one occasion resulting from unintentional memory lapse at time of administration’. The questions delivered to respondents are reported in section 6.5.1.1.5.

Of the respondents, 64% (153/240) reported forgetting medicines on at least one occasion. A total of 35% (85/240) of respondents reported forgetting to administer medicines in the six months prior to interview and 23% (55/240) in the week prior to interview.

The frequency of medicines reported to be forgotten on at least one occasion, within six months and one week prior to interview are displayed in Figure 23 below.

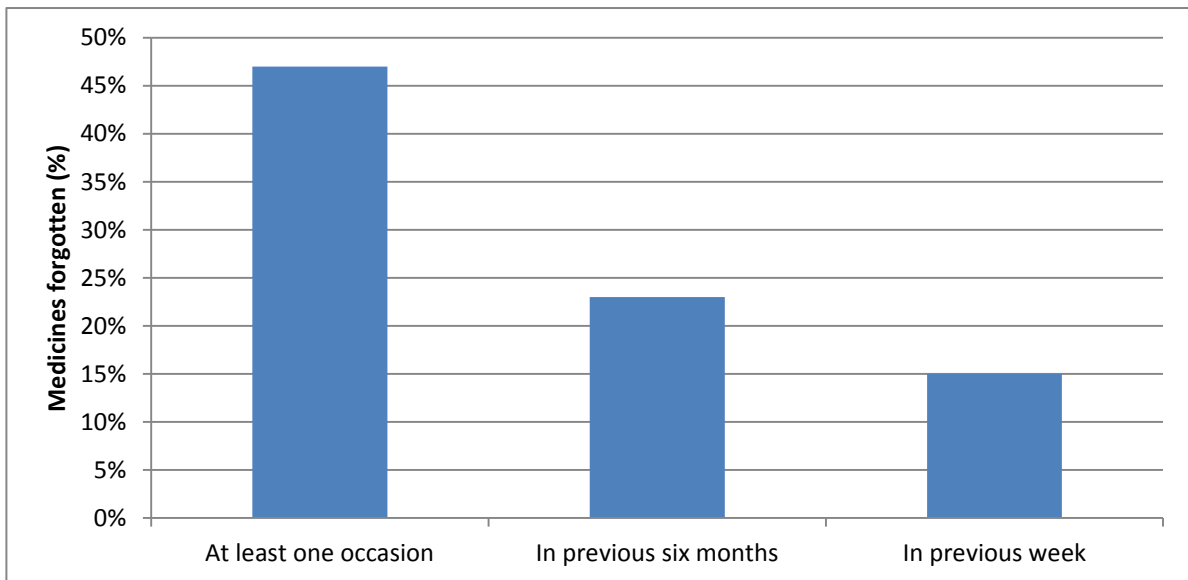


Figure 23 A histogram displaying the frequency of medicines reported to be forgotten on at least one occasion, within one week and six months prior to interview.

Forgetting to administer medicines on at least one occasion was reported for 47% (215/462) of medicines in total. In the six months prior to interview, 23% (106/462) of medicines were reported to be forgotten and in the week prior to interview, 15% (67/462) of medicines.

6.6.4.5.1 Multivariable analysis

To identify which factors significantly influenced forgetting medicines, binary logistic regression using multivariable models were used to analyse reports as discussed in section 6.5.5.3. Variable factors that required adjustment for the statistical model to converge are reported in Appendix 22. The results of the multivariable analysis on forgetting medicines on at least one occasion and within six months prior to interview are reported in Tables 49 and 50 below. Odds ratios with 95% confidence intervals and associated p values are reported for the variables used in the analysis.

Table 49 Multivariable analysis results: Reports of forgetting to administer medicines on at least one occasion.

	Odds Ratio (95% CI)	p Value
Age of child at Interview		0.026*
0-4 years	1	
5-11 years	1.67 (0.93-2.99)	0.086
12-18 years	2.98 (1.32-6.74)	0.009*
Number of prescribed oral medicines		<0.001*
1	1	
2	0.74 (0.40-1.36)	0.334
≥3	0.28 (0.15-0.51)	<0.001*
Who is responsible for medicines administration		0.150
Parent/Guardian	1	
Child plus Parent/Guardian	1.22 (0.56-2.61)	0.618
Child	8.30 (0.98-69.97)	0.052

p values marked with * identify statistically significant results (p<0.05).

Table 50 Multivariable analysis results: Reports of forgetting to administer medicines within the six months prior to interview.

	Odds Ratio (95% CI)	p Value
Age of child at Interview		
		0.069
0-4 years	1	
5-11 years	0.67 (0.24-1.89)	0.449
12-18 years	1.82 (0.59-5.58)	0.297
Number of prescribed oral medicines		
		0.003*
1	1	
2	0.58 (0.28-1.18)	0.132
≥3	0.27 (0.13-0.57)	0.001*
Who is responsible for medicines administration		
		0.286
Parent/Guardian	1	
Child plus Parent/Guardian	2.05 (0.84-5.03)	0.116
Child	1.77 (0.41-7.60)	0.444
Additional educational help		
		0.018*
No	1	
Yes	0.40 (0.17-0.95)	0.039*
N/A	0.38 (0.16-0.94)	0.036*
Other health-related need of patient		
		0.869
No	1	
Yes	0.94(0.45-1.95)	0.869
BNFC Chapter in which medicine is classified		
		0.013*
1	1	
2	0.73 (0.22-0.39)	0.606
3	0.20 (0.05-0.85)	0.029*
4	0.67 (0.37-1.21)	0.180
5	1.13 (0.52-2.47)	0.761
6	0.30 (0.13-0.69)	0.004*
8	0.26 (0.11-0.61)	0.002*
9	0.66 (0.33-1.33)	0.244
Other	0.54 (0.24-1.22)	0.139

p values marked with * identify statistically significant results (p<0.05).

The 'other' group includes medicines from chapters 7, 10 and those medicines not featuring in BNFC.

The unadjusted reported frequencies of medicines forgotten from each BNFC chapter are displayed in Figure 24 below.

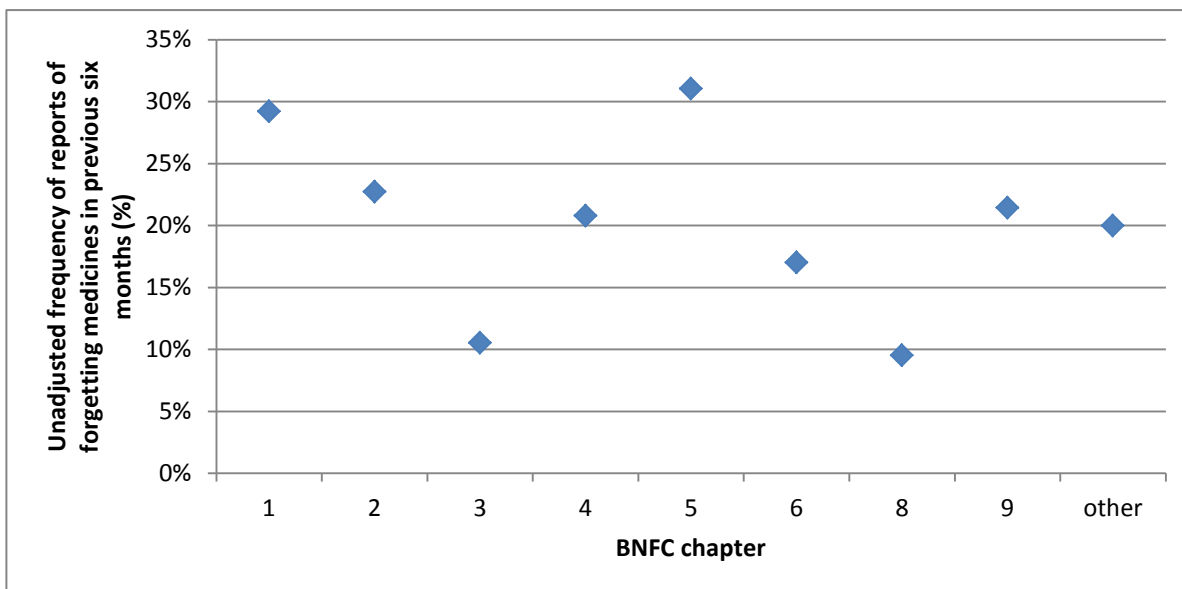


Figure 24 Unadjusted reported frequencies of medicines forgotten from each BNFC chapter in the previous six months.

Figure 24 above shows that medicines in BNFC chapters 8 (drugs used to treat malignant diseases and immunosuppressants), 3 (respiratory drugs) and 6 (drugs used to treat the endocrine system) were least likely to be reported as forgotten in the six months prior to interview.

6.6.4.6 Reminding systems for administering medicines

When asked about reminding systems used to help parents, carers and young people to remember to administer medicines (see section 6.5.1.1.6), the majority (170/208) of respondents reported that they relied on the familiarity of daily routine or medicines. Some

parents provided additional comments that familiarity of their child’s disabilities also reminded them to administer medicines.

One parent reported using disease symptoms to help to remember medicines administration. The use of alarms (on clocks and phones), written instructions (on cupboards, fridges, charts and in calendars, diaries, nursery day books), and medicine organisation boxes were reported as systems used to prompt medicines administration. The results of the question regarding reminding systems are displayed in Figure 25 below for the valid responses.

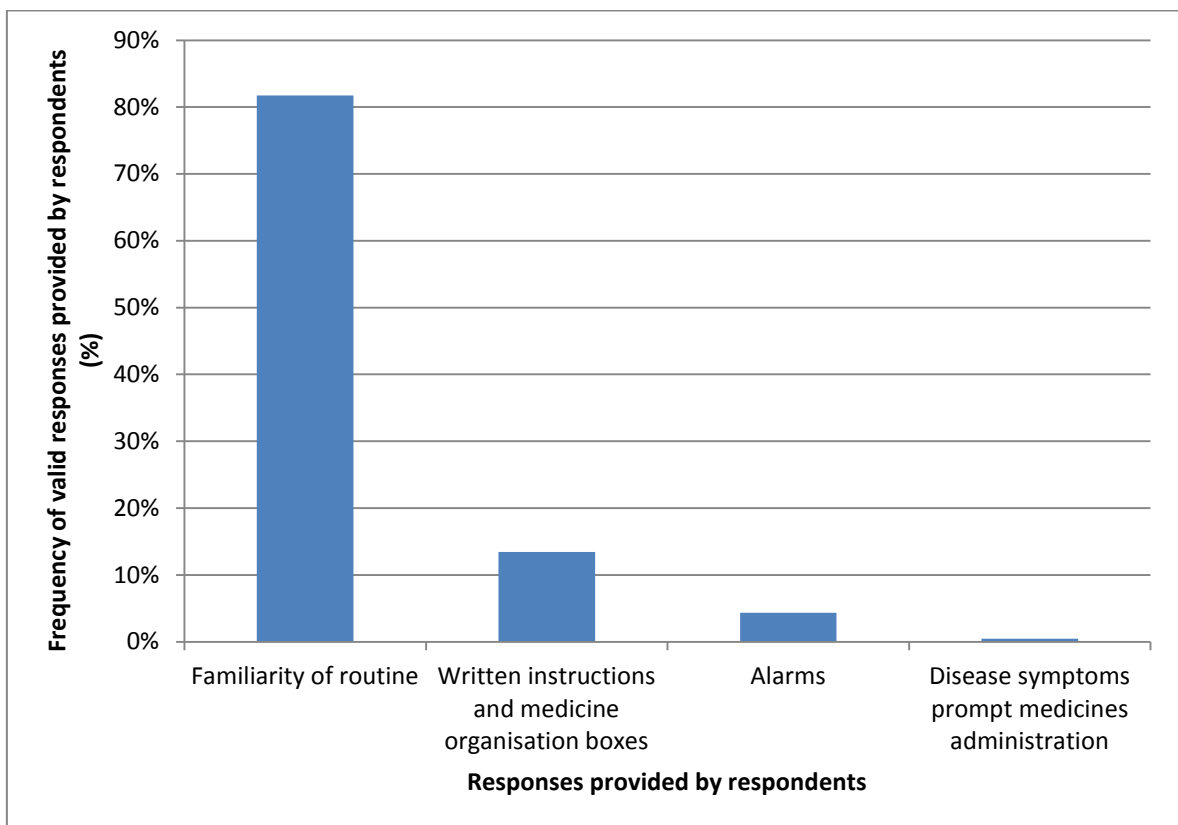


Figure 25 A histogram displaying valid responses to the questions: How do you remember to administer medicines? What reminding system do you use?

6.6.4.7 Reports of intentional discontinuation of medicines

The questions designed to reveal if parents, carers or children discontinued medicines unilaterally (i.e. without the advice of a healthcare professional) are provided in section 6.5.1.1.7.

When examining if medicines were discontinued, only 8% (20/238) of respondents reported that they had discontinued a medicine without consulting a healthcare professional if it was perceived to have made a child feel worse. The majority of respondents stated that they would seek the advice of a healthcare professional before discontinuing medicines administration (responses included phoning a nurse or GP).

Similarly, a minority of respondents, 2% (5/239) reported that if a child seemed better they had discontinued medicines administration unilaterally.

These questions were not applicable to all medicines as 47/542 medicines were prescribed to be taken 'when required' as displayed in Figure 11. For these medicines, participants frequently revealed that they had been advised by a medical practitioner to stop or adjust the prescribed dose based on clinical response.

6.6.4.8 Reported adverse effects and treatment effectiveness of medicines

The questions delivered to parents, carers and young people regarding their experience of adverse effects of medicines can be found in section 6.5.1.1.8.

Over one quarter, 26% (123/481) of medicines were reported to cause adverse effects. For less than 1% (3/481) of medicines, respondents reported being unsure as to whether a perceived adverse effect was instead associated with a child's disease state.

A question was delivered to parents, carers and young people to explore their views on the effectiveness of medicines (see section 6.5.1.1.8). Of the valid responses, 38% (180/476) of medicines were perceived to always be effective (Likert score = 1), whilst only 5% (24/476) of medicines were perceived to rarely or never make a child better (based on reports of Likert scale scores 4 or 5).

6.6.4.9 Additional barriers to medicines adherence and medicines adherence status

Barriers to medicines adherence were defined for the purpose of this study as reasons for dose omissions.

The question used to identify reasons for omitting a dose of medicine in addition to refusing, forgetting, and discontinuing medicines is provided in section 6.5.1.1.9. Independently, additional barriers to medicines adherence were not reported by sufficient respondents to conduct statistical analyses. Also, the additional barriers reported were not specific properties of oral formulations and therefore were not a focus of the present study.

All reported reasons for non-adherence were grouped into two themes, unintentional and intentional barriers to medicines adherence.

Reports of unintentional barriers to medicines adherence included parents not re-ordering medicines on time and thus omitting doses, delays in obtaining medicines from pharmacies (e.g. stock problems), delays in obtaining prescriptions from GP surgeries, forgetting to take medicines out (e.g. when children stayed with other parent, at sleepovers or on holiday), and not administering when child is ill or sleeping. These included reports of forgetting to administer medicines from section 6.6.4.5.

Intentional barriers to adherence included concerns of the stigma associated with medicine taking (e.g. choosing not to take to sleepovers or for weekend activities), parents choosing not to administer for additional reasons (e.g. feel that medicine is not working). These included reports of children refusing medicines and parents/young people discontinuing medicines administration from section 6.6.4.3 and 6.6.4.7 respectively.

Any reason reported for omitting a dose of medicine classed a child as not fully adherent in this study.

In total, 21% (51/245) of respondents did not report missing any doses of medicines.

Of the respondents, 79% (194/245) reported at least one reason (i.e. forgetting, refusing, discontinuing if it was perceived that child felt worse or better or an additional reason) for omitting a dose of a medicine. These 194 respondents were categorised according to the type of non-adherence behaviour/s reported; 56% (108/194) were classified as unintentionally non-adherent, 10% (19/194) intentionally non-adherent and 35% (67/194) both unintentionally and intentionally non-adherent. The categorisation of respondents reporting non-adherent behaviour is displayed in Figure 26 below.

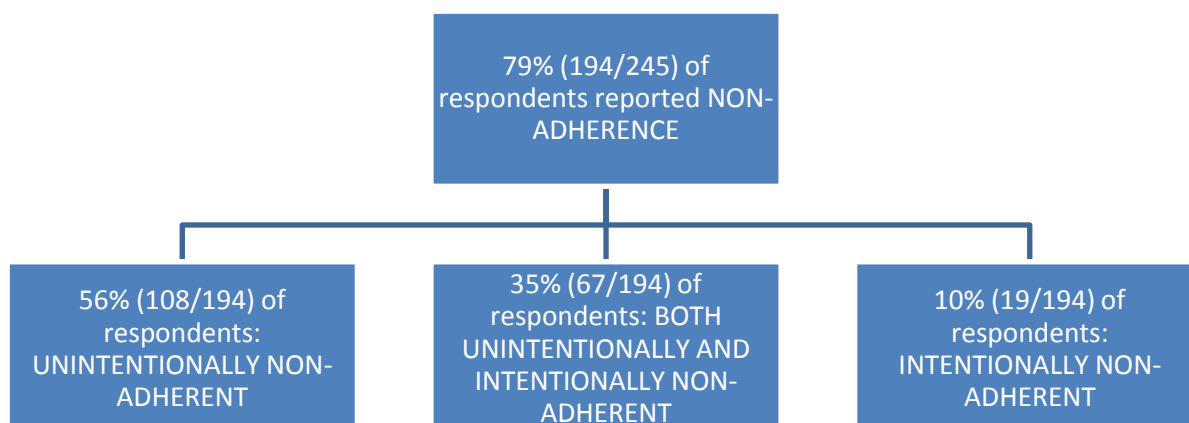


Figure 26 A diagram displaying the categorisation of respondents reporting unintentional and intentional non-adherent behaviours.

Reason for percentages exceeding 100% is due to rounding up results.

6.6.4.10 *Reported issues surrounding the supply of medicines*

Participants were asked if they had encountered problems when obtaining medicines from pharmacies (see section 6.5.1.1.10).

When investigating problems encountered by parents, carers and young people when obtaining medicines, over one third (36% (86/241)) of respondents claimed to have experienced issues with a total of 23% (110/472) of medicines.

Supplementary comments were provided by two participants, concerning difficulties with obtaining oral syringes and the problems with re-sterilising them (i.e. numbers erasing).

6.6.4.10.1 Obtaining Specials medicines

One quarter (25% (27/110)) of problems reported with medicines supply were associated with Specials medicines.

Almost three quarters (71% (27/38)) of Specials medicines with a valid response for the question regarding obtaining were described as difficult to obtain.

Difficulties reported by respondents regarding the supply of Specials medicines included shortened expiries i.e. frequent re-ordering, GPs unhappy to prescribe (or not prescribing quantities requested by specialists), delays at GP surgeries and pharmacies (time periods of 24 hours to one week for pharmacies to obtain medicines from Specials suppliers).

6.6.4.10.2 Obtaining non-Specials medicines

Problems obtaining non-Specials medicines were reported and included insufficient medicines stock in pharmacies, delays at pharmacies (e.g. when ordering specific brands of medicines, pharmacists querying off-label prescribing), delays in receiving prescriptions from consultants, waiting times in pharmacies and short medicine expiries resulting in frequent pharmacy visits (flucloxacillin solution was provided as an example).

6.6.4.11 *Problems with PILs*

The question designed to explore problems experienced with PILs is provided in section 6.5.1.1.11.

Data regarding problems experienced with PILs is reported in Figure 27 below for the valid responses (see Figure 11 for missing data).

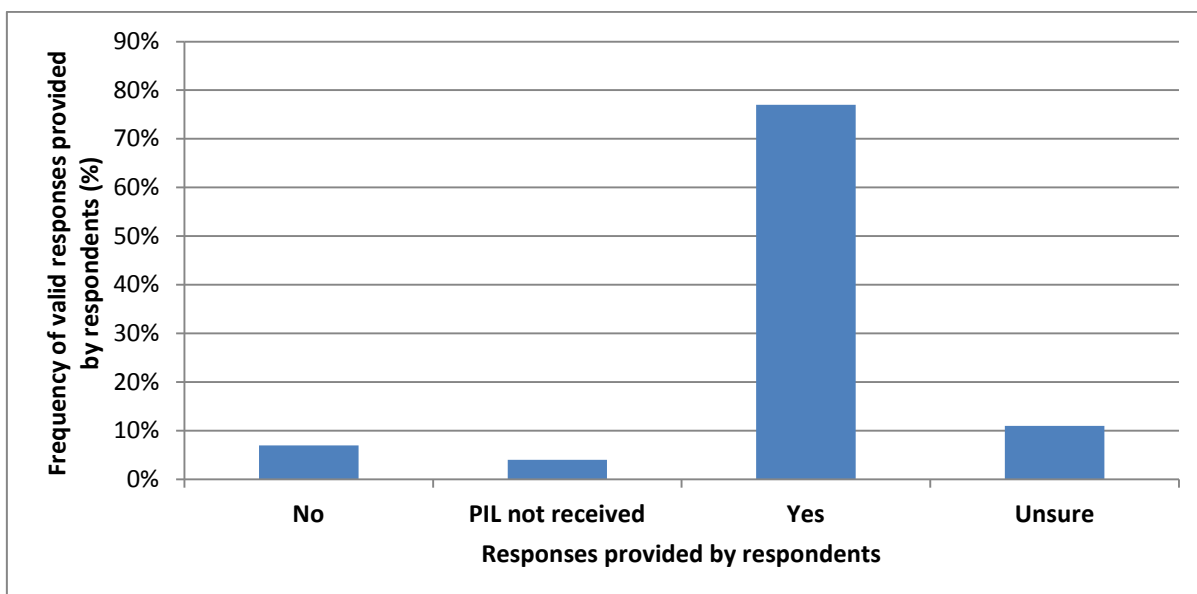


Figure 27 A histogram displaying valid responses to the question: Do you feel that the information you get is in plain English and clear/easy to understand?

Problems were reported for 7% (33/456) of medicines and included conflicting information provided by healthcare professionals and printed in PILs (e.g. PILs stating that a medicine is not to be administered to children), PILs described as ‘complicated’ and ‘difficult’, discrepancies between doses on labels of medicines and in PILs, PILs in non-English language, and difficulties with the English language written in PILs.

For 4% (20/456) of medicines it was reported that no PIL was received. For the remaining medicines either no problems were reported (77% (351/456)) or respondents could not recall reading the PIL so were unable to answer the question (11% (52/456)).

6.6.4.12 Reports of problems with medicines at school

Questions regarding medicines administration in schools (see section 6.5.1.1.12) were delivered to participants if children were receiving education (see Figure 10 for missing data).

The responses provided regarding problems with medicines at school for children in education are displayed in Figure 28 below.

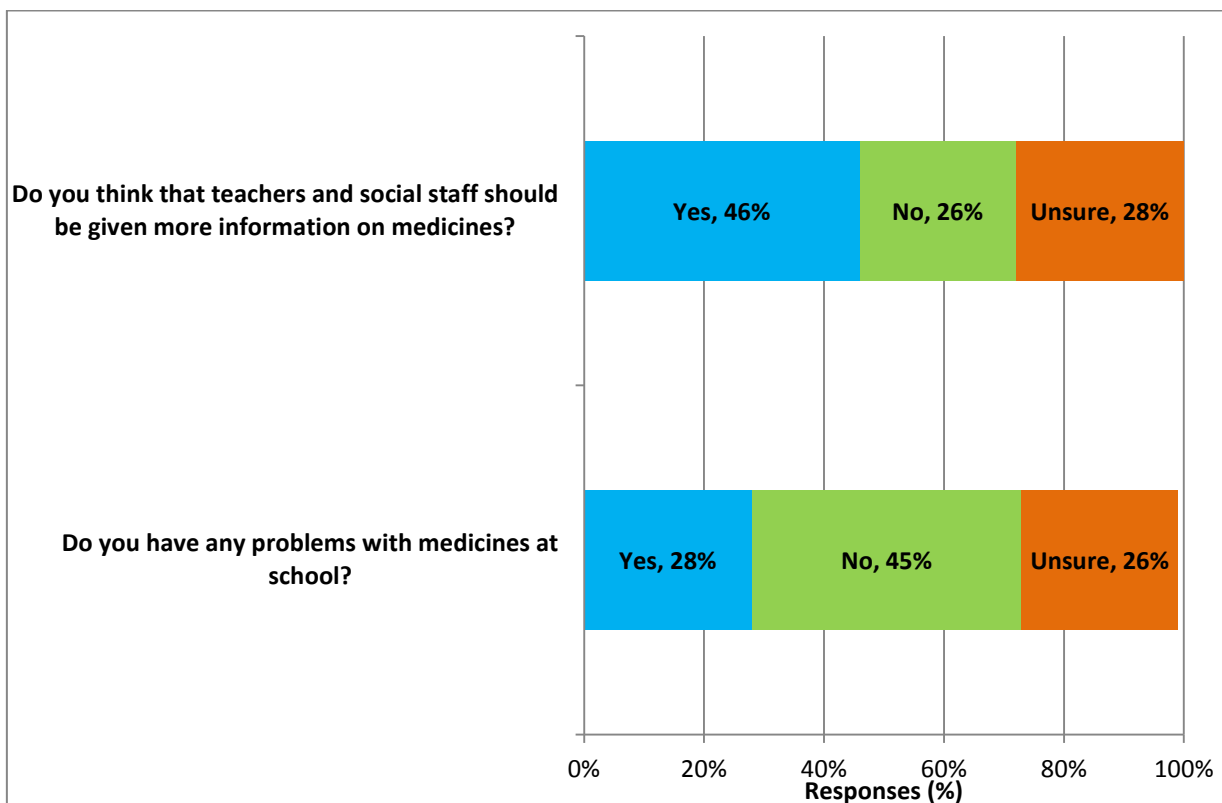


Figure 28 A histogram displaying valid responses to the questions: **Do you have any problems with medicines at school?** and **Do you think that teachers and social staff should be given more information on medicines?**

Uncoloured sections of bars represent missing data.

Whilst nearly half (45%) of the respondents did not report any problems with medicines administration at school, 28% of the respondents reported such problems. Issues included teachers and school staff refusing to administer medicines, teachers and social staff not permitting children to take medicines at school, parents expected to administer medicines at school, too much paperwork (i.e. parental permission required) and schools not willing to manage medicines.

Where problems were not reported, often parents praised the support offered by teaching staff at specialist educational institutions for children with delayed development.

Almost half (46%) of the respondents perceived that it would be beneficial for teachers and social staff to be better educated regarding medicines management at school, however, 26% felt that teachers and social staff did not require more information. Some parents reported that schools were good with managing medicines and felt that administering medicines was beyond teachers' responsibilities.

For some children, medicines were not required during the school day. This was the most common reason highlighted by respondents reporting indifferent ('unsure') responses to the questions regarding problems with medicines at school.

6.7 Discussion

6.7.1 Oral formulation-related barriers to medicines administration

This study uniquely identified the prevalence and nature of oral formulation-related barriers to medicines administration across various chronic conditions in a large population of paediatric patients. No other study has investigated this (see Chapter 4).

Study findings indicate that problems with the properties of oral formulations are those associated with the taste, texture, quantity or volume, size or aversion to or difficulty swallowing, colour/appearance and smell in descending order of reported prevalence.

Issues that were grouped to form 'other formulation and administration problems' revealed obstacles to administration (e.g. frequent daily dosing) that were not associated with the

specific properties of oral medicines. Such barriers to medicines administration are beyond the current project aims and require further exploration in future studies.

Oral formulation-related barriers to medicines administration were observed across individual medicines and across drug therapeutic classes (based on BNFC chapter classification). This study identified that at least 20% of medicines prescribed from each BNFC chapter were reported to have taste problems. Medicines featuring in BNFC chapters 5 (antibiotics antivirals and antifungals), 6 (drugs used to treat the endocrine system) and 1 (gastro-intestinal drugs) were reported to have the largest proportion of taste problems in descending order.

Taste problems highlighted with some medicines had been anticipated in the early stages of this research through personal communication with healthcare professionals and the YPG. However some findings were more surprising; anecdotally iron formulations have been perceived to be unpalatable, however in this study, taste problems were reported for only one quarter of children prescribed a liquid iron preparation.

The most prevalent taste problems were reported amongst children prescribed ranitidine liquid, prednisolone soluble tablets and trimethoprim liquid in order of descending prevalence. These findings warrant further investigation to determine if similar problems are experienced by patients suffering from acute conditions, as these medicines are often prescribed.

Prednisolone soluble tablets were commonly identified with taste, texture and quantity problems. This medicine is frequently prescribed to treat acute asthma flare-ups in the primary setting, therefore it is of paramount importance that this formulation is addressed.

Such findings need to be used to direct healthcare professionals when prescribing medicines, and pharmaceutical companies when designing medicines for children.

In this study, oral formulation-related barriers to medicines administration, texture, volume or quantity, size or aversion to/difficulty swallowing, colour and smell were reported across fewer medicines compared to taste, however such properties of oral formulations should not be ignored. Statistical results (see spearman's correlation test, Table 41) found that a weak, yet significant positive correlation existed between taste reports and texture, smell, volume/quantity, (correlation coefficients 0.151 ($p < 0.001$), 0.143 ($p = 0.001$) and 0.102 ($p = 0.017$) respectively). This suggests that although significant correlation exists between taste and other oral formulation-related barriers to medicines administration, further investigation in future studies is needed as the correlation is weak.

Prescribers need to be alert with regard to oral formulation properties when prescribing medicines for children. Based on study findings, problems with texture were commonly associated with medicines used to treat malignant diseases and immunosuppressants (chapter 8 of BNFC) and also co-trimoxazole liquid, omeprazole soluble tablets and lactulose liquid. Problems reported with the quantity of solid dosage forms or volume of liquids/powders were most prevalent across medicines prescribed for gastro-intestinal disorders (BNFC chapter 1). The quantity of pancreatic lipase capsules and the volume of macrogol 3350 oral powder and prednisolone soluble tablets (when added to liquids) were highlighted most commonly by respondents reporting problems with the volume or quantity of medicines.

The size and ease of swallowing of solid dosage forms also need to be carefully considered. Over one fifth (21%) of antibiotics, antivirals and antifungals (from BNFC chapter 5) prescribed were identified as being too large or difficult to swallow through reports. Co-trimoxazole tablets were most frequently reported by participants with respect to problems with their size.

Colour/appearance and smell were not reported to serve as obstacles to medicines administration as frequently as the other oral formulation-related problems discussed. Administering colourless medicines through an NG tube was reported to cause confusion for one mother. She perceived coloured medicines to be most useful for remembering which medicines had been administered.

Parents or carers may influence child acceptance of a medicine. If parents or carers perceive that a property of an oral formulation (e.g. smell, colour) is unfavourable this could reduce child acceptance. When recording parent or carer reports of unfavourable oral formulation properties, respondents were asked to provide details to support the problems experienced by children as reported in section 6.5.1.1.1. This was performed to optimise the accuracy of parental reports.

The plethora of oral formulation-related barriers to medicines administration reported in this study warrant further exploration in future studies. Problems identified with the oral formulation properties of individual medicines in this study need to be addressed by pharmaceutical companies and also carefully considered by prescribers when prescribing medicines for children. The overarching aim will be to help to improve medicines for children in the future and through this improve adherence to medicines.

6.7.2 Medicines manipulation

It has been documented that many medicines administered to paediatric patients are not age-appropriate, as a consequence of this some parents or carers (either on their own accord or following the advice of a healthcare professional/information provided in a PIL) manipulate medicines. Reports of parents, carers and young people mixing medicines with different foodstuffs were provided in the interviews. The limited awareness of parents, carers and young people regarding potential consequences of medicines manipulation was observed during the interviews.

Reassuringly, 82% (405/499) of medicines were reported to be administered in a manner defined as 'gold standard'. However, this study identified that almost one third (29%) of participants reported medicines manipulation for the purpose of giving a specific dose or to facilitate medicines administration. Several studies conducted in HIV and oncology patients included in Chapter 4, reported similar findings to the present study. Manipulation strategies used to administer medicines to children were highlighted by between 24% and 32% of parents or carers (Byrne *et al.*, 2002, Christiansen *et al.*, 2008, Goode *et al.*, 2003, Wrubel *et al.*, 2005) (see Table 2).

The qualitative analysis of reported administration techniques identified several examples of medicine manipulations (see Tables 44 and 45) that could affect drug bioavailability and thus therapeutic response. The potential physicochemical effects of these manipulations are reported in Table 51 below.

Table 51 Potential physicochemical effects of medicines manipulation.

Manipulation technique	Potential physicochemical effects
Splitting tablets or sachets manually	Inaccurate segmentation resulting in administration of inaccurate dose (underdose versus overdose)
Mixing non-soluble tablets with liquids	Non-uniform dosing, aggregation and sedimentation of insoluble drug particles
Milling tablets	Thermal degradation
Mixing with foodstuffs	Fruit juices (altering pH), drug binding to dairy proteins, formation of insoluble complexes

Drug-foodstuff incompatibilities and effects on drug absorption were previously discussed in section 2.5.3. It is well documented that the tetracycline antibiotics form an insoluble complex with calcium and thus drug absorption can be reduced by between 50 - 80% if taken with milk or other dairy products (Baxter, 2010). The binding of calcium with levothyroxine is less well appreciated than binding with the tetracyclines (Baxter, 2010). A young person in this study reported swallowing levothyroxine tablets with a large glass of milk, and although this was not classed as a medicine manipulation, drug bioavailability may be altered as a result of drug-foodstuff binding. Sub-optimal clinical response of a drug could be the outcome.

However, it is probable that the extent of drug-foodstuffs binding is lesser when solid dosage forms are swallowed immediately with foodstuffs, compared to when mixed with foodstuffs and in contact for a period of time prior to administration (cf medicines manipulation). Whilst it could be argued that for some reports of medicines administration with foodstuffs, only a negligible effect on drug absorption may present, for some medicines such as those with a narrow therapeutic index, this may be of clinical significance. In addition, administering medicines with foodstuffs affects gastric transit time and this can also influence drug bioavailability (Bowles *et al.*, 2010).

Limited evidence is available on the effects of mixing drugs with various foodstuffs prior to medicines administration (see section 2.5.3). Prolonging the contact time of a drug with a foodstuff is likely to increase the binding capability of foodstuff to drug and therefore may risk reducing drug bioavailability, thus affect therapeutic response.

Additionally, if a drug-foodstuff mixture is not consumed in its entirety, the desired dose will not be administered. Examples of parents adding medicines to bottles of milk and breakfast cereals are reported in Table 45. In addition, children may associate certain foodstuffs with the administration of unpalatable medicines and refuse to consume these foods.

Informal recommendations on how to manipulate medicines were retrieved from the BNFC and other sources as reported in section 2.5.3 (AstraZeneca, 2011, BNF for Children, 2011-2012, Norgine Pharmaceuticals Ltd, 2009). Also, the Great Ormond Street Hospital website (GOSH, 2010) and Medicines for children website (Medicines for Children, 2011a, b) offer advice for administering medicines to children. However, the data retrieved was not largely supported by a robust scientific evidence base.

Statistical results of this study have identified that medicine manipulations were significantly less likely to be reported for children aged 5-11 years and 12-18 years, compared to children aged 0-4 years in this study, with odds ratios 0.29 (95% CI 0.13-0.67) ($p=0.004$) and 0.18 (95% CI 0.06-0.59) ($p=0.005$) respectively. See Table 46 for multivariable analysis results for medicines manipulation discussed in this section.

It is probable that younger children have less experience with different flavours and 'mouth-feels' and therefore may be more likely to resist medicines administration or refuse to take

medicines in the study defined 'gold standard' manner (i.e. in their existing form). It was discussed earlier (section 4.5) how similarly, delaying feeding infants lumpy foods can influence acceptance of foodstuffs (Northstone *et al.*, 2001).

The person/s responsible for administering medicines significantly influenced reports of medicines manipulation ($p=0.049$) in this study. When the responsibility of administering medicines involved children, the likelihood of reporting medicine manipulations was significantly lower compared to when parents or carers had sole responsibility with an odds ratio of 0.28 (95% CI 0.10-0.81) ($p=0.019$). These findings are supported by interview reports of parents and carers revealing manipulation techniques that had been mastered, including reports of parents concealing medicines in various foodstuffs unbeknown to their child. Some *ad hoc* administration techniques were whispered to RV by parents and carers.

Medicine manipulations were significantly more likely to be reported for 'other' medicine formulations (encompassing granules, powders, soluble tablets, chewable tablets and melts) and also solid dosage forms (tablets and capsules) compared to liquids, with odds ratios of 23.97 (95% CI 9.14-62.84) ($p<0.001$) and 9.66 (95% CI 3.48-26.87) ($p<0.001$) respectively. As granules, powders and soluble tablets often need to be dissolved in water prior to administration, manipulation techniques, e.g. adding dosage forms to various fruit juices or foodstuffs or measuring specific volumes of medicines (see Tables 44 and 45) are more likely to be adopted. As dissolvable formulations have varying solubilities this may influence parents and carers to mix these with various foodstuffs (sometimes at different temperatures) to mask unfamiliar textures, tastes and/or reduce dissolution time (e.g.

reports of macrogol 3350 oral powder added to hot chocolate and zinc soluble tablets added to warm water were provided, see Table 45).

Tablets and capsules are pre-measured solid dosage forms. Tablets may need to be segmented or capsules opened either to measure commercially unavailable doses or to facilitate medicines administration. Splitting tablets or measuring the powder or granules within capsules poses the risk of administering an inaccurate dose and could contribute to a medicine overdose or underdose. A minor dosing error could have a significant clinical effect if the drug concerned has a narrow therapeutic index.

Tablets may require milling prior to administration where there is no equivalent liquid formulation available to administer a required dose and/or swallowing a solid dosage form is an obstacle to administration. The majority (21/24) of medicines that were manipulated for purpose of administering a specific dose in this study were tablets, soluble tablets or melts (see Table 44). Richey and co-workers (2011) similarly found that tablets were more likely to be manipulated to administer a specific dose compared to other dosage forms. However, Richey and co-workers (2011) investigated the practices of nursing staff administering medicines in a ward environment, not parents, carers and young people in the domiciliary setting as in the present study.

Statistical results indicate that medicines identified with size problems or child aversion to/difficulty swallowing are significantly more likely to be manipulated compared to those not associated with such problems (odds ratio of 4.52 (95% CI 1.37-14.90) (p=0.013). This study finding was anticipated as such difficulties are associated with solid dosage forms, e.g. tablets were segmented or crushed and capsules were opened and contents mixed with

various foodstuffs to facilitate administration and/or to improve child acceptance. This can affect the integrity of the dosage form and risks altering the pharmacokinetic profile of a drug. Modified release preparations in particular should not be crushed (Lowey and Jackson, 2007).

Statistical results of the present study showed that the likelihood of reporting medicine manipulations was significantly increased for medicines identified with unfavourable textures with an odds ratio of 3.15 (95% CI 1.39-7.14) ($p=0.006$). *Ad hoc* administration techniques were reported in circumstances where the consistency of a medicine was a barrier to administration. Mixing pancrealipase Micro gastro-resistant granules with pureed fruit was one example provided in an interview by a parent (see Table 45). This administration technique was used in an attempt to minimise the gritty texture of the granules, to improve child acceptance.

It is evident that many available medicines are inappropriate for children, therefore parents are often left with little choice except to manipulate medicines to administer a specific dose or to facilitate medicines administration. This can pose risks including inaccurate dosing and altered drug bioavailability as a result of drug-foodstuffs binding.

As there is a paucity of evidence regarding the safety and efficacy of such manipulation techniques, laboratory investigation (involving stability tests) beyond the scope of the present study is required to provide a scientific evidence base to support manipulations. This robust, evidence-based approach is warranted to inform guidelines on safe and effective medicine manipulation techniques to optimise drug therapy in paediatric patients. Administration techniques reported in this study should be used as case examples to guide

pharmaceutical companies in designing future paediatric formulations. Addressing medicines commonly reported to be manipulated in this study should be a priority (i.e. omeprazole soluble tablets, macrogol 3350 oral powder and co-trimoxazole tablets, see Figure 20).

Future formulation work needs to be implemented to develop age-appropriate medicines that are accepted by paediatric patients and also available in appropriate unit doses. Ideally, medicines for paediatric patients should be available in pre-measured dosage units covering child dosing ranges and be small enough to taper doses accurately.

Dosage form technologies such as mini-tabs as reported in two studies (Spomer *et al.*, 2012, Thomson *et al.*, 2009) may help to reduce medicines manipulation through minimising barriers that were found in this study to be significantly associated with physical adaptation, i.e. tablet size and texture of medicine. Dosing with mini-tabs can easily be adjusted and in addition the dosing counter device provides a more accurate dosing method compared to manipulation techniques (Thomson *et al.*, 2009). However, it should be acknowledged that for some medicines, it may be more feasible for practical and economical reasons to use safe and effective manipulation techniques.

Also, it would be useful for future studies to investigate if education to help children with chronic conditions to learn to swallow tablets could improve medicines adherence. Encouraging children to accept solid dosage forms from a younger age may be beneficial, supported by studies investigating infant acceptance of different tastes and textures of foodstuffs as discussed earlier in section 4.5.1. This could reduce child aversion to some medicines and also reduce unnecessary medicine manipulations.

The majority (79%) of patients with NG or PEG tubes fitted were administered medicines via these routes. For this group of patients, solid dosage forms needed to be crushed where liquids were unavailable and part volumes of liquids measured following the dispersion of tablets/granules. Personal communication with parents and carers revealed that much time is spent, and many problems and concerns encountered when administering medicines via NG or PEG tubes. It is vital that the healthcare team responsible for the care of a child fitted with an NG or PEG tube understand the complex issues that surround these routes of administration. Administering medicines through NG and PEG tubes potentiates pharmaceutical risks including sedimentation and caking of drug particles.

Medicines manipulation was not as high (14%) as anticipated for patients administering medicines via NG or PEG tubes. This is likely to be related to the increased prescribing of Special liquid formulations in these patients. In the present study, prescribing of Specials was found to be five times more prevalent in patients with NG or PEG tubes fitted. A cascaded prescribing process should always be followed to ensure that commercially available products are prescribed where possible. Rigorous implementation of a prescribing cascade for administering oral medicines to children both orally and via the NG/PEG tube route may help to achieve a nationally standardised, safe and cost-effective prescribing practice.

Nonetheless, to supply some drugs it may be justified to order a Specials medicine, for example if the equivalent licensed medicine formulation poses a risk such as blocking an NG or PEG tube. An example reported by parents in this study involved Losec MUPS granules blocking NG/PEG tubes. Such administration difficulties highlighted by parents of children

with complex health needs should be used to direct formulation work, and have highlighted a niche for extemporaneous dispensing.

6.7.3 Medicines refusal

Statistical results of this study indicate that medicine refusals at some point or in the six months prior to interview were significantly less likely to be reported for 5-11 year olds than for 0-4 year olds with odds ratios of 0.42 (95% CI 0.19-0.89) ($p=0.024$) and 0.06 (95% CI 0.01-0.48) ($p=0.009$) respectively. See Tables 47 and 48 for multivariable analysis results for medicines refusal discussed in this section.

A possible explanation for this finding could be associated with the increased understanding of children regarding medicines as they enter school age. They may begin to understand why they need to take medicines and the importance of medicines adherence. It should be remembered that parental or carer guidance and persuasion may also be more feasible with 5-11 year olds as generally they are more developed compared to 0-4 year olds.

The rate of reporting medicine refusals in the six months prior to interview significantly differed across the child age ranges at diagnosis ($p=0.030$). Although not reaching statistical significance between each age group and the youngest age group (less than one month old), the findings of this study suggest that when paediatric patients are diagnosed with chronic conditions later in childhood (12-18 years), medicines are more likely to be refused. Young people with limited knowledge of their chronic condition may be striving for autonomy and left by parents or carers to be fully responsible for medicines administration (Michaud *et al.*, 2004) thus may be more vulnerable to poor medicines adherence. A study conducted by

Shemesh and co-workers (2004) found that young people were left responsible for medicines administration from an average age of 12 years.

It is likely that young people recently diagnosed with a chronic condition will be less familiar with regular medicines administration compared to children diagnosed with a chronic condition at a younger age. This finding supports the need to increase education in young people recently diagnosed with chronic conditions in order to improve their understanding of the importance of adhering to medicine regimes. A study conducted by Clarke and co-workers (2005) concluded that amongst oncology children, those with more information on their disease had improved understanding of the importance of adhering to medicines.

Regarding adherence, paediatric studies conducted in CF and oncology have found that patients have a tendency to be less adherent to medicine regimes if they are less knowledgeable of their disease and treatment (Gudas *et al.*, 1991, Tebbi *et al.*, 1986). However, a further study by Beck and co-workers (1980) found no association between medicines adherence and patient knowledge in children with renal disease. It is acknowledged that refusal is only one factor influencing medicines adherence, however these study findings on adherence support findings of the multivariable analysis results regarding medicines refusal in this study.

Results of multivariable analysis suggest that reporting medicine refusals is more likely for patients living in more deprived areas (higher IMD 2010 scores) than those living in less deprived areas with odds ratios 3.19 (95% CI 1.37-7.43) ($p=0.007$) and 4.75 (95% CI 2.02-11.18) ($p<0.001$) in ascending order of IMD 2010 score for the two uppermost quartiles. It is likely that this finding is related to lower educated parents and carers living in more deprived

areas. It is probable that parents and carers living in more deprived areas have a poorer understanding regarding the importance of medicines adherence.

In more deprived areas there may be a higher prevalence of poorer health and parents or carers with learning disabilities, increased social difficulties, and poorer housing and living conditions (more inhabitants per household, more children and potentially less one-to-one care) based on IMD 2010 scoring (see footnote to Table 34). Inevitably in such circumstances adherence to medicines may not be the number one priority in life. Additionally, it is likely that more immigrants and ethnic groups live in more deprived areas, therefore cultural, social and language issues may act as barriers to medicines administration.

Several studies have found associations between low socioeconomic status (including low level of parent education) and non-adherence, in child populations suffering from renal disease, HIV, CF and Juvenile Rheumatoid Arthritis (JRA) (Brownbridge and Fielding, 1994, Davies *et al.*, 2008, Patterson, 1985, Rapoff *et al.*, 2005). The education and knowledge regarding medicines administration and the importance of medicines adherence amongst parents living in more deprived areas needs to be addressed.

Problems identified with taste (odds ratios 3.82 (95% CI 2.11-6.92) ($p < 0.001$) and 2.66 (95% CI 1.16-6.07) ($p = 0.021$)), texture (odds ratios 3.38 (95% CI 1.24-9.22) ($p = 0.017$) and 3.34 (95% CI 1.20-9.32) ($p = 0.021$)), volume/quantity (odds ratios 12.79 (95% CI 4.41-37.12) ($p < 0.001$) and 4.44 (95% CI 1.05-18.82) ($p = 0.043$)) all significantly increased the rate of reported medicine refusals on at least one occasion and in the six months prior to interview (odds ratios and p values reported respectively).

When examining the influence of reports of poor palatability on reported medicine refusals, taste-related problems were associated with 64% (54/85) of medicines that were refused. Supporting the findings of the present study, Zelikovsky and co-workers (2008) conducted a study in 56 young people listed for a renal transplant and found that participants reporting 'hate the taste' as a barrier, missed more doses of medicines ($p=0.02$), see Table 2.

The type of formulation (e.g. liquid versus solid dosage form versus other) was not significantly correlated with reports of medicine refusals in this study ($p=0.336$). This finding suggests that medicine refusal is not related to the type of formulation prescribed.

Van Dyke and co-workers (2002) reported lower medicines adherence rates in children suffering from HIV who were administered tablets compared to those administered liquid medicines. However, this study was conducted in a narrow patient population prescribed antiretrovirals and it is widely accepted that the size of antiretroviral tablets are troublesome for children (Van Dyke *et al.*, 2002). The present study was conducted in children with different chronic conditions therefore limited comparisons can be drawn with findings from studies conducted in narrow patient populations.

A further study (FormPIC- REC no 13/NE/0020) previously discussed in section 4.5.1, evaluates which specific factors influence healthcare professionals when choosing to prescribe, dispense or administer a particular dosage form. Additionally, determining the factors perceived as important by children, parents and carers when choosing a liquid or tablet formulation will be crucial.

6.7.4 Child acceptance

When examining the influence of reports of child acceptance of medicines, children were reported to be rarely or never happy to take over half of the medicines reported to be refused on at least one occasion. Child acceptance of medicines could influence child refusal, thus further studies in children are warranted to explore the obstacles to medicines administration.

Not all medicines that were disliked in this study were reported to be refused. For some medicines, dose administration was delayed. Resisting medicines administration was commonly reported in the interviews and described as time consuming and often distressing for parents and carers. Additionally, for some medicines with critical dosing intervals this could result in sub-optimal therapy.

6.7.5 Forgetting to administer medicines

In this study, rates of forgetting to administer medicines on at least one occasion were found to differ significantly across child age ranges at interview (0-4, 5-11 and 12-18 years) ($p=0.026$). A history of omitting medicines through forgetfulness was significantly more likely to be reported for young people (12-18 years) compared to 0-4 year olds with an odds ratio of 2.98 (95% CI 1.32-6.74) ($p=0.009$), see Tables 49 and 50 for multivariable analysis results for forgetting to administer medicines discussed in this section.

Forgetting to administer a dose of medicine is one barrier to medicines adherence. Other reasons can contribute to non-adherence. Several studies have reported that young people are more likely to be non-adherent than younger children when prescribed medicines to treat HIV, immunosuppression (post-transplant), CF and oncology (Beck *et al.*, 1980,

Brownbridge and Fielding, 1994, Elise *et al.*, 2005, Feinstein *et al.*, 2005, Gudas *et al.*, 1991, Patterson, 1985, Reddington *et al.*, 2000, Serrano-Ikkos *et al.*, 1998, S.D. Smith *et al.*, 1979, Tebbi *et al.*, 1986). The results from the multivariable analysis of forgetting a dose of medicine are supported by these previous study findings on non-adherence conducted in specific patient populations.

In contrast to these findings, Gibb and co-workers (2003) found that HIV-infected children over 10 years of age were more likely to be adherent to antiretroviral medicines than those younger than 10 years, however a small patient population (19/128) aged less than 10 years may have influenced these results (Gibb *et al.*, 2003). In two further studies no significant difference was found in adherence to medicines between children and young people suffering from HIV (Davies *et al.*, 2008) and JRA (Litt and Cuskey, 1981).

Findings of the present study suggest that medicines administration is not always a priority in the day-to-day life of a young person. As a child matures in to adolescence, generally reduced parental guidance and supervision is observed. It has been discussed earlier (in section 2.2) that young people begin to desire independence and empowerment over their medicines. Often, parents become less responsible for administering medicines and also reminding their child to administer medicines as the child gets older (WHO, 2003).

The majority of young people strive to lead a stereotypical 'teenage life' and are likely to undergo peer pressure, and feel the stigma associated with administering medicines (e.g. when attending social events) (Michaud *et al.*, 2004). The desire to answer in a socially acceptable manner may have encouraged some young people in this study to report

medicine taking behaviour inaccurately (Butz, 2006). For example, some reports of 'forgetting' medicines may represent intentional medicine omissions.

Statistically significant findings of this study indicate that forgetting to administer medicines was less likely to be reported for children prescribed three or more medicines (i.e. polypharmacy based on prescribed oral medicines) compared to children prescribed one medicine (odds ratio 0.28 (95% CI 0.15-0.51) ($p < 0.001$)) and similarly within the six months prior to interview (odds ratio 0.27 (95% CI 0.13-0.57) ($p = 0.001$)).

A study in HIV patients conducted by Reddington and co-workers (2000) concluded that children taking three to four medicines were more likely to be adherent than those taking fewer (one to two) and also those taking more (five to seven) medications (study details reported in Table 2). A further study conducted to validate medication adherence scales in 78 young people with organ transplants, found that parents provided more prompts to remind young people to administer medicines when a greater number of medicines were prescribed (Simons and Blount, 2007). However, in contrast to the present study which included children with various chronic conditions these studies were conducted in narrow patient groups.

It is probable that when patients are prescribed multiple medicines, routine and familiarity of medicines reduce the risk of forgetting to administer doses. Also, parents, carers and children may recognise the synergistic effect of different medicines on therapeutic response when prescribed multiple medicines to treat a chronic condition. In addition, polypharmacy may indicate that a child is suffering from multiple conditions, this could promote increased parental concern towards adhering to medicines.

Reports of parents using drug charts on kitchen walls for children with complex therapeutic regimes were recorded in the interviews. Drug charts were not discussed by any young people. Encouraging parents, carers and young people to use reminding systems as discussed later (see section 6.7.6), irrespective of the number of medicines that they are prescribed may help them to remember to administer medicines throughout the day and thus improve medicines adherence.

Forgetting to administer medicines within the six months prior to interview was significantly less likely to be reported for children requiring additional educational help compared to those children not requiring additional educational help, with an odds ratio of 0.38 (95% CI 0.16-0.94) ($p=0.036$). This finding suggests that parents and carers accept more responsibility with regard to medicines administration in circumstances where children require additional educational help.

Parents and carers may have more concern towards their child's health if s/he requires additional support at school, suggesting that they are more likely to understand the importance of adhering to medicine regimes. A general observation from data on medicines at school (see section 6.6.4.12) was that specialist schools for children with learning difficulties dealt better with medicines administration during the school day compared to non-specialist institutions.

Reports of forgetting to administer medicines in the six months prior to interview were significantly associated with drug therapeutic class (based on BNFC chapter) ($p=0.013$). The unadjusted rates of forgetting doses of medicines across drug therapeutic classes were calculated and followed a similar pattern to the multivariable model. Medicines featuring in

chapters 8 (drugs used to treat malignant diseases and immunosuppressants), 3 (respiratory drugs) and 6 (drugs used to treat the endocrine system) were least likely to be reported as forgotten (in descending order) in the six months prior to interview, see Figure 24.

Medicines featuring in chapter 8 of the BNFC include those used to treat malignant diseases. This finding suggests that remembering to administer medicines is more likely when the condition treated is perceived to be of a more serious nature. A review of adherence rates across chronic disease regimens in children reported higher adherence to medication regimes used to treat paediatric patients with HIV/Acquired Immune Deficiency Syndrome (AIDS) (Rapoff, 2010). The results of the present study support the finding of Rapoff and co-workers (2010) in terms of linking adherence with illness.

It also should be noted that medicines adherence may be influenced by how patients perceive the benefits and risks of their medication. A study conducted in adults suffering from different chronic conditions concluded that significant differences in beliefs and reported adherence between illness groups existed, with cardiac and asthma patients more likely to perceive that concerns regarding their medication outweighed the benefits compared to oncology or dialysis patients (Horne and Weinman, 1999).

When considering reports of forgetting to administer medicines in the six months prior to interview, the influence of additional educational help and other health-related need of a child followed a similar pattern, although other health-related need did not reach statistical significance ($p=0.869$). There are limitations to the factor other health-related need as this covered a wide range of problems including visual-related and multiple needs associated with chronic physical and/or mental impairment.

6.7.6 Reminding systems for administering medicines

Encouraging and reinforcing effective reminding systems may be useful for parents, carers and young people administering medicines in the domiciliary environment. The majority (82%) of respondents reported remembering to administer medicines as being part of 'daily routine', yet 64%, reported forgetting to administer medicines on at least one occasion. During the interviews, young people who reported forgetting to take medicines were counselled (if appropriate) to use devices with alarms (e.g. mobile phones); such technological methods may be effective. Parents using medication charts in the domiciliary environment reported positive feedback regarding their value. Families struggling with complex regimes should be encouraged to use a medication chart.

Reminding systems used to remind parents and young people to administer medicines should not be overlooked as they can prompt accurate and timely dose administration. Prescribers and other healthcare professionals need to ensure that such systems are in place to aid medicines adherence where remembering to administer doses is difficult. In addition reminding systems should be considered for children who are prescribed complex regimens and those prescribed medicines requiring medicines to be administered at critical dose intervals. Further investigation in to the effectiveness of medicine reminding systems is required that is beyond the scope of this study.

6.7.7 Intentional discontinuation, adverse effects and treatment effectiveness of medicines

Reassuringly, less than 10% of respondents claimed that they had discontinued medicines without the instruction of or in agreement with a healthcare professional if it was perceived

that a child was worse (i.e. adverse effects were experienced). Even fewer respondents (2%), reported that they had discontinued a medicine if a child seemed better. Reports suggest that the majority of parents, carers and young people understood that medicines prescribed to treat chronic conditions should not be discontinued without professional guidance. Comments were provided by respondents to support this (see section 6.6.4.7).

Education plays a key role in developing the knowledge of parents, carers and young people regarding a chronic condition and the importance of regular and accurate timing of medicines administration. Discouraging patients from discontinuing medicines is critical to achieve full adherence, thus it is essential that allied healthcare professionals are educated to counsel patients and their carers effectively. Healthcare professionals ought to discuss common adverse effects of medicines thoroughly with parents, carers and young people so that they are able to deal with them safely and effectively. This may help to minimise parental stress and negative attitudes towards medicines.

The importance of taking medicines with a preventative value and taking medicines when not feeling unwell is not always understood by children up to the age of 11 years (Sanz, 2003). In addition, several studies have reported that medicines adherence can reduce over time (Lancaster *et al.*, 1997, Tebbi *et al.*, 1986), indicating that close, regular monitoring is required post-diagnosis.

If parents, carers and young people were provided with a better understanding of how individual medicines work this could improve medicines adherence. For example parents, carers and young people should be advised of the time period that exists before clinical effects of a medicine ought to be experienced. Similarly for medicines where clinical effects

are not expected to be seen or experienced by patients this information should be provided to patients and their carers.

6.7.8 Additional barriers to medicines adherence and medicines adherence status

This study identified barriers to medicines adherence. Over half (56%) of the respondents reported unintentional non-adherence behaviours. Only one tenth (10%) of respondents reporting non-adherence behaviours reported solely intentional barriers, however over one third (35%) of respondents reported a combination of unintentional and intentional reasons for omitting doses of medicines, see Figure 26.

Medicines adherence in children is more complex than in adults as reasons for unintentional and intentional non-adherence behaviours can be influenced by parents/carers and/or children (e.g. parents may choose not to administer medicines and/or children may refuse medicines). Adherence is a complex multi-factorial phenomenon, therefore these findings provide a general insight in to overall medicines adherence patterns in this study, yet are not particularly useful alone. It is evident that in order to understand how to improve medicines adherence, healthcare professionals need to explore the obstacles experienced by individual patients and their parents or carers. Education needs to be addressed accordingly with the aim of minimising barriers to medicines adherence where this is possible.

6.7.9 Issues surrounding the supply of medicines

This study identified that issues with medicines supply were reported for almost three quarters (71%) of Specials medicines that were prescribed. When medical practitioners are

prescribing for children, it is not only crucial that they choose a suitable formulation; they also need to be vigilant with regard to potential problems surrounding medicines supply.

Prescribing protocols need to be addressed to ensure that healthcare professionals have the necessary resources to prescribe effectively. Healthcare professionals (especially prescribers and pharmacists) need to work collaboratively to ensure that a prescribing cascade is followed. This should direct prescribers to select medicine formulations commercially available before choosing unlicensed products as previously discussed in sections 5.5.4 and 6.7.2.

Communication between hospital prescribers and GPs is crucial in promoting the continuation of drug treatment in a smooth, unaffected manner following patient discharge from hospital. Optimisation of patient safety, satisfaction of therapeutic treatment (including ease of obtaining) and reduction in the drugs bill is the overarching aim.

6.7.10 Problems with PILs

Community law requires that for all medicinal products placed on the 'community market' a PIL is provided to enable safe and appropriate use of a medicinal product (European Commission, 2009). Guidance on presentation of patient information is also provided in the guideline (European Commission, 2009).

The majority (77%) of respondents claimed to be happy with the information provided in PILs. When prescribing a medicine off-label (outside of the terms of the product licence), it is essential that effective counselling is provided by healthcare professionals to ensure that parents, carers and young people are happy to administer it. It is crucial to alleviate any

unnecessary concerns, for example parents reading information suggesting that a particular medicine should not be administered to children (prescribed off-label), as this could result in non-adherence.

For 4% of medicines prescribed, it was reported that no PIL had been provided. In circumstances where unlicensed medicines are prescribed, often there is no PIL available. It is necessary for prescribers to reassure parents, carers and young people of their personal expertise in prescribing the unlicensed medicine concerned and where possible to provide them with alternative sources of medicines information.

6.7.11 Problems with medicines at school

Observations of the present study data indicate that medicines administration and responsibility in the school environment varies across different schools. Over one quarter of respondents revealed that they had experienced difficulties with medicines at school. Similarly, a study exploring family perceptions of medicines administration at school concluded that between 15% and 50% of children taking medicines for asthma, diabetes and ADHD experienced problems (Clay *et al.*, 2008).

Almost half of the respondents in the present study agreed that teaching/social staff require more information on children's medicines and chronic conditions. A variety of views regarding the medicines management support of teaching and social staff was reported by parents, carers and young people (see section 6.6.4.12). F.J. Smith and co-workers (2008) examined the experiences and concerns of 27 young people and their parents and carers regarding medicines management at school and similarly reported wide variations in support with medicines management at school. They found that over one third (10/27) of

parents/young people reported negative attitudes regarding the support received from school staff (F.J. Smith *et al.*, 2008). These findings are supported by a study promoting the collaborative work of pharmacists and nurses to educate teaching staff personnel (Clay *et al.*, 2008).

6.8 General limitations and ethical issues

The ethical nature of the study recruitment process involved posting study invitation letters to all patients on the selected outpatient lists. It was anticipated that a significant proportion of children attending clinics would not be eligible for study participation (e.g. child not prescribed medicine for at least one month). However, only a minority, (3% (47/1559)) of the invited population declined to take part in the study.

Prior to providing consent, some parents clarified with RV that their child's medication would not be changed as a result of this study. Further parents sought reassurance that their personal information would be held confidentially and would not be disclosed when reporting results. Two parents sought to ensure that there was no follow-up to the study before providing consent.

During the study period, language barriers and parental concern regarding the exposure of personal information impeded the consent of some participants. However, interpreters were utilised where possible. One interview was conducted utilising an interpreter. Parental consent to participate in the study was obtained for ten young people who were unable to provide consent as it was perceived that they were not Gillick competent.

Time was an impending factor for parents and carers when asked to provide consent. Some parents had work commitments or had to return children to school so were unable to participate at the time of appointment. Owing to consultation with a multidisciplinary team, the increased duration of HIV and CF clinics affected recruitment in these patient groups as parents and young people did not want to stay at hospital any longer than was necessary. Further problems were encountered when a parent or carer (with legal guardian status) was not present at the clinic appointment. In such circumstances, RV advised that a parent or carer could choose to arrange a mutually convenient time in the future. Seven participants did not have time to answer any questions on barriers to medicines adherence, however data on medicines manipulation and oral formulation-related barriers to medicines administration was collected.

Differences in the number of patients on specific clinic lists and the frequency of specific clinics affected the numbers of individual clinics targeted. Recruitment rate was lower in some clinics. A cardiologist informed RV that recruitment would be low in cardiology clinic as only few patients are prescribed medicines. Observation during diabetic clinics revealed that the majority of children were not prescribed oral medicines. As oral medicines were pertinent to the present study fewer diabetic clinics were targeted. Recruitment rates across orthopaedic clinics were low as the majority of patients were not prescribed oral medicines for at least one month. Specialist HIV and sickle cell anaemia clinics were conducted less frequently (monthly) and additionally there were many repeat visits, reducing the potential recruitment population.

A limitation of using a self-report tool is the risk of inaccurate reporting, as acknowledged in section 2.2.1, and discussed in section 6.7.5. Interview design attempted to minimise this as far as possible. Questions were designed to not be threatening and prior to conducting interviews, participants were advised that responses would not be reported back to clinicians unless something dangerous was revealed, see section 6.5.3. Also, as the researcher (RV) was not a member of the clinical care team it was not anticipated that false reports would limit this study.

The number of participants reporting forgetting or refusing medicines within one week or six months was small. It is not known whether this was the result of underreporting or indicative of the true behaviour of the participants. It is important to also understand that some reports of forgetting medicines may represent medicine refusals. Underreporting of medicines refusal may be represented by some 'forgetting' results as participants could be more likely to report an unintentional reason for not taking medicines, (i.e. it may be that a participant chooses to answer in a more socially acceptable manner and fears blame) (Butz, 2006).

Irrespective of the causes of low reporting, this resulted in a paucity of positive outcomes on which to perform statistical analyses. As a consequence of this, statistical tests involving these variables had limited statistical power within these time frames (i.e. one week and six months prior to interview). This resulted in the minimal detectable differences in the analyses being very large, hence factors that may have had small but genuine effects on these variables may not have been identified.

In this study, one mother reported that medicines had not been omitted, however the young person in her care provided an opposing report. This finding reinforces the need for future studies to investigate parent and teenager reports independently. In the present study, there was insufficient time and resources for parents and young people to be interviewed independently and the study was designed to be pragmatic, thus reflect a family environment. A study by Buchanan and co-workers (2012) (see Table 2) found significant similarity between independent reports of 'taste/cannot get it down' ($p < 0.001$), forgetting ($p < 0.001$), and also refusing doses ($p = 0.01$) amongst young people with HIV and their carers. These findings suggest that reporting of such outcomes is fairly consistent between carers and young people, however this is only one study, conducted in children with HIV.

Optimising the accuracy of parent/carer reports was important as some children were too young to describe problems experienced with medicines. When exploring reports of oral formulation-related barriers to administering medicines to babies and young children, RV asked parents/carers to describe the child's reaction to medicine administration. Parents and carers described how some medicines were easier to administer than others and provided examples to support poor palatability of a medicine (including wry face, shrugging shoulders).

6.9 Direct patient benefit of interview

The interview process itself had a direct patient benefit as RV was able to utilise her professional role as a pharmacist in circumstances where it was necessary. Advice was provided to parents and young people with regard to optimising medicines management

(i.e. patient benefit, clinical benefit, and safety). Examples of advice provided by RV can be found in Appendix 23.

7 FINAL DISCUSSION

7.1 Introduction

Perspectives of parents, carers, children and healthcare professionals were explored in this study to develop a thorough understanding of the problems that prevail when administering oral medicines to the paediatric population. This study has examined the prevalence and nature of oral formulation-related barriers to medicines administration and also medicines manipulation in a large population of paediatric patients suffering from chronic conditions. The data collected in the interviews and focus groups of this study has provided new information, adding to the published literature to date.

7.2 Oral formulation-related barriers to medicines administration

The present study has expanded the pre-existing, narrowly focussed literature and identified the prevalence and nature of oral formulation-related barriers to medicines administration in children suffering from various chronic conditions. In the literature to date, no study has explored problems experienced in the domiciliary environment across such a wide patient population.

Taste was the most prevalent oral formulation-related barrier to medicines administration reported in the systematic review (Chapter 4), and similarly in the present study interviews and focus groups. In the majority (93%) of review studies (see Table 2) taste was identified as a central obstacle to medicines administration, and additionally associated with a drug or specific formulation in the key 7 (antiretroviral) studies. In the present study interviews over one third (35%) of currently prescribed oral medicines were associated with taste-related

(taste, aftertaste and lack of taste) problems. Taste was reported as a barrier to medicines administration for almost two thirds (64%) of currently prescribed oral medicines that were refused. In addition to medicines refusal, resisting medicines administration was described in cases where medicines were poorly accepted and caused unnecessary parental stress, yet still taken by children.

Findings from the interviews in this study indicate that at least 20% of medicines prescribed from each BNFC chapter are associated with taste-related problems. Antibiotics, antivirals and antifungals (BNFC chapter 5), endocrine drugs (BNFC chapter 6) and gastro-intestinal drugs (BNFC chapter 1) in descending order were associated with the largest proportion of taste issues. When considering individual medicines, ranitidine liquid (82%), prednisolone soluble tablets (81%) and trimethoprim liquid (75%) were identified as having the highest proportion of taste issues in descending order (see Figure 13 for further results).

It has been documented that fruity, sweet formulations are preferred and in general citrus and red berry flavours are favoured across Europe (EMEA, 2006). The present study results support this evidence. Positive attitudes towards Strawberry flavoured Calpol suspension were revealed across the healthcare professional focus groups and also by interview participants in the present study. Findings from study interviews show that flavours including mint (e.g. ranitidine liquid), 'bitter' flavoured prednisolone soluble tablets and aniseed (e.g. trimethoprim liquid) are disliked largely across a paediatric population suffering from chronic conditions.

Discussion in the UHCW pharmacist focus group supports the argument that poor medicines acceptance may result from unfamiliar flavours. Strawberry Calpol suspension was a

medicine reported to be better accepted than flavours perceived to be more 'unusual'. This concept may similarly apply to further organoleptic properties of medicines (e.g. poor acceptance of textures amongst children as reported in section 6.6.4.1.2).

A plethora of further oral formulation-related barriers to medicines administration, texture, quantity or volume, size or aversion to/difficulty swallowing, colour and smell were endorsed across the present study interviews and focus groups. In particular, problems with the texture of lactulose liquid and the volume of macrogol 3350 oral powder (in liquid) were reported in focus groups and interviews. Such barriers were reported less frequently than taste, however significant correlation was found with some of these properties and unfavourable taste, thus they should not be overlooked. Taste problems were found to be correlated with texture, smell and also volume or quantity in the study interview reports (see Spearman's correlation test of interview responses, Table 41) and also across the focus groups. The relationship between medicine volume and taste has been previously reported in the reflection paper (EMA, 2006). These findings warrant that pharmaceutical companies consider oral formulation-related barriers carefully when designing medicines.

Prednisolone soluble tablets were commonly identified as problematic to administer across the focus groups and interviews in the present study. The reasons reported for this included taste, texture and volume. Administering bitter tasting soluble prednisolone tablets in minimal volume was advised in the medical practitioners group to improve child acceptance. It is of paramount importance that further investigation of this specific formulation is prioritised. Prednisolone is commonly prescribed to children to treat acute asthma flare-ups in the community setting. Investigating if similar problems are experienced by children

treated in primary care would complement the present study. Such findings should be considered carefully by prescribers and institutions in all healthcare settings.

There is a potential opportunity to use key findings to reduce medicines wastage and improve cost-benefit. The positive economic impact of changing prednisolone soluble tablets to prednisolone tablets for general use in children was calculated. It is estimated that this will generate a cost improvement saving of £5000 per annum at UHCW (personal communication, UHCW healthcare professionals).

It should be noted that some organoleptic properties (e.g. colour and smell) may be considered unfavourable by parents, and therefore these should be dealt with very carefully as this may or may not influence child acceptance. Problems related to the colours or smells of medicines need to be explored to ensure that their impact is fully understood. Psychology assistance is warranted, to investigate such perceptions further.

Feedback directly in to formulation development work is critical to improve children's medicines of the future. Findings of this study should help pharmaceutical companies to prioritise formulation work. Formulation teams should be advised to review organoleptic and physical properties of medicines that are generally well-accepted across a paediatric population to direct the procurement of future medicines that are better suited to children. This could decrease the economic cost of medicine wastage in the future.

Following literature searches conducted in the present study it was evident that the majority of studies used taste-tests which had been conducted in specific patient populations and often in healthy children or adults (see Chapter 1). Taste-tests investigating flavour preferences across the paediatric population are warranted and are detailed in PIP guidance

(European Commission, 2008). It is vital that such studies consider paediatric patients suffering from various chronic conditions so that factors with potential to influence taste preference in specific patient groups can be considered (e.g. oncology patients may have increased taste-recognition errors) (Matsui, 2007a).

However, it is appreciated that taste-masking certain drug flavours can be troublesome, and more pharmaceutical drive to overcome this is needed as a matter of urgency. When formulating medicines for children, pharmaceutical companies need to be vigilant regarding the safety of excipients used. Concerns related to the safety of excipients when prescribing in children were raised in the pharmacist focus groups (see section 5.5.7). Supporting this, the EMA draft Guideline on pharmaceutical development of medicines for paediatric use provides guidance on the selection of excipients (EMA, 2013).

7.3 Medicines manipulation

The lack of appropriate paediatric formulations creates a barrier to safe and effective medicines administration. The systematic review (see Chapter 4) identified some examples of medicines manipulation reported in literature. In the majority of studies reporting such techniques there was a paucity of detail. Additionally, no scientific evidence base was referenced to support these medicines manipulation techniques in the review studies.

Findings from the present study interviews with parents, carers and patients have shown that nearly one third of respondents (29%) reported manipulating medicines. Almost one fifth (19%) of medicines were manipulated. A variety of reasons for manipulating medicines was reported across the interviews. Over one quarter (26%) of medicine manipulations were performed to administer a specific dose, however, the majority (79%) were carried out to

facilitate medicines administration (e.g. to mask unfavourable formulation properties, to improve child acceptance).

The present study has uniquely focussed on the prevalence and nature of manipulations to medicines performed by parents, carers and patients in a domiciliary environment. Complementing the findings of the current study, two investigations (Richey *et al.*, 2011, Skwierczynski and Conroy, 2008) as discussed earlier in section 2.5.2 identified the nature and frequency of manipulations to medicines administered to children on paediatric wards.

The risks of dosing inaccuracy (resulting in under or overdosing) are concerning and especially when the dosage required is not commercially available in a pre-measured unit. Amongst the reported medicines manipulation techniques, parents described having to measure fractions of powders or solid dosage forms. Human error may result in inaccurate doses being measured. The therapeutic response of a drug may be altered as a result of inaccurate dosing. This could cause a fatal dosing error if the drug concerned has a narrow therapeutic index, for example digoxin.

The medicines manipulated for the purpose of administering a specific dose, as identified in the study interviews (see Table 44), highlighted drugs for which age-appropriate formulations may not be commercially available. This should direct future paediatric formulation work.

Paradoxically, it is important that the MHRA are vigilant regarding the potential risks, e.g. parental confusion and dosing errors associated with licensing too many different strengths of the same drug formulation. The variety of dose units available need to be carefully rationalised in view of patient safety and risks associated with overdose, as has been done

with warfarin, where the number of tablet strengths are limited (BNF for Children, 2011-2012). Similarly, the unlimited variety of strengths of Specials formulations needs to be acknowledged. This was a concern highlighted in the focus groups and interviews. Additionally, to increase safety through prevention of prescribing, dispensing or administration errors, it would be sensible if strengths of liquid formulations were provided in a standardised fashion where possible (e.g. Xmg in 1ml) as discussed by pharmacists in this study (see section 5.5.8).

Qualitative analyses of medicines manipulation techniques (e.g. adding doses of levetiracetam liquid and sodium valproate liquid to breakfast cereal - see Table 45) used to facilitate administration reported in study interviews, revealed potential physicochemical effects that could alter drug bioavailability and additionally therapeutic response (see Table 51). Drug-dairy protein binding may occur when milk is added to breakfast cereal. Prolonging contact time of drugs with foodstuffs prior to dose administration increases the drug-foodstuff binding capability and therefore has the potential to reduce drug absorption, bioavailability and affect therapeutic response.

Although it is universally acknowledged that tetracyclines chelate calcium ions in dairy products as discussed in section 6.7.2, for the majority of medicines manipulation techniques the potential effects on pharmacokinetic responses are unknown. Limited data is available regarding the safety and efficacy of mixing medicines with foodstuffs, yet this study has shown that medicines manipulation is a common occurrence for the families interviewed. When parents or carers add medicines to meals or bottles of milk it is additionally concerning as incomplete consumption of a dose may result which could lead to

an altered therapeutic response. This was a concern raised in the focus group with medical practitioners.

An understanding of medicines manipulation is needed by all healthcare professionals involved in the care of an individual. Education of healthcare professionals to ensure that they fully understand the potential risks of medicines manipulation on therapeutic response is essential. This should guide them to prescribe the most appropriate formulation to attain accurate dosing, efficacy and patient safety. Collaboration between a multidisciplinary team of pharmacists, medical practitioners and nurses is crucial to achieve best patient care in more complex cases.

To minimise unnecessary medicines manipulation it is essential that medical practitioners prescribe the most suitable dosage form for a patient. It is important that they consider age-appropriateness, the type of formulation (in relation to patient acceptability and ease of administration), swallowing problems and patient capability to swallow tablets according to size, and also whether the individual has difficulty with various textures. These factors were found to significantly influence medicines manipulation in statistical analysis of the interview responses in this study (see Table 46, for odds ratios and associated p values).

Findings from the present study have directed the design of further research to determine which factors influence dosage form selection (FormPIC study REC no 13/NE/0020) as discussed in section 4.5.1. Such parameters need to be at the forefront of the prescribing process in an attempt to minimise inappropriate modifications of medicines. Furthermore, it is necessary to address the benefits of implementing training courses to help children to

learn to swallow solid dosage forms from a younger age, as discussed in the focus groups and published studies, see section 5.5.5.

It is appreciated that for some drugs, procuring a medicine that is well-accepted by paediatric patients is difficult, therefore medicine manipulations are inevitable. However, the lack of knowledge regarding the scientific evidence for medicines manipulation was evident across the healthcare professional focus groups. This was similarly reported in a study by Akram and Mullen (2012) which explored nurses' knowledge of mixing medicines with foodstuffs. These findings were anticipated owing to the limited scientific data available.

It is therefore vital that laboratory work is conducted to support the safety and efficacy of commonly used medicines manipulation techniques. This would provide a robust scientific evidence base to inform standardised protocols that could be used nationally. Suitable medicines manipulation techniques should be clearly referenced in commonly used reference sources (e.g. BNFC, PIL, Summary of Product Characteristics - SmPC). This is supported in the EMA draft guideline (EMA, 2013) which states that information on mixing medicines safely with food should be provided by pharmaceutical companies.

Medicines commonly reported to be manipulated in the study interviews were omeprazole soluble tablets, macrogol 3350 oral powders and co-trimoxazole tablets in descending order of endorsement (see Figure 20). Focus group participants highlighted similar manipulation techniques used to administer omeprazole soluble tables and macrogol 3350 oral powder (see Table 26). Reported examples of medicines manipulation provided in the study interviews, focus groups and the systematic review support the need for further laboratory

investigation and thus should feed in to pharmaceutical development work. In addition this may reduce time for preparation of medicines, medicines wastage and through this, cost. Optimisation of the education of both consumers of healthcare and those involved in the prescribing, dispensing or administration process is critical.

7.3.1 Patients with NG or PEG tubes

In addition to medicines manipulation, reports of parents administering medicines via unlicensed routes (e.g. NG or PEG tubes) were provided. Parents that needed to administer medicines via such routes described difficulties. The time taken to prepare and administer medicines plays a huge role in the day-to-day life of a parent, carer and patient. Personal communication with paediatric consultants at the start of this project identified difficult patient cases that had been highlighted to them by parents with complex dosing regimens (see patient cases in Appendix 6).

Across the present study interviews, reports of problems with feeding and medicines administration via NG and PEG tubes were prevalent. Losec MUPS granules blocking feeding tubes were discussed in the study focus groups and interviews, highlighting a problem to be considered carefully by pharmaceutical companies.

Nurses and pharmacists in the present study focus groups reported interactions between specific formulations (e.g. ciprofloxacin) and feeds when administered together via NG or PEG tubes, unlike the medical practitioners, who did not discuss the extent of problems encountered when administering medicines via these routes. This finding suggests that the medical practitioners were unaware of the scope of issues associated with NG/PEG tube administration. Parents additionally reported their concerns regarding the accuracy of

dosing following the preparation/manipulation of medicines for NG or PEG tube administration.

Guidance informed by a scientific evidence base would be especially useful to advise healthcare professionals, parents and carers on optimal and safe medicines administration in children with complex needs (e.g. where multiple medicines need to be administered via an NG or PEG tube, see Appendix 6). This should minimise current concerns of healthcare professionals, parents and carers regarding inefficacy of dosing through potential drug-food (including drug-nutrient) and drug-drug interactions.

7.4 Problems with Specials medicines

Specials medicines created many problems from the perspectives of parents, carers, young people and healthcare professionals in the interviews and focus groups of this study. Of the oral medicines prescribed to the children in the present study, 8% were identified as Specials.

For almost three quarters (71%) of Specials medicines prescribed, problems with medicines supply were revealed including shortened expiries e.g. frequent re-ordering, GPs unhappy to prescribe (and not prescribing quantities requested by specialists), delays at GP surgeries and pharmacies (medicines supply taking between 24 hours and one week in pharmacies).

Prescribing of Specials medicines was five times higher in study patients with NG or PEG tubes compared to patients not fitted with NG or PEG tubes. This increased Specials prescribing could be the reason for medicines manipulation not being as high as may be expected amongst this patient group. Future formulation work needs to target commonly

identified Specials medicines that were reported to cause difficulties across the focus groups and interviews e.g. omeprazole liquid. Increasing the practice of extemporaneous dispensing in pharmacy premises may help to reduce Specials prescribing (i.e. decrease expenditure on paediatric drugs), however, focus groups with pharmacists indicated that the suitability of pharmacy premises, staffing and quality assurance need to be addressed (see section 5.4.4.4.4). Portugal is an example where there are significant state controls on compounding. In Portugal, every community pharmacy must have a compounding laboratory and its dimensions are specified by law (Carvalho et al., 2008, INFARMED, 2007). It may be beneficial to introduce similar regulations in the UK and across Europe. This requires further investigation.

The medical practitioners seemed to have the least understanding and knowledge of the depth of issues with Specials and referred to fewer, more specific Specials medicines in comparison to the nurses and pharmacists whom reported an array of issues. The lack of credible evidence supporting efficacy and safety supplied with some Specials medicines (i.e. Certificate of Analyses) and absence of PILs were reported by the pharmacists. These issues clearly need to be addressed by pharmaceutical companies. To assure the safety and efficacy of Specials medicines, supporting scientific evidence should be provided in a standardised fashion.

Following analysis of focus group data it was evident that the knowledge of Specials medicines varied amongst healthcare professionals. The flow of events from prescribing intentions of medical practitioners through to interpretation and conversion in to a labelled

medicine by pharmacists (see Figure 7) will not be achieved if flow is interrupted by lack of awareness of medicine categorisation.

If a medical practitioner does not understand the implications of prescribing certain medicines (e.g. if s/he prescribes an unlicensed formulation which is ordered from a Specials manufacturer) this will affect the patient who will not be aware of the impending issues until they visit a pharmacy. Reports of parents experiencing unexpected problems with the supply of medicines were provided in the study interviews (see section 6.6.4.10). Supply problems were also associated with non-Specials medicines and liquid measuring devices (e.g. oral syringes) in parent interviews and across focus groups. The reported problems regarding difficulty in obtaining oral syringes through the NHS need to be addressed by Government funding bodies.

It is fundamental to ensure that healthcare professionals are educated to understand the importance of continuity of medicines supply. Communication between secondary and primary care must be improved to try to ensure smooth, continuous medicines supply at patient level. Furthermore, the cost of Specials procurement may not be considered during the prescribing process, this will have an impact on the economics of national drug costs. It is necessary to minimise Specials prescribing as far as is possible using a cascaded prescribing process to ensure that all commercially available products are primarily considered (as previously discussed in sections 5.5.4 and 6.7.2). Although the education of prescribers should be a primary focus, it is prudent to also address the knowledge of other healthcare professionals involved in supplying and administering medicines.

It is vital that parents, carers and young people are educated by healthcare professionals when prescribed unlicensed medicines or medicines in an off-label manner. This will aim to reduce confusion and concern when patient information is not provided (as discussed in pharmacist focus groups) or contradicting information is found in PILs (e.g. 'not suitable for children').

Although the absence of PILs with Specials medicines was commonly acknowledged in this study, problems reported with PILs by interview respondents were not confined to Specials medicines. For 4% of medicines, it was reported that no PILs were provided and for 7% of medicines, problems with PILs were reported (see section 6.6.4.11). The translation requirements for patient information supplied with parallel imported medicines were reported in the pharmacist focus groups. It is essential that patient information is provided with prescribed medicines, following guidance from the European Commission (2009). Furthermore, pharmacists should be extra cautious when supplying parallel imported medicines or unlicensed medicines. They need to ensure that protocols are in place and adhered to, regarding the provision of suitable and comprehensive patient information.

When prescribed unlicensed medicines or medicines in an off-label manner, it is important that parents understand the exact dose to be administered owing to varying strengths of formulations (as discussed in section 2.4.4). Also, it is essential that parents are counselled appropriately so that they understand when receiving the same brand of a formulation is not essential. Effective collaboration is needed between medical practitioners and pharmacists to improve prescribing practice and to increase patient understanding and satisfaction of care.

7.5 Medicines refusal

Refusal of medicines by children was an outcome influencing adherence, pertinent to the present study. It was necessary to investigate the proportion of subjects that had refused medicines and also the factors influencing medicines refusal. Reports of forgetting medicines and other reasons for poor adherence were also identified so that an overall indication of non-adherence (i.e. unintentional versus intentional versus both) could be ascertained. However, this was not a primary focus of this study.

In total, 31% of interview respondents reported medicines refusal on at least one occasion, accounting for the refusal of 19% of medicines prescribed. Medicines associated with the oral formulation-related barriers: taste, texture, volume or quantity were significantly more likely to be refused by paediatric patients in the present study (for odds ratios and associated p values see Tables 47 and 48). Across the focus groups these oral formulation-related barriers were also frequently reported to influence medicines adherence. Similarly, the systematic review highlighted these obstacles to acceptance of or adherence to medicines, albeit in narrow patient populations (see Chapter 4); however, only one study linked taste to child refusal (Lin et al., 2011). It would be beneficial for future studies to correlate oral formulation-related barriers with medicines refusal in order to identify if significant relationships exist.

The type of formulation prescribed was not associated significantly with history of medicines refusal in the multivariable analysis of the interview data in this study. This finding is supported by focus group reports which suggest that formulation choice varies between individual patients. Examples of adolescents insisting that they were prescribed liquids and

younger children preferring tablets were provided across the interviews and focus groups in this study. The relationship between influential factors and dosage form choice will be investigated in the study, FormPIC (REC no 13/NE/0020) as discussed earlier.

Statistical results of the interviews suggest that children 5-11 years are less likely to refuse medicines than those younger (for odds ratios and associated p values see Tables 47 and 48). Focus group reports support this finding. As far as medicines adherence is concerned, suggestions that toddlers and teenagers are problematic and also children who are less familiarised with different flavours and textures were reported in the groups.

It is probable that from school-age, children begin to experiment with more textures and flavours, thus they may be more likely to accept medicines that may be perceived by a pre-school infant to be 'unusual'. Additionally, children from school-age begin to learn and therefore may understand the importance of taking medicines regularly. Supporting this, Birch (1998) discussed the importance of early experience on children's developing food acceptance patterns and also reported how the quantity and quality of children's experiences with food influence food intake patterns and food preferences. Parental influence may play a role in medicines refusal and the suggestion that parents may influence medicines adherence was reported across the study focus groups.

The introduction of education for teenagers, parents and carers at clinic appointments may help to improve their understanding of a chronic condition and thus the importance of adhering to medicine regimens. It may be beneficial to introduce educational counselling at the point of diagnosis and also periodically during clinic appointments. The aim of this would be to identify any problems encountered at an early stage. Once identified, potential

solutions to barriers should be proposed and an agreement reached between healthcare professional and parent/patient. The overarching aim is to minimise medicines refusal, thus improve adherence to medicines.

Children living in increased poverty may be more likely to refuse medicines, this is supported by the statistical findings of the present study interviews (for odds ratios and associated p values of IMD 2010 score, see Table 47). There may be issues with large families and also poor understanding due to a lower level of parental education. Several studies as discussed earlier (see section 6.7.3) have reported associations between low socioeconomic status (including low level of parent education) and non-adherence. Issues with 'disorganisational social problems' were reported in the UHCW pharmacist focus group with regard to medicines not necessarily being a priority in complex life circumstances.

Patient, parent and carer education needs to be targeted to try to improve medicines adherence in families of lower socioeconomic status. Supplementary advice and support should be provided to such families to ensure that they understand the importance of adhering to therapeutic regimes.

7.6 Additional barriers to medicines administration (i.e. those not directly associated with oral formulations) for future work

7.6.1 Forgetting to administer medicines

Forgetting to administer medicines on at least one occasion was reported by 64% of interview respondents. Almost half (47%) of the medicines prescribed were reported to have been forgotten on at least one occasion.

Statistical findings suggest that young people (12-18 years) compared to 0-4 year olds were more likely to forget medicines (see odds ratios and associated p values in Table 49). In addition, for children prescribed three or more oral medicines, statistical results indicate that forgetting medicines is less likely (see Tables 49 and 50 for odds ratios and associated p values). When taking multiple medicines: routine, familiarity of medicines, synergistic effects of medicines and increased parental concern (e.g. if child has multiple chronic conditions) may reduce the likelihood of forgetting medicines. In contrast to these findings, discussions in the BCH pharmacist and medical practitioner focus groups suggested that rationalising prescribing in patients prescribed several medicines may help to improve medicines adherence. This requires further investigation.

Statistical results from forgetting medicines in the six months prior to interview (see odds ratio and associated p value in Table 50) suggest that for children requiring additional educational help, medicines are less likely to be forgotten compared to those not requiring educational help. These children may require more parental support than their peers in all areas of their life and so parents are more used to providing additional support.

Medicines in BNFC chapters 8 (drugs used to treat malignant diseases and immunosuppressants), 3 (respiratory drugs) and 6 (drugs used to treat the endocrine system) were significantly less likely to be reported as forgotten in the previous six months based on the multivariable model (see Table 50 for odds ratios and associated p values). The unadjusted rates of forgetting medicines in the previous six months as displayed in

Figure 24, similarly showed that medicines in these groups were reported to be forgotten less frequently. Also, reports of forgetting antibiotics, antivirals and antifungals, gastrointestinal drugs and cardiac drugs were higher (see Figure 24).

Perceived severity of disease may affect medicines adherence as discussed in section 6.7.5. Also, the perceived balance of risk and benefit of a medicine may affect adherence (see sections 5.5.6 and 6.7.5). Prescribers need to be aware of factors that may affect adherence when prescribing medicines to children. These findings should also highlight to prescribers, particular patient groups that may require extra help to support medicines adherence.

Study interview data revealed that the majority of respondents (82%) reported that daily routine helped them to remember to administer medicines. As almost half of medicines prescribed were reported to be forgotten on at least one occasion, it seems evident that reminding systems (e.g. phone alarms and wall calendars) need to be implemented to remind parents, carers and young people to administer medicines throughout the day. Counselling parents, carers and young people on the importance of regular and correct timing of doses is crucial for some medicines, especially those with a short half-life and a narrow therapeutic index.

7.6.2 Intentional discontinuation, adverse effects and treatment effectiveness of medicines

Although interview reports in the present study suggest that the majority of interview respondents did not discontinue medicines without guidance from a healthcare professional (see section 6.6.4.7), a minority reported stopping medicines if the child seemed worse or better (8% and 2% respectively). It is prudent that patients are closely monitored post-

diagnosis. This should help parents/carers and children to develop a better understanding of the importance of adhering to medicines.

A thorough understanding of pharmacology and adverse effects of medicines is required by healthcare professionals in order to counsel parents, carers and young people effectively. This should help to improve their understanding of the therapeutic responses that should be expected and also highlight key adverse effects of medicines and how to deal with them, thus to discourage medicines non-adherence. Ideally, counselling should be performed by pharmacists when dispensing medicines. Time was reported to be an obstacle to effective counselling of parents in the pharmacist focus groups. Time constraints owing to staff shortages within the NHS were acknowledged in this study and need to be urgently addressed by Government funding bodies.

7.6.3 Problems with medicines at school

Reports on problems with medicines administration at school varied across the interviews and focus groups. For over one quarter (26%) of children in full-time education, problems with taking medicines at school were reported. Almost half (46%) of respondents voiced that teachers and social staff require more information on chronic conditions and medicines.

Across the focus groups, inconsistent reports regarding the acceptance of children's medicines at school were provided, indicating variation in the adoption of medicines policies between different schools. Further reports from the focus groups suggested that prescribing for school-aged children should be carefully considered, and where possible, formulations allowing dosing outside of the school day should be prescribed. Prescribing doses outside of the school day was similarly reported to be beneficial by some parents in the interviews.

Present study data on problems with medicines administration at school should be used to reinforce the standardisation of and adherence to policies regarding medicines in the school environment. Addressing the education of teaching staff with regard to treatment of chronic conditions is necessary to improve their acceptance and understanding of medicines. The values on 'roles and attitudes of staff' reported in a study by F.J. Smith and co-workers (2008) reflect the views on teaching and social staff reported in the present study interviews, as discussed in section 6.7.11. It may be useful to explore the specific role of school nurses in a further study.

The goal of investigating medicines management within the school environment is to support and direct the standardisation of care provided to children suffering from chronic conditions at school, in line with the National Service Framework for Children, Young People and Maternity Services (DOH, 2004).

7.7 Medicines adherence

Medicines adherence remains a multi-factorial phenomenon, which is more complex in children owing to the additional influence of a patient's family (Osterberg and Blaschke, 2005). An inconsistency of outcome reporting was observed across the included review studies (see section 4.4.4.7.1), although oral formulation properties were described as, or implied to be barriers to medicines adherence.

The present study identified that 79% of interview respondents reported a reason for missing at least one oral medicine on an occasion. Over one third (35%) of these non-adherent respondents reported both intentional and unintentional reasons for missing doses of medicines (see Figure 26). To address ways to improve adherence this information alone

is inadequate. Future studies need to design methodology similar to that adopted in the present study to explore the specific factors that compromise medicines adherence when administering medicines to children.

Additional barriers to medicines adherence were identified, yet are beyond the scope of the present study as they were not specifically related to oral formulations (see section 6.6.4.9, e.g. parents not re-ordering medicines on time and stock problems in pharmacies). These need to be investigated further in future research.

8 CONCLUSION

Owing to its explorative (inductive) yet consumer informed (deductive) design this was a unique and multi-perspective study investigating oral formulation-related barriers to medicines administration across paediatric patients suffering from various chronic conditions. This pragmatic study has filled the research gap that existed through investigating such problems in a large sample of paediatric patients in a domiciliary environment. Identification of the difficulties experienced by families when administering medicines to children is essential for directing future formulation development work. It was necessary to ask children and their parents/carers the right questions to obtain the answers needed to fulfil the original project aims, thus parent, carer and patient involvement has played a fundamental role throughout this study.

In total, 31% of interview respondents reported medicines refusal on at least one occasion, accounting for the refusal of 19% of medicines prescribed. Medicines refusal was found to be significantly influenced by age of child, socioeconomic status (IMD 2010 score), taste, texture and volume (of liquid/powder) or quantity (of solid dosage form).

This study found that taste was the main oral formulation-related barrier to medicines administration; associated with 35% of medicines prescribed and 64% of medicines that were refused.

Out of the interview respondents, 29% reported manipulating medicines. In total, 19% of medicines were manipulated, of which 26% were performed to administer a specific dose. However, the majority (79%) were carried out to facilitate medicines administration. Factors found to significantly influence medicines manipulation were: age of child, type of

formulation prescribed, size of solid dosage form or aversion to/difficulty with swallowing, texture and the person responsible for medicines administration.

The initial study objectives are supported by PIP guidance, which states that paediatric formulation studies should include 'palatability and taste-masking' and data on 'compatibility and stability in the presence of relevant common foods and drinks particularly if food is used to facilitate administration of the dosage form' (European Commission, 2008). The project findings should be used to inform and direct future paediatric medicines formulation design. This will assist with the development of age-appropriate formulations to provide suitable dose units and improve child acceptance.

8.1 Future Work

The key five findings from this thesis that require further exploration are:

(i) Almost one third (31%) of oral medicines were reported to have been refused by children suffering from chronic conditions. This demonstrates that a significant number of children with chronic conditions are refusing medicines. It is crucial that healthcare professionals are asking parents, carers and young people non-threatening questions regarding adherence, to identify any difficulties experienced with medicines. This will prompt prescribers to ensure that they are prescribing the most appropriate formulation for a patient. The education of healthcare professionals with regard to effective parent/carer counselling needs to be addressed in future studies.

In addition, it is appreciated that a significant proportion of medicines prescribed to children do not meet their needs and it is crucial that pharmaceutical companies prioritise paediatric

formulation work based on current study findings, which have identified factors related to oral formulations that are significantly associated with medicines refusal: taste; texture and volume (of liquid/powder) or quantity (of solid dosage form). Additional factors found to be significantly associated with medicines refusal were child age and socioeconomic status (IMD 2010 score). These factors need to be explored in future studies.

(ii) Almost one third (29%) of oral medicines administered to children suffering from chronic conditions were reported to have been manipulated. Age-appropriate formulations should be developed to provide both suitable dose units and acceptable palatability for paediatric patients. Additionally, pharmaceutical companies should undertake further laboratory work based on the findings of this study to provide robust scientific evidence to support medicines manipulation techniques suitable for parents, carers and young people to use in the domiciliary environment - with attention to patient safety and maintaining drug efficacy. Such guidance should be referenced and available to healthcare professionals and parents, carers and young people in clear, appropriate formats (e.g. within BNFC monographs and PILs respectively). Healthcare professionals should advise parents, carers and young people based on this guidance.

In addition, healthcare professionals should carefully consider factors found to be significantly associated with medicines manipulation when making prescribing decisions, especially those related to palatability and ability to swallow.

(iii) Findings from focus groups with healthcare professionals suggest that the knowledge and understanding of such professionals regarding prescribing, dispensing and administering

medicines to children with chronic conditions needs to be investigated and addressed in future studies. It would be useful to explore this in both a community and hospital setting.

(iv) This study has reported barriers to administering oral medicines to children suffering from chronic conditions in the domiciliary environment. Further studies should investigate if similar problems are encountered by parents, carers and children prescribed oral medicines for acute conditions in a primary care setting.

(v) This study has identified that there are significant problems experienced by parents, carers and children when administering oral medicines to children, thus further studies should determine the prevalence and nature of barriers to administering non-oral medicines to children.

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Appendix 1 Views of West-Midlands Young people, parents and carers regarding medicines

This present study has developed with the support of the Consumer Liaison Team for the WM-MCRN who have facilitated focus groups to provide a lay perspective to inform research undertaken by MCRN. This work has brought to light the issues that children and young people have with the type of medication that they are prescribed. This research project evolved through public involvement and user involvement was utilised throughout this study. The initial design of this study was influenced using feedback from work conducted by the team with young people in the Birmingham and Coventry area to investigate young peoples' perceptions on what medicine studies should address.

The ideas surrounding this research was initially discussed during different activities with consumers (parent support groups, school visits, MCRN consumer liaison work). Feedback revealed a vast amount of support from consumers of all ages, with different conditions and from different ethnic and social groups. Consumers felt that patients will benefit directly as lay individuals will have had a role in future drug developments. Information about medicines adherence, especially for individuals with chronic conditions and of a vulnerable age group is perceived as very helpful.

Consultation has also taken place at UHCW's Youth Council comprising members aged 11-18 years, of mixed ethnicity, with a range of medical conditions. Members consulted about this project agreed that this research was important and felt that those involved in medicinal developments need to listen to the views of both the individuals taking problematic medication and their parents/carers who support their adherence. The group were delegated the task of designing posters to publicise the project and formulated the top 5 questions that they think should be asked in questionnaires to aid experimental design of the template interview sheet. The responses given were: side effects, taste, formulation, forgetting medicines and issues at school.

Side effects quotations

“I had mood swings so I stopped taking that medication.”

“Steroids for colitis, my sister has to take 20 tablets a day. This had an effect on her immune system and now she can’t go swimming at schools which she was really upset about.”

“Steroids make you pale- appearance and social issues especially when you’re a teenager it affects your confidence. They also make you gain weight.”

Taste of medicines quotations

“Horrible taste of some medicines.”

“I had to take protein drinks and it was meant to be blackberry flavour but it tasted of salt still. Another young person had the same experience of this.”

Formulation quotations

“I can’t take tablets- my parents always crush my paracetamol.”

Forgetting medicines quotations

“I forget a lot to take my long-term medication.”

“My sister’s school always forget to give her medication at lunchtime. She is only 10. Now my mom has to put stickers in her lunch box to remind her to ask.”

Issues with medicines at school quotations

“Social staff on school trips aren’t informed enough about medicines!”

“It’s a big worry for teachers.”

“More information is needed for teachers as we have to explain how to give our medicines.”

(Consumer liaison personal communication)

General opinions from public involvement

The young people were asked what they thought about the study, and they all agreed it was worthwhile and would be happy to take part if they thought that improvements may be made.

Consumer Liaison Officer for the WM-MCRN team has confirmed that parents, carers and young people have expressed strong requests for research on paediatric medicines. This has influenced the need for the study. An anonymous quotation from a parent:

“We aren’t asked about the medicines.” (Consumer liaison personal communication)

Appendix 2 Personal communication with healthcare professionals at UHCW

The attitudes of many paediatricians towards this study were very positive. A Paediatric Consultant with specialist interests in neonatology and general paediatrics reported personal interest:

“Issues with the taste of Kaletra”- a commonly prescribed antiretroviral combination formulation in HIV paediatric patients.

A discussion with a Rheumatology Consultant with regard to her perception of issues with paediatric medicines took place. The consultant’s response:

“Methotrexate tablets are commonly complained about by patients.”

Consultation with a paediatric pharmacist raised some issues with specific medicines: Taste issues associated with the following liquid medicines: rifampicin, chloral hydrate, cephalosporins and oseltamivir

Regimes identified as problematic by the paediatric pharmacist: Antiretrovirals and tuberculosis regimes - described as “intense.”

The Paediatric pharmacist was asked to reveal any advice given to parents administering medicines to children. The advice that was given:

“Avoid too much disruption to drug” – an example provided was to add hydrocortisone tablets to minimal water and swirl around as crushing may generate energy and influence molecular characteristics of the drug, thus potentially affecting activity and effectiveness.

Further points identified by the paediatric pharmacist: Drug naïve patients seem to be less compliant with taking medicines, i.e. for short-term, acute conditions such as infections, whereas chronic patients are less likely to spit out/refuse medicine as parents/carers will have developed their own specific way of administering medication to their child.

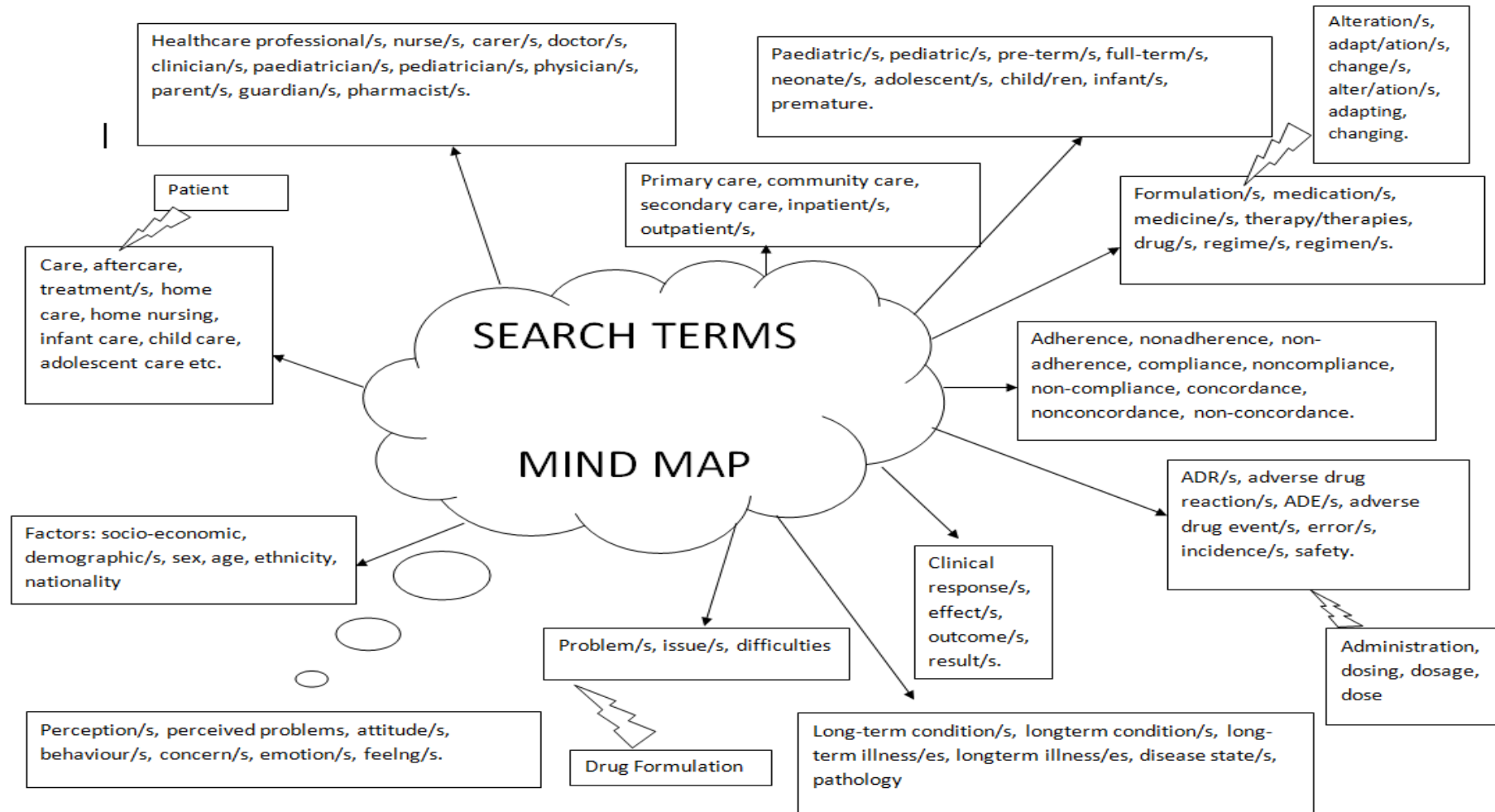
She queried: “Firstly, how are dosage forms adapted to make them palatable and secondly are they still effective in this form?”

Further laboratory study required beyond the scope of the current project was proposed by the pharmacist.

Consultation with the paediatric pharmacist with regard to the use of unlicensed medicines at UHCW clarified the order and procurement process followed. Normally unlicensed medicines prescribed in hospital are ordered from a specials manufacturer. The orders to specials manufacturing units are usually performed consistently (i.e. the same manufacturers are used when ordering specific medicines) to try to ensure homogeneity and maintain continuity for patients. Usually two main specials manufacturing units are used. When there is difficulty, other specials units are used, this inevitably alters consistency of formulations obtained.

The pharmacist revealed that sometimes medicines that are assumed to be specials prove too difficult to procure, and in these cases hospital best practice guidance is followed and a specific formulary is utilised. Unfortunately a seven day expiry exists with most extemporaneous medicines due to lack of preservative, and thus can create inconvenience and wastage. Following hospital best practice, 'Novo diluents' are often used at UHCW, (diluents A and C). A reference list showing compatibility of the diluents with various drugs is available. The diluent: C is flavoured, but this does not always mask drug taste.

Appendix 3 A mind-map of key search terms guided by Buzan and Buzan (2006)



Appendix 4 Summary of quality assessment and risk of bias in included review studies

Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Shemesh <i>et al.</i> , 2004)	Medication adherence in pediatric and adolescent liver transplant recipients	YES	YES	YES	NO	NO	YES	NO	YES
(Tucker <i>et al.</i> , 2002)	Associations with medication adherence among ethnically different pediatric patients with renal transplants	YES	YES	YES	YES	NO	YES	NO	YES
(Zelikovsky <i>et al.</i> , 2008)	Perceived barriers to adherence among adolescent renal transplant candidates	YES	YES	NO	YES	NO	Reference to an existing self-report tool (MAM)	NO	YES
(Christiansen <i>et al.</i> , 2008)	Oral chemotherapy in paediatric oncology in the UK: problems, perceptions and information needs of parents	YES	NO	YES	NO	NO	UNCLEAR	NO	YES

Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Ingerski <i>et al.</i> , 2010)	Barriers to Oral Medication Adherence for Adolescents with Inflammatory Bowel Disease	YES	YES	YES	YES	NO	Reference to an existing self-report tool (MAM)	NO	YES
(Modi and Quittner 2006)	Barriers to Treatment Adherence for Children with Cystic Fibrosis and Asthma: What Gets in the Way?	YES	YES	YES	YES	NO	UNCLEAR		
(Boni <i>et al.</i> , 2000)	Compliance to combination antiretroviral therapy in HIV-1 infected children	UNCLEAR	NO	NO	YES	NO	Reference to an existing self-report tool (used by Gross and co-workers 1998)	NO	YES
(Buchanan <i>et al.</i> , 2012)	Barriers to Medication Adherence in HIV-Infected Children and Youth Based on self- and caregiver report	YES- refers to a longitudinal study of a multicenter cohort study (random recruitment from multicenter study population)	YES	NO	YES	NO	YES	NO	YES
(Byrne <i>et al.</i> , 2002)	Achieving Adherence With Antiretroviral Medications for Pediatric HIV Disease	YES	NO	NO	YES	YES (reported that interviewer was not part of care team)	UNCLEAR	NO	YES

Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Esteban Gomez <i>et al.</i> , 2004)	Influencia de las características del tratamiento antirretroviral en la adherencia del paciente pediátrico	YES	NO	NO	YES	YES (Pharmacist dispensing medicines – unclear if known to respondents)	YES	NO	YES
(Farley <i>et al.</i> , 2003)	Assessment of Adherence to Antiviral Therapy in HIV-Infected Children Using the Medication Event Monitoring System, Pharmacy Refill, Provider Assessment, Caregiver Self-Report, and Appointment Keeping	UNCLEAR	NO	YES	YES	YES (reported that interviewer was not part of care team)	Reference to an existing self-report tool (PACTG)	NO	YES
(Feingold <i>et al.</i> , 2000)	Protease Inhibitor Therapy in HIV-Infected Children	YES	NO	NO (different requirements considered as review of patient medical records)	NO (different requirements considered as review of patient medical records)	N/A	UNCLEAR (no information on methodology for reporting in medical records)	NO	YES
(Hammami <i>et al.</i> , 2004)	Integrating Adherence to Highly Active Antiretroviral Therapy Into Children's Daily Lives: A Qualitative Study	YES	NO	NO	YES	YES (reported that interviewer was not part of care team)	UNCLEAR	NO	NO (all qualitative reporting)

Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Leprevost <i>et al.</i> , 2006)	Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children	YES	NO	YES	YES	NO	UNCLEAR	NO	YES
(Marhefka <i>et al.</i> , 2004)	Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP)	YES	NO	YES	YES	NO	YES	NO	YES
(Paranthaman <i>et al.</i> , 2009)	Factors influencing adherence to anti-retroviral treatment in children with human immunodeficiency virus in South India- a qualitative study	NOT IDEAL – convenience sample	NO	NO	YES	YES (interviewer reported to be principal investigator, not part of care team)	UNCLEAR	NO	NO (all qualitative reporting)
(Plipat <i>et al.</i> , 2007)	Evaluation of a practical method to assess antiretroviral adherence in HIV-infected Thai	YES	NO	YES	YES	NO	Reference to an existing self-report tool (PACTG)	NO	NO (all qualitative reporting)

	children								
Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Pontali <i>et al.</i> , 2001)	Adherence to Combination Antiretroviral Treatment in Children	YES	NO	NO	NO	YES (interviewer known to respondents)	YES	NO	YES
(Roberts, 2005)	Barriers to antiretroviral medication adherence in young HIV-infected children	YES	YES	NO	YES	NO	UNCLEAR	NO	NO (all qualitative reporting)
(Wrubel <i>et al.</i> , 2005)	Pediatric adherence: Perspectives of mothers of children with HIV	NOT IDEAL - Convenience sample	NO	YES	YES	NO	YES	NO	NO (all qualitative reporting)
(Bunupuradah <i>et al.</i> , 2006)	Use of taste-masking product, FLAVORx, to assist Thai children to ingest generic antiretrovirals	UNCLEAR	NO	YES	YES	NO (potential risk highlighted as study was reported to be conducted by FLAVORx company)	Reference to an existing self-report tool (PACTG)	YES	YES

Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Davies <i>et al.</i> , 2008)	Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study	YES	NO	YES	YES	YES (interviewer known to respondents)	Reference to an existing self-report tool (PACTG)	YES (did not specify specific formulation)	YES (the prevalence of problems for individual drugs was not reported quantitatively)
(Gibb <i>et al.</i> , 2003)	Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial	YES	NO	YES	YES	NO	UNCLEAR	YES	YES (the influence of individual oral formulation-related barriers was not reported quantitatively)
(Goode <i>et al.</i> , 2003)	Adherence issues in children and adolescents receiving highly active antiretroviral therapy	YES	NO	YES	NO	NO	UNCLEAR	YES	YES (the prevalence of problems for individual drugs was not reported quantitatively)

Authors	Study title	Was the recruitment strategy appropriate to meet the aims of the research?	Participants recruited: child involvement is discussed in study	Ethical approval discussed	Informed consent discussed	Details on interview personnel reported in study (including if interviewer is a member of patient's care team and/or their role)	Transparency of content (questions) of self-report tool (UNCLEAR – indicates where themes were discussed but not specific questions)	Detail of reporting relevant findings (oral formulation-related barrier/s associated with drug/specific formulation)	Reporting influence of oral formulation-related barrier/s on acceptance of or adherence to medicines (quantitatively)
(Lin <i>et al.</i> , 2011)	Palatability, adherence and prescribing patterns of antiretroviral drugs for children with human immunodeficiency virus infection in Canada†	YES	NO	NO (different requirements considered as review of patient medical records)	NO (different requirements considered as review of patient medical records)	N/A	UNCLEAR (no information on methodology for reporting in medical records)	YES (did not specify specific formulation)	YES (not reported quantitatively for specific formulations)
(Reddington <i>et al.</i> , 2000)	Adherence to medication regimens among children with human immunodeficiency virus infection	YES	NO	YES	YES	NO	YES	YES	NO (all qualitative reporting)
(Van Dyke <i>et al.</i> , 2002)	Reported Adherence as a Determinant of Response to Highly Active Antiretroviral Therapy in Children Who Have Human Immunodeficiency Virus Infection	YES (Patients from PACTG 377 randomised clinical trial)	YES	YES	YES	NO	Reference to an existing self-report tool (PACTG)	YES	YES (formulation of nelfinavir not reported in study)

Appendix 5 Email sent to Medical Practitioners at UHCW

Dear All

We are really fortunate to have the opportunity to work with John Marriott from Aston University and the MCRN in a very patient-orientated formulation project. We have funding for a PhD research fellow and Rebecca Venables will be starting in July. I have already spoken to some of you about this and we have been very encouraged by the support and enthusiasm for the study so far.

She is a pharmacy graduate and will be looking at the ways patients and carers alter/adapt/disguise or otherwise manipulate medications to encourage the children to take them (or otherwise). The aim is to inform and direct future formulation work at Aston. She will initially be based at Aston, but once her honorary contract, CRB checks etc come through will be spending significant amounts of time here.

Rebecca and I would like your help in 2 ways please:

1. Initially she would like to sit in on some outpatient sessions – as she is a pharmacy graduate she would like to develop some more knowledge of how we work in outpatients, doctors and patients expectations at a consultation etc. She may well approach you and ask if she can join you at a clinic. Please can you let me know if you would NOT be happy if she approaches you to join in a clinic.
2. Once we have the patient questionnaires finalised and through ethics etc we would like to know if you would NOT be happy for her to approach your patients in out patients or on the wards.

The questionnaire will be facilitated by Rebecca, will be relatively brief and will not delay the running of your clinics!!

We envisage the questionnaire will be anonymous but will be offering the patients the opportunity of Rebecca feeding back information about drugs/formulations to the relevant clinician if the families would like this.

Also if she picks up any potentially dangerous usages of medications this will be fed back to you.

PLEASE would you let me know if you wish to opt out– if I do not here from you I will assume it is OK!!

Thanks and best wishes

Heather Stirling Consultant Paediatrician

Responses from Medical practitioners:

“I am happy to help in any way.”

“I'm sure my rheumatology patients would be very happy to help!!”

“I have no objection to Rebecca sitting in clinics – as long as parents agree. Also no objections to her questioning parents about medication.”

Appendix 6 Complex patient cases highlighted by parents to paediatric consultants

“Children and parents bring specific medicines related questions to paediatric consultations which require clear pharmaceutical advice- is there any evidence for what how they should administer cocktails of medicines safely and effectively?” (Personal communication with paediatric consultant).

The following patient cases were highlighted by parents to paediatric consultants. Cases are included with parental permission.

Patient Case 1:

A 3yr old boy with congenital adrenal hyperplasia, autism, significant feeding difficulties (dependent on NG tube), and gastro-oesophageal reflux with frequent vomiting was receiving a complex medication regimen administered via NG.

Drug regimen:

Hydrocortisone 4mg tds

Fludrocortisone 100mcg od

Sodium Chloride (NaCl) (1mmol/ml) 1ml three times daily (tds) and reducing – previously on 6 mls tds

Calcium Sandoz (liquid) – mum unsure of dose

Dalivit vitamin drops

Feeds:

Nutrini Peptisorb 275mls four times a day (qds)

Mum also gives “thickened water” (not sure what she thickens it with - Nestargel or similar – to clarify)

This involved a complex time consuming daily routine:

Daily Routine:

07.00 275mls Nutrini feed over 45 minutes (given via NG tube with a pump)

07.45 Dissolves 10mg hydrocortisone in 10 mls sterile water – gives 4mls (?crushes tablets)

Fludrocortisone: crushes tablet and mixes and gives in a small amount of water

NaCl – prepared by pharmacy 1mmol/ml

Always gives HC, FC and salt at end of feed. Sometimes vomits.

If vomits up to 30mins after drugs, mum repeats them

Mid morning at nursery: thickened water – prepared by mum and sent into nursery with child

13.00 275mls Nutrini feed

Hydrocortisone and NaCl (as above)

1600 275mls Nutrini feed

1900-2000 275mls Nutrini feed

Hydrocortisone and NaCl (as above)

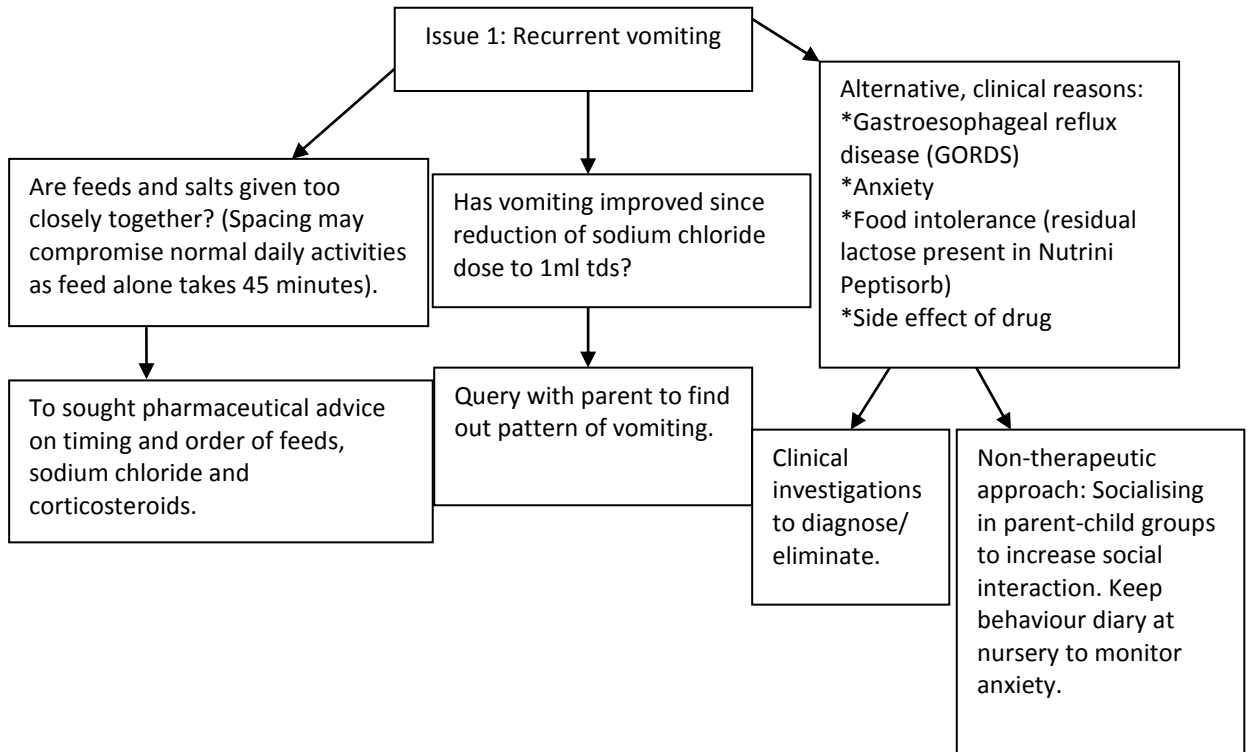
Each feed takes 45 minutes to go through, plus the time to give the drugs.

The mother's concerns centred around the time it took to prepare and give the drugs in the morning prior to nursery, what to do if the child vomited some/all of the medication and was there anything she could do (e.g. order of giving the medication) to minimise the chances of vomiting. The child was dependent on arranged transport to take him to nursery and if he was not ready on time then he would not be able to go to.

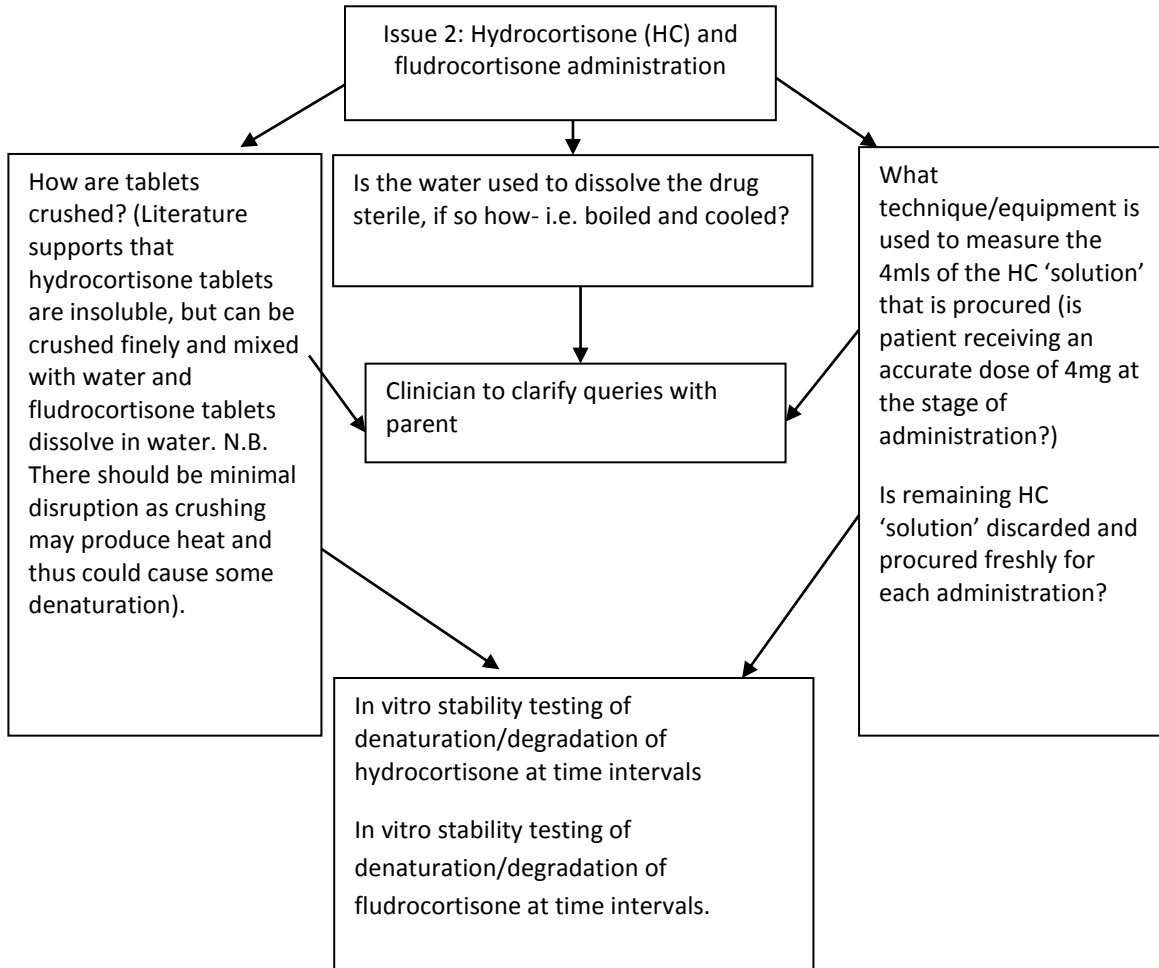
The flow charts that follow display preliminary evaluation of patient case 1.

Preliminary evaluation of Case Study 1

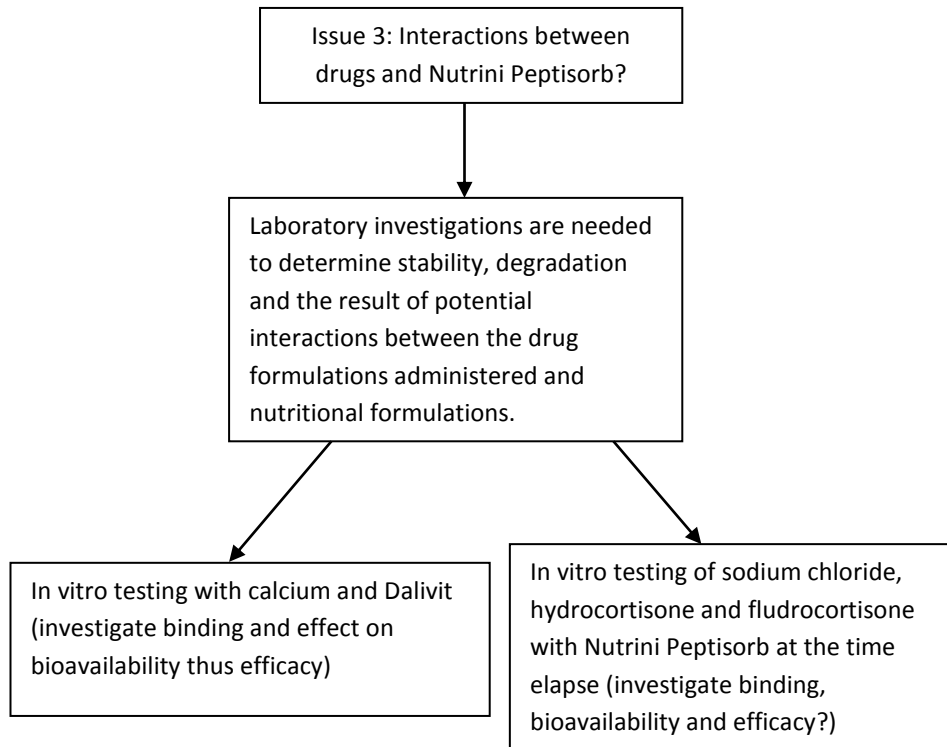
A flow chart to show preliminary evaluation of case study 1, issue 1: recurrent vomiting



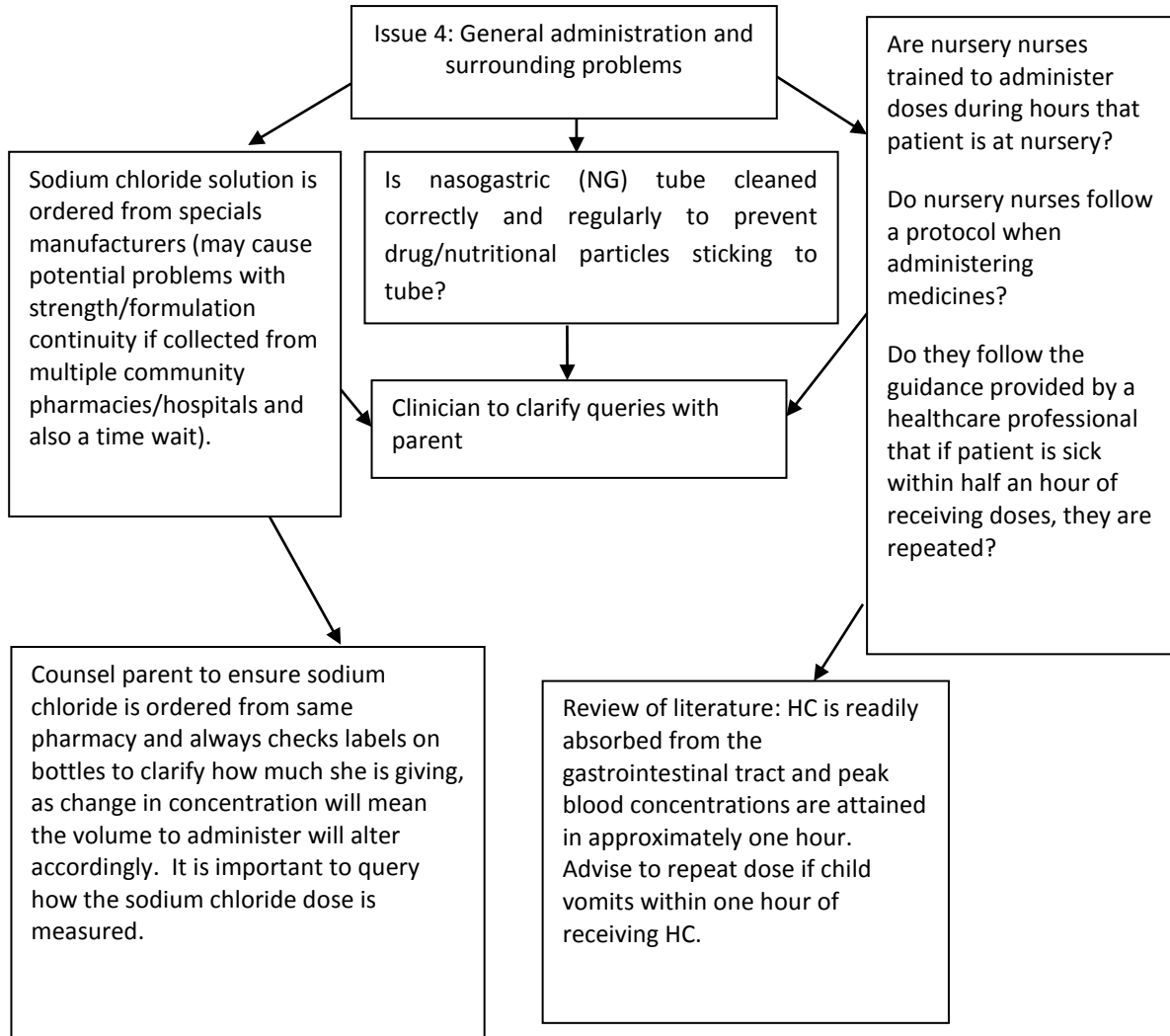
A flow chart to show preliminary evaluation of case study 1, issue 2: Hydrocortisone and fludrocortisone administration.



A flow chart to show preliminary evaluation of case study 1, issue 3: Interactions between drugs and Nutrini Peptisorb?



A flow chart to show preliminary evaluation of case study 1, issue 4: General administration and surrounding problems



Patient Case 2:

A six year old Afro-Caribbean old girl with Ornithine transcarbamylase (OTC) deficiency had recently received a liver transplant.

Post transplant her oral feeding was supplemented with nasogastric feeds of Nutrini Fibre twice daily (morning and pre-bed)

She had developed steroid – induced diabetes and had been established on sc glargine with Novorapid as necessary, and as well as medicines administration the mother was now checking the child’s blood glucose four times daily.

She had a complex regimen of medication (anti-rejection and gastro-intestinal) involving 10 oral medications in addition to sc insulin (see medication charts provided below) involving up to 26 episodes of medicine administration per day, several of which had to be prepared/manipulated prior to administration.

Her mother described the burden of care this posed – particularly in terms of time in the morning whilst getting the child to school efficiently, and particular difficulties with specific medications. On review of the medication charts she freely admitted that some doses were missed or refused because of these constraints.

bloods 2wrs

POST TRANSPLANT MEDICATION

DRUG NAME	USE/ACTION	DOSE	TIME	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	
TACROLIMUS Liquid	Helps to stop the body rejecting the new liver (Immunosuppressant) Before food	1.7mg =	Morning	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Mid day										
			Evening										
			Bedtime										
PROGRAF® Capsules	Helps to stop the body rejecting the new liver (Immunosuppressant) After food	3.4 mls	Morning	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Mid day										
			Evening										
			Bedtime										
PREDNISOLONE Soluble tablet	Helps to stop the body rejecting the new liver (Immunosuppressant) After food	5mg 1 x 5mg tablets dissolved in water	Morning	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Mid day										
			Evening										
			Bedtime										
ONCE DAILY MYCOPHENOLATE MOFETIL (MMF)	Helps stop the body rejecting the new liver (Immunosuppressant)	360mg = 1.8 mls	Morning	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Mid day										
			Evening										
			Bedtime										
TWICE DAILY DIPYRIDAMOLE Liquid	Helps to stop blood clots forming in the blood vessels leading to the new liver (antiplatelet) After food	50mg = 5 mls	Morning	✓	✓	✓	✓	✓	✓	✓	✓	✓	
			Mid day										
			Evening										
			Bedtime										
THREE TIMES DAILY ASPIRIN Soluble tablet	Helps to stop blood clots forming in the blood vessels leading to the new liver (antiplatelet) After food	55mg Dissolve 1 x 75mg tablet in 3 mls of water give 2.2 ml	Morning										
			Mid day										
			Evening										
			Bedtime										

repeat prescription uricodexyphobic acid, Spironolactone?

DRUG NAME	USE/ACTION	DOSE	TIME	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE				
<u>URSODEOXYCHOLIC</u>	Take with or after food	200mg = 4mls	Morning	✓	18-12	19-12	20-12	21-12	22-12	23-12	24-12	25-12	26-12	27-12	28-12	29-12	30-12			
			Mid day																	
			Evening	✓																
			Bedtime																	
<u>Twice daily</u>			Morning	✓																
			Mid day																	
			Evening																	
			Bedtime																	
<u>LOPERAMIDE</u>		1.5 mg 3mg = 0.6mls 0.5mls	Morning	✓																
			Mid day																	
			Evening																	
			Bedtime																	
<u>Once daily</u>		(1mg/5mls = 1.5mls) 7.5 mls	Morning																	
			Mid day																	
			Evening																	
			Bedtime																	
<u>LANTUS</u>	Check blood sugars	No feed = 3 units Feed = 12 units	Morning																	
			Mid day																	
			Evening																	
			Bedtime	✓	nd	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
<u>NOVA RAPID</u>	Check blood sugars	Carb counting See instructions	Morning																	
			Mid day																	
			Evening																	
			Bedtime																	
			Morning																	
			Mid day																	
			Evening																	
			Bedtime																	


DRUG NAME	USE/ACTION	DOSE	TIME	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE	DATE					
OMEPEAZOLE	Tablet to be dispersed in water	10mg = 1 Tablet	Morning	✓	17-12	18-12	19-12	20-12	21-12	22-12	23-12	24-12	25-12	26-12	27-12	28-12	29-12	30-12			
			Mid day																		
			Evening																		
			Bedtime																		
<u>Twice daily</u> NYSTATIN	Helps to treat and prevent infections of the mouth due to immunosuppression (antifungal) After food	1 ml	Morning	✓																	
			Mid day																		
			Evening																		
			Bedtime																		
CO-TRIMOXAZOLE SEPTIN® Liquid/Tablet <u>1 x Alternate days</u>	Helps to prevent infections which may affect the lungs due to immunosuppression (antibiotic)	480mg = 10mls	Morning	✓																	
			Mid day																		
			Evening																		
			Bedtime																		
ACICLOVOR ZOVIRAX® Liquid/Tablet <u>4 times daily</u>	Helps to reduce the effects of viruses after transplant (antiviral)	400mg = 1 tablet Dispersed in water	Morning	✓																	
			Mid day																		
			Evening																		
			Bedtime																		
SPIRONOLACTONE	Diuretic	20mg = 2mls	Morning	✓																	
			Mid day																		
			Evening																		
			Bedtime																		

Appendix 7 A poster inviting healthcare professionals to participate in focus groups

Do you have issues with medicines you prescribe?
FIND OUT
how you can help improve children's medicines?

Would you like to help us identify barriers to medication adherence?

- Inviting all Healthcare Professionals to take part in focus groups that will explore the difficulties with administering medicines to babies, children and adolescents.
- We aim to explore how medication formulations create administration issues and how formulations are altered by health care professionals, parents, carers and children to make them more acceptable.
- Your participation could help improve future medicines.



For more Information please contact:
Dr Heather Stirling
[Redacted]
OR
Rebecca Venables
[Redacted]

FIND OUT Poster for healthcare professional recruitment to focus groups v1.2, 25.06.10

Appendix 8 Invite letter and information sheet for focus groups with healthcare professionals



Dear Dr/Nurse/Pharmacist (as appropriate)

In collaboration with Aston University and the Medicines for Children Research network (W Mids) we are currently looking at issues and problems with children's medicines, particularly in relation to administration and formulations. We are very fortunate in having a dedicated PhD research fellow (Rebecca Venables) to support this study.

We would like to ask for your help in attending a focus group which will look at these issues in more detail.

Please would you read the attached information sheet and if you would like to participate please would you contact me by reply email and we will then arrange a mutually convenient time for the focus groups.

Many thanks

Heather Stirling

Consultant Paediatrician UHCW



FIND OUT Focus group invitation email v1.1, 23.03.10



Would you like to help us with research to improve children's medications?

What is this research about?

The study is in two parts:

Part A: Focus groups for Healthcare professionals

Part B: Patient/guardian semi structured facilitated face-to-face interview

We are examining issues and problems involved with children's medicines, and their administration. We hope that the information you give will help us to influence children's medicines in the future and overcome any current issues that are present with many medicines. This information should also help to inform the healthcare team types of problems that are experienced with different medicines in children and young people. The aim is to improve the knowledge of the healthcare team with day to day problems experienced in order to positively influence medicines in children and young people in the future.

We would like to invite you to take part in the **Part A: focus group part of the study**. You are invited to join one of the focus groups of which there will be three:

1. Medical Prescribers (including: paediatric consultants, specialist registrars and GPs) – main areas to be discussed prescribing intent
2. Paediatric pharmacists – principal topics for discussion include formulation issues, prescriptions, specials, unlicensed drugs
3. Paediatric nurses (inpatient and community) – key area for discussion to revolve around the administration of drugs

The aim of the focus groups is to develop an understanding of parent/caregiver/children's issues, as perceived by Medical Professionals and other Healthcare Professionals. The three focus groups will be facilitated by the research fellow (RV), who will be assisted by a second member of the research team (JM/HS). The focus groups will be audio recorded on digital disc and transcribed (by RV) for analysis using thematic content analysis. After transcription the digital audio recordings will be destroyed. Each focus group will consist of 6-8 participants.

In Part B of the study we intend that around 300 people will take part to begin with: including children, young people, parents and guardians. Most of those taking part will visit the University hospital of Coventry and Warwickshire outpatients department others will be children admitted to hospital at the time of the study. This study has been approved by South Birmingham REC.

How long will the focus group take??

Focus groups should last a maximum of 2 hours.

Refreshments will be provided. Travel expenses (including parking) will be reimbursed for those who make a special journey in to hospital to participate.



FIND OUT

how you can help improve children's medicines?

University Hospitals 
Coventry and Warwickshire
NHS Trust

What exactly will happen if decide to take part in this research?

Before you take part in this study it is important you carefully read and consent to the information given to you. Before agreeing to take part, it is important to make sure you ask any questions at all to the research team. This allows any unclear information or concerns to be addressed.

How will taking part help me?

If you agree to take part in this research, the results from part A will be looked at alongside Part B and from this we hope to find information that may help us influence and/or change medicines for children in the future and help to improve advice given to healthcare professionals.

What will happen once the project ends?

All of the information collected will be studied by the research team to help to find common issues/problems with medicines in children and young people. This will happen once enough people have taken part in the study.

What will happen with the results?

Information found from the study will be reported by the research team and may appear in medical/scientific journals. If statements/opinions are published they will be anonymised. The results will be accessible on Meds4kids website: <http://www.meds4kids.nhs.uk/>

What if I have any questions?

If you have any questions/queries at all please contact us. Contact details are below at the end of this information sheet.

If you would like independent advice about this study or have any complaints about this research, please contact the hospital's Patient Advice and Liaison Service (PALS) office on 0800 0284203.

What if I have a patient who I think is eligible to participate in part B of the study?


Information posters for parents/guardians and children can be found in the paediatric outpatient department and on the paediatric wards. Please feel free to pass on the contact details below and we will happily send out an information sheet if patient is eligible to join. Patients included will be outpatients and inpatients 0-18 years and their parents/guardians providing they have had a chronic condition diagnosed for at least one month and they are taking at least one medicine regularly. For more details please contact us.

THANK YOU FOR YOUR TIME

Dr Heather Stirling (Consultant Paediatrician)



OR **Rebecca Venables (MCRN Research Fellow)**



FIND OUT Healthcare Prof info sheet v1.2, 23.06.10
2



Appendix 10 Additional taste quotations regarding flucloxacillin from focus groups

Description from nurses group referring to the bad aftertaste: “cos I’ve tasted it you taste it and you think that’s not too ergh, and there’s a sort of after..” (Nurse 4)

MP 4: “flucloxacillin it’s got a really bitter aftertaste, and if they’ve got to take it four times in a day and it tastes horrible and they have a challenge to do that,”

MP 5: “yep fluclox is disgusting”

MP 3: “flucloxacillin, avoid if I possibly can.”

Appendix 11 Results from study on Specials prescribing

Healthcare professionals' understanding of children's medicines

(Venables, R., Marriott, J. and Stirling, H. (2012b) Poster 0073 Healthcare professionals' understanding of children's medicines. **International Journal of Pharmacy Practice**, 20: (Supplement 2): 68-69).

Focal points

- The study aimed to determine just how much (or how little) paediatric healthcare professionals understand about medicines they are prescribing or administering.
- The study identified significant gaps in the knowledge of paediatric healthcare professionals.
- Further education of healthcare professionals (especially junior doctors in training) about prescribed formulations is required to ensure clinical effectiveness and cost-efficiency of paediatric prescribing.

Introduction

Approximately 200 million paediatric prescriptions are issued annually in the UK and many are used outside of the terms of their medicine licence. One in ten prescriptions for children in primary care is for an unlicensed or off-label medicine which can lead to an unsuitable formulation. Manufacture of "specials" is a major issue with significant cost implications. Doctors and health care professionals at all levels of training are often unaware of the licensing requirements for paediatric drugs and the implications of these on how they prescribe medication for children, but there is little information assessing their knowledge. This study was designed to determine the level of understanding of paediatric healthcare professionals about the legal status of medicines that they are prescribing or administering.

Methods

Health care professionals attending a paediatric continuing professional development afternoon on paediatric research were invited to complete a questionnaire at the start of the session. The participants were asked to provide five definitions related to the prescribing of children's medicines: 1) Off-licence, 2) Off-label 3) "Specials", 4) NICE approved and 5) Marketing authorisation. Answers were evaluated as correct, partly correct or incorrect/unknown according to standard definitions. The local ethics body indicated that approval was not necessary given anonymity of responses.

Results

36 questionnaires were distributed and 32 (89%) were returned from 12 paediatric consultants, 9 paediatric trainee doctors, 4 senior paediatric nurses and 7 pharmacists. Participants were asked to provide 5 definitions each, giving a total of 160 potentially correct answers. 64/160 (40%) were defined correctly, with 28/160 (17.5%) being partially correct and 68/160 (42.5%) incorrect or unknown. There were significant differences between the groups (Chi squared $p < 0.01$).

	<u>Correct</u>	<u>Partially correct</u>	<u>Incorrect/unknown</u>
Paediatric consultants	33/60 (55%)	9/60 (15%)	18/60 (30%)
Paediatric trainees	3/45 (7%)	7/45 (16%)	35/45 (77%)
Paediatric nurses	5/20 (25%)	5/20 (25%)	10/20 (50%)
Pharmacists	23/35 (66%)	7/35 (20%)	5/35 (14%)

There were also significant differences in the ability to define the definitions (Chi squared $p < 0.01$).

	<u>Correct</u>	<u>Partially correct</u>	<u>Incorrect/unknown</u>
Off- licence	17/32 (53%)	3/32 (9%)	12/32 (38%)
Off- label	15/32 (47%)	1/32 (3%)	16/32 (50%)
“Special”	13/32 (41%)	1/32 (3%)	18/32 (56%)
NICE approved	13/32 (41%)	13/32 (41%)	6/32 (18%)
Marketing authorisation	6/32 (18%)	10/32 (32%)	16/32 (50%)

There was particularly poor understanding of the term “Special”. 50% consultants were able to define it adequately but no doctor in training was able to. The pharmacists had the best understanding of “Specials”.

Discussion

All levels of paediatric doctors (in particular, Juniors), appear to have a poor understanding about the legal status of medicines (off -label or off- licence drugs), hence may be ignorant of their prescribing responsibilities. Many would not be aware when prescribing a “special” and could also be unaware of the possible supply problems, variations in formulations’ pharmacokinetics, and their costs. Paediatric consultants fared slightly better, but have gaps in understanding which if addressed could lead to more effective and cost efficient prescribing. Further detailed studies are required to establish the effect of doctors’ lack of knowledge re paediatric prescribing on practice outcomes and the potential beneficial effects of utilising paediatric pharmacists’ knowledge in improving the prescribing process.

Appendix 12 Semi-structured interview prompt sheets for parents/guardians

Interview sheet for adults

1. Drug name?

Drug formulation- if liquid-specials/commercially available? Capsule, tablet, inhaler, injection

Route-oral, ng, IV, im, sc, INH

2. Dose-how much at one time?

Frequency-How often/how many times a day/week etc

3. Problems with frequency/timing

Q 1 Do you find it difficult to space this medicine correctly?? I.e. does it interfere with school/other daily activities/their life in general? Y/N

Q 2 Have you ever forgotten to give this medicine? Y/N (DO NOT MEAN CHOSEN NOT TO GIVE)

How many times in last week? 1 2 3 4 5 6 7

if YES when was the last time you forgot? Yesterday, 2 days ago, 3 days ago etc

4. Changes to formulation

How exactly do you measure.. Syringe spoon.. Measuring cup? How accurate do you think you are with giving dosage?

Q 3 Do you give medicine in a different way? i.e. mix with food/juice, Crush or cut tablet/open capsule/dilute medication? Y/N

How often? 1 Always 2 most of the time 3 not sure 4 rarely 5 never

How do you get the child in your care to take this once you get it home? i.e. exactly like it is or does it need to be dissolved?

If you could change one thing about this medicine, or how child takes it what would this be? How would you like it to be changed if you could decide?

5. How happily does the child in your care take this medicine?

Q 4 How often is child happy to take this medicine? 1 Always 2 most of the time 3 not sure 4 rarely 5 never

Q 5 Has the child in your care ever refused (chosen not) to take the medicine? Y/N (DO NOT MEAN FORGOTTEN)

How many times in last week? 1 2 3 4 5 6 7

If YES when was the last time s/he refused to take? Yesterday, 2 days ago, 3 days ago etc

6. Does/has the child in your care experienced side effects?

Q 6 Does/has the child in your care experienced side effects? Y/N

Can you please describe to me.. i.e. sickness, headache Pain, rash?

Q 7 If the child in your care is feeling worse do you stop giving the medicine? Y/N
(ACTUALLY STOP, NOT JUST FEEL LIKE STOP GIVING)

7. Compliance

Q 8 When the child in your care is feeling better do you stop giving this medicine? Y/N So if the child in your care is having a good day and seems well do you stop giving medicine that day?

Q 9 How often do you feel that the medicine makes the child in your care better? 1 Always 2 most of the time 3 not sure 4 rarely 5 never

8. Any specific problems???

Q 10 Do you have any problems getting this medicine in hospital/community pharmacies? Y/N

Q 11 Understanding information (English) Do you feel that the information you get is in plain English and clear/easy to understand? Y/N

School specific problems

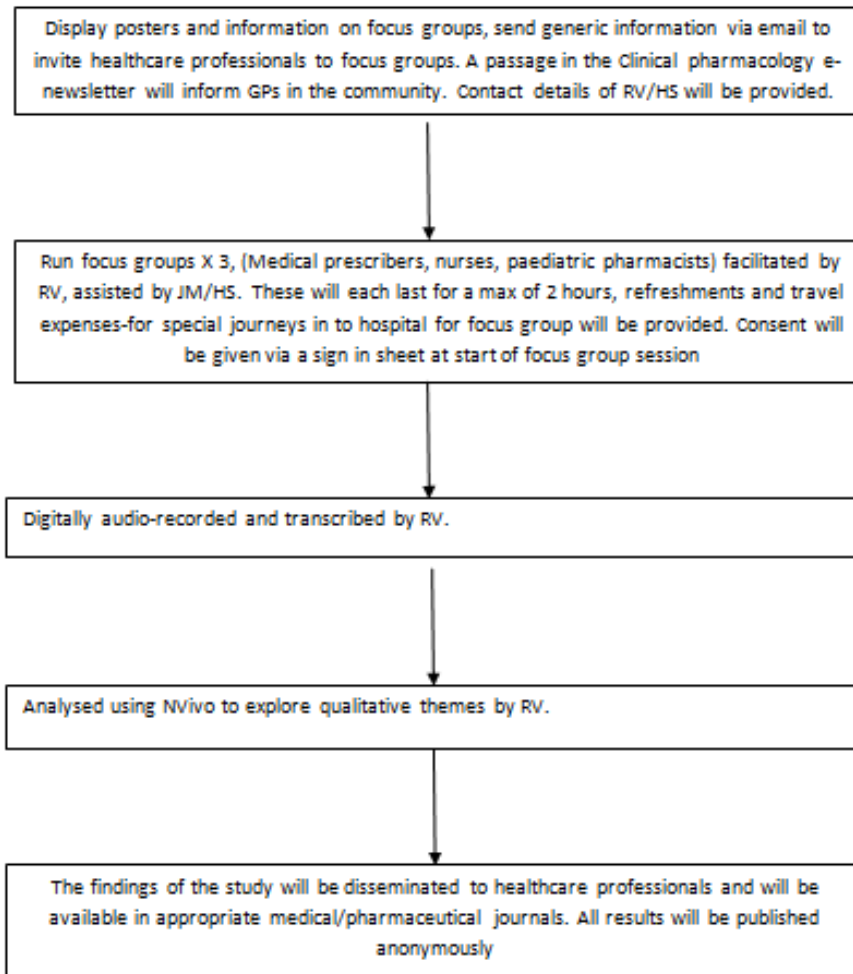
Q 12 Do you have any problems at school, are teachers happy to store medicines safely and give out medicines? Y/N

Q 13 Do you think that teachers and social staff should be given more information on medicines? Y/N

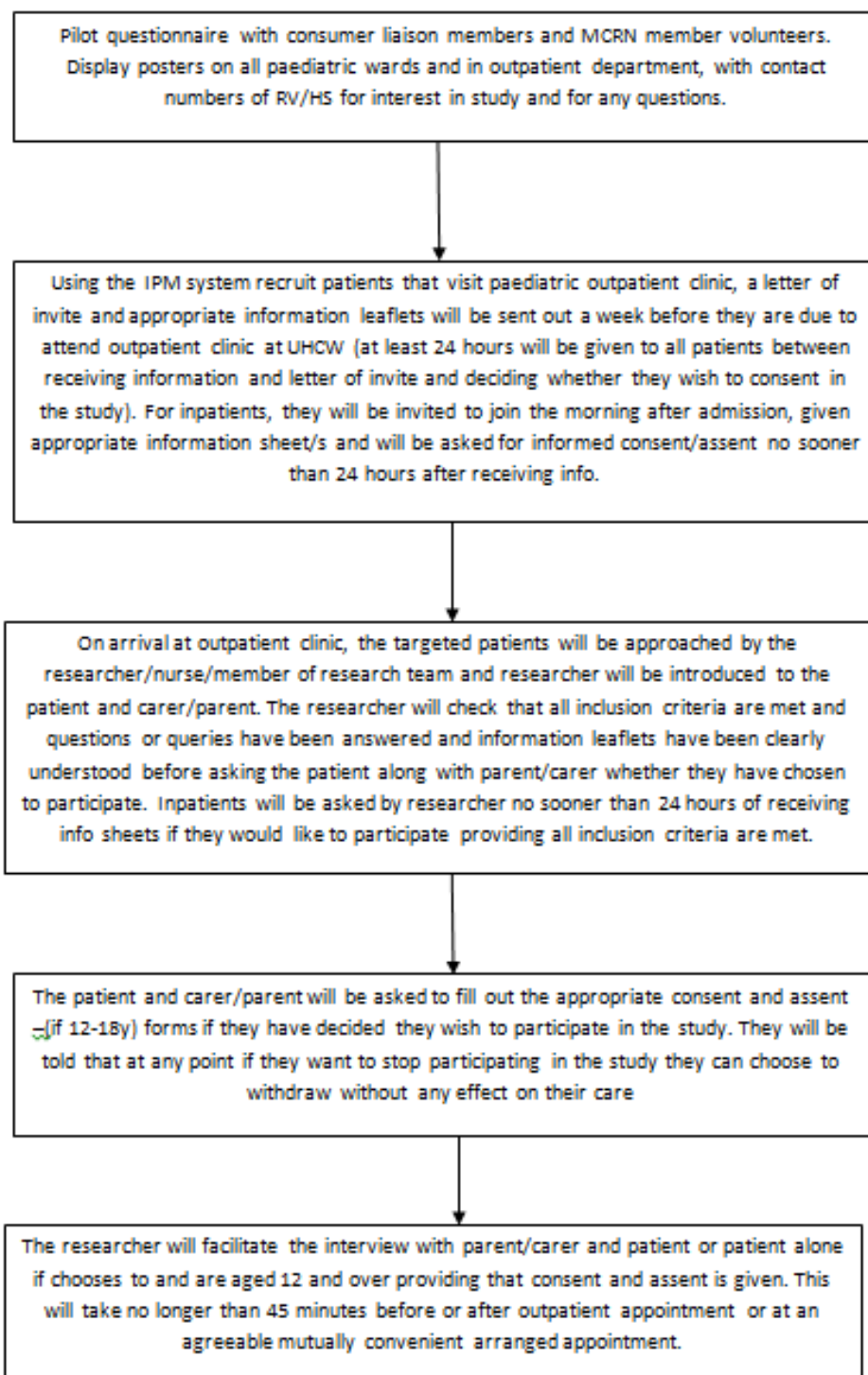
Appendix 13 Research protocol flow chart

Research protocol flow chart

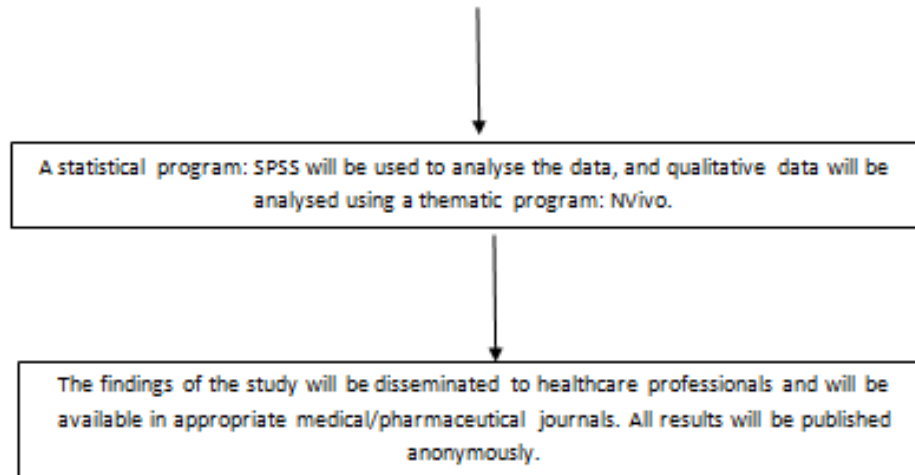
Study Part A



Study Part B



FIND OUT flow chart summary of protocol v1.1, 23.03.10



Appendix 15 Sample size calculations based on medicine adherence rates for children with long-term conditions

A sample size calculation is carried out for the comparison of adherence rates between three pre-defined age groups. The adherence rate is denoted p_1 for age group one, p_2 for age group two and p_3 for age group three. An adherence rate $p_1 = 0.6$ means that 60% of the children in this age group comply with the prescription. 100 children are supposed to be followed up in each age group, giving a total sample size of $n=300$. The usual significance level of $\alpha = 0.05$ is used throughout.

In order to investigate whether the adherence rates differ between the three groups a χ^2 -test is conducted. This statistical test is readily available in SPSS. It tests the hypothesis that the three adherence rates are all equal and if this hypothesis is rejected (i.e. the test gives a p value of less than 0.05), it can be concluded that the rates are not all the same. The test does not inform which groups are significantly different from each other. A multiple testing procedure for pair-wise comparisons would have to be used to investigate differences between pairs of age groups. This more complicated procedure is not discussed here.

The following table shows the power to detect an overall difference for 10 combinations of adherence rates. Usually a power of 80% or 90% is desirable. The power for detecting a difference if one rate is 60% and the other two are 50% is only 29.1%. This means that it is very unlikely to be picked up. The power is 86.1% if one rate is 70% whilst the others are 50%, i.e. the study is sufficiently powered to detect this difference. For a doubling of the adherence rate from 30% to 60% in one group the power would be almost 100%.

p₁	p₂	p₃	Power
0.5	0.5	0.5	5.0%
0.5	0.5	0.6	29.1%
0.5	0.5	0.7	86.1%
0.5	0.5	0.9	100%
0.5	0.6	0.6	2.5%
0.7	0.7	0.9	97.0%
0.5	0.45	0.55	22.5%
0.5	0.4	0.6	72.1%
0.5	0.3	0.7	99.9%
0.3	0.3	0.6	99.6%

Another way of examining the adequacy of the sample size is to consider the precision with which the adherence rate (for each group separately) can be estimated from the sample. Usually statistical analysis programs give confidence intervals (CI) for estimated parameters. A narrower interval is desirable. The following 95% CIs are calculated using a normal approximation which should be fairly good for the anticipated sample size.

Assuming that the adherence rate is 50% the confidence limits would be approximately $\hat{p}_1 \pm 0.098$. So if the estimate were 50%, the confidence limits would be roughly 40% and 60% adherence. Similarly, if the adherence rate were 80% for one group, the confidence limits would be approximately 72% and 88%.

If on the other hand a CI with a width of 10% is requested, for example ranging from 45% to 55%, a sample size of 385 children per age group would be necessary.

Appendix 16 Parent/guardian invite letter and information sheet



Dear Parent/Guardian,

(Date:)

We are conducting a study at the University Hospital of Coventry and Warwickshire looking in to problems with different medicines used in babies, children and adolescents with chronic conditions. This letter is being sent out to all families with babies, children and adolescents who attend the outpatient department at UHCW so please ignore this letter if the child in your care is not taking at least one medicine for a long-term condition. We will also be asking inpatients to join in the study. This study is funded by the West Midlands Medicines for Children Research unit (WM-MCRN).

We would like to invite you and your child- if s/he is taking at least one medicine for a long-term condition to join the study. By joining the study you could help to improve medicines for children in the future.

Information about the study can be found in the patient information sheets with this letter, (one for parents/guardians and one for 12-18 year olds) so please feel free to read them if this letter applies to you. Choosing to participate is voluntary and if you/your child choose not to join the study it is fine and neither your care nor your child's will be affected in any way.

Study contact details (emails and phone numbers) are listed at the end of the information sheets. Please contact us with any queries/questions.

Thank you very much for your time

UHCW Dr Heather Stirling (Consultant Paediatrician)



Rebecca Venables (MCRN Research Fellow)



FIND OUT Parent/guardian invite letter v1.1, 23.05.10
1





FIND OUT

how you can help improve children's medicines?

University Hospitals
Coventry and Warwickshire
NHS Trust

Where the word 'Parent' is used please read parent/guardian i.e. those who have parental responsibility, which may include a legal representative.

Would you like to help us with some research about children's medicines?

You and your child are invited to take part in some important research which is taking place at University Hospital of Coventry and Warwick. We would like you to help us when you bring your child to their next outpatient appointment or whilst your child is an inpatient on the paediatric ward at the hospital.

Before we ask you to take part we need to make sure you understand all information about the research. Please read the following information carefully, and discuss the research with family, friends, your doctor or nurse. Please ask us any questions, our contact details are at the end of this information sheet.

Why are we doing this research?

We are looking at issues and problems with children's medicines, and giving children's medicines. We hope that the information you give will help us to influence children's medicines in the future and overcome any current issues that are present with medicines. This information will also help the healthcare team including: Doctors, pharmacists, nurses to understand the types of problems that are experienced with different medicines in children and young people. We aim to improve the knowledge of the healthcare team with day to day medicine problems in order to positively influence medicines in children and young people in the future.

Why have you been invited to take part?

You have been invited to take part in this study as the child in your care is taking a medicine that we are interested in looking at and finding out more information about. We hope that around 300 people will take part in this study to begin with: including children, young people, parents and guardians. Most of those taking part will visit the University hospital of Coventry and Warwickshire outpatients department others will be children admitted to hospital at the time of the study.



Is this study okay?

All of the information for this study was sent to an 'ethics committee' before we could begin the study. This is a group of people who decide if the study is okay to carry out. The South Birmingham research ethics committee have decided that this study is okay.



FIND OUT Parent/guardian info sheet v1.2, 25.06.10
1





FIND OUT

how you can help improve children's medicines?

Do you have to take part?? Does the young person in your care have to take part?

NO!!! It is your choice, and whether you decide you do or do not want to take part your health care and the child's health care in your care will not be affected in any way. Likewise the child in your care does not have to take part either.

If you or the child in your care decide at any point in this research that you no longer want to take part that is fine. You are able to change your mind and stop at any time. Do not worry you will not upset anyone. However we will ask you to tell us if you do not mind the reason why you no longer want to take part as it may be important for other young people. If you do not want to give us a reason- again do not worry, this is fine.

What exactly will happen to you or the child in your care if you decide to take part in this research?

Before you take part in this study it is important you carefully read and consent to the information given to you. Before agreeing to take part, it is important to make sure you and the child in your care ask any questions at all to the research team. This allows any unclear information or concerns to be addressed.

Only once you and the child in your care is happy that all the study information is clear and you have had the opportunity to ask all questions that you would like to you will be given a consent form and the child in your care will be given a form to print and sign your names on (if your child is able to consent). The forms let us know that you understand why you're taking part in this research and what will happen in this study.

When the forms have been completed, and you can take part in this research you and/or the child in your care will be asked some questions about the medicines the child in your care takes, and any issues or problems experienced when administering these medicines. These questions will be asked at the hospital in a private place where nobody else can hear you talk.



A researcher will ask these questions. When the answers to the questions are written down, the sheets will be kept confidentially so no-one else can see the answers that have been given unless something is identified that could have an effect on the healthcare of your child or pose a risk to somebody. If this occurs this information will be passed on in confidence to your child's doctor. The sort of questions asked will be about the child in your care's medicines, medication routine and any issues surrounding these.

How long will these questions take and when will the research be done?

This should take no longer than 45 minutes, and at the most convenient time before or after outpatient clinic for families visiting clinic. For inpatients on the ward this time will be arranged with the researcher or nurse. It may be possible to arrange another date and time that is mutually agreeable with the researcher.



FIND OUT

how you can help improve children's medicines?

University Hospitals 
Coventry and Warwickshire
NHS Trust

Will the questions cause any upset?

We do not think that the questions will cause any upset-but anything that you or the child in your care do not want to answer is fine. We will not be offended. However if you would like independent advice about this study or have any complaints about this research, please contact the hospital's Patient Advice and Liaison Service (PALS) office on 0800 0284203.

How will taking part help you?

If you agree to take part in this research, your answers will be looked at alongside others answers involving similar medicines and with these results we hope to find information that may help us influence and/or change medicines for children in the future and help to improve advice given to healthcare staff such as doctors and information given to parents/guardians.

What will happen once the research ends?

All of the information collected will be studied by healthcare professionals to help to find common issues/problems with medicines in children and young people. This will happen once enough people have taken part in the study.

Will the information you give be kept private?

All of the answers you/ the child in your care give us will be kept private in a locked cupboard. Only the research team involved in the conduct of the study will be allowed to see the consent and assent forms. These people are not allowed to tell anybody that you/the child in your care has taken part in the study.



The researchers may see your answers, but they will be kept in private in a locked cupboard. Your name will not be on them, only first part of postcode and hospital number. If the information from the interview highlights something that could present as a serious risk to you or your child we will inform your child's doctor in confidence in order to ensure that your child's medicines will be used in a safe and effective manner.

What if you decide that you or the child in your care decides that we no longer want to take part?

Just tell us, and we can stop the questions at any point. Do not worry no one will be offended by this.

What will happen with the results??

Information found from the study will be reported by the lead doctor in the study with the research team. This will allow other people in research to read about the results from this study as the results may appear in specific magazines (i.e. medical/scientific journals).



FIND OUT

how you can help improve children's medicines?

University Hospitals 
Coventry and Warwickshire
NHS Trust

Your name and the child in your care's name will not be mentioned. No-one will know that you or the child in your care participated in the study- apart from you and the research team. The study results will be available on the Meds4kids website: <http://www.meds4kids.nhs.uk/>

What if I have any questions at any part of this study?

If either you or the child in your care has any questions or worries at all... feel free at any time to contact us. Contact details are below at the end of this information sheet. It is important that if your child wants to take part in this study that they discuss this with you before taking part.



THANK YOU FOR YOUR TIME

Contact details:

Dr Heather Stirling (Consultant Paediatrician)



OR

Rebecca Venables (MCRN Research Fellow)



Appendix 17 16-18 year olds consent form, parent/guardian consent form and young persons assent form



A study exploring adherence to medication regimes and the administration of medicines in children which aims to improve future formulation developments

Consent form for 16-18 year olds (v1.1, 25.06.10)

(to be completed by participant)

Participants Name: Date of Birth: Patient Hospital Number:

Please read all information below carefully initial by each box:

1	I confirm that I have read and understood the information sheet for the study, dated: 25/06/2010 (v1.2) and that I have had the opportunity to consider the information, ask any questions and had them answered satisfactorily.	1 <input type="checkbox"/>
2	I understand that my participation is voluntary and I can choose to withdraw from the study at any time, without giving any reason and without my care or legal rights being affected in any way.	2 <input type="checkbox"/>
3	I understand that data and any information collected during the course of this study may be looked at by responsible individuals from the Medicines for Children Research Network, Aston University, and University Hospital Coventry and Warwickshire, from regulatory authorities or NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my responses to questions asked.	3 <input type="checkbox"/>
4	I agree for myself to be registered for this study	4 <input type="checkbox"/>
5	I agree that if something arises in the interview that could cause harm or risk to someone then my clinician will be informed confidentially	5 <input type="checkbox"/>
6	I agree to be contacted with regards to any follow up study as a result of findings from the above study.	6 <input type="checkbox"/>

Name of patient

Date:

Signature:

Name of person taking consent

Date:

Signature:



THANK YOU FOR YOUR TIME
(When completed: 1 for participant; 1 for researcher site file; 1 for case notes)
FIND OUT 16-18 year old Consent v1.1, 25.06.10

1



A study exploring adherence to medication regimes and the administration of medicines in children which aims to improve future formulation developments

Consent form for parent/guardian (v1.2, 25.06.10)

(to be completed by parent/guardian)

Participants Name: Date of Birth: Patient Hospital Number:

Please read all information below carefully initial by each box:

1	I confirm that I have read and understood the information sheet for the study, dated: 25/06/2010(v1.2) and that I have had the opportunity to consider the information, ask any questions and had them answered satisfactorily.	1 <input type="checkbox"/>
2	I understand that my participation and my child's is voluntary and I can choose to withdraw from the study at any time, without giving any reason and without my care or my child's care or legal rights being affected in any way.	2 <input type="checkbox"/>
3	I understand that data and any information collected during the course of this study may be looked at by responsible individuals from the Medicines for Children Research Network, Aston University, and University Hospital Coventry and Warwickshire, from regulatory authorities or NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my responses to questions asked.	3 <input type="checkbox"/>
4	I agree for myself and the child in my care to be registered for this study	4 <input type="checkbox"/>
5	I agree that if something arises in the interview that could cause harm or risk to someone then the patient's clinician will be informed confidentially	5 <input type="checkbox"/>
6	I agree to be contacted with regards to any follow up study as a result of findings from the above study.	6 <input type="checkbox"/>

Name of patient:

Name of parent/guardian

Date:

Signature:

Name of person taking consent

Date:

Signature:



THANK YOU FOR YOUR TIME
(When completed: 1 for participant; 1 for researcher site file; 1 for case notes)
FIND OUT Parent/guardian Consent v1.2, 25.06.10





A study exploring adherence to medication regimes and the administration of medicines in children which aims to improve future formulation developments

Assent form for young people (v1.1, 23.03.10)

(to be completed by the young person and their parent/guardian)

Participants Name: Date of Birth: Patient Hospital Number:

Please read all information below carefully, young person or parent/guardian on behalf to circle all they agree with:

- Have you read the information or has someone read this information about the interview to you? YES/NO
Has someone explained this project to you? YES/NO
Do you understand what this interview is about? YES/NO
Have you asked all the questions that you want to ask? YES/NO
Have you had all your questions answered in a way that was easy to understand? YES/NO
Do you understand that it is okay to stop taking part at any point during the interview? YES/NO
Are you now happy to be asked questions about your medicines and how you take them? YES/NO

If any of the above answers are NO and you don't wish to take part, please do not sign your name. If you do want to take part, please write your name and today's date

Your name: Date:

Your parent/guardian must also print and sign their name below if they're happy for you to take part in the questionnaire.

Name of parent/guardian Date: Signature:

The researcher who explained the project to you also needs to print and sign.

Name of person taking consent: Date: Signature:

THANK YOU FOR YOUR TIME



(When complete: 1 copy for child/young person; 1 copy for researcher's site file; 1 for case notes) FIND OUT Young person Assent v1.1, 23.03.10



Appendix 18 Data recording template sheet for parent/guardian



If you do not wish to answer any of these questions please just tell me at any point in time and we can stop and move on to next question.

A	Who is being interviewed?	A
1	Child	1 <input type="checkbox"/>
2	Parent	2 <input type="checkbox"/>
3	Carer	3 <input type="checkbox"/>
4	Other-please state	4 <input type="checkbox"/>

B	Who is responsible for giving medicines on a regular basis?	B
1	Child	1 <input type="checkbox"/>
2	Parent	2 <input type="checkbox"/>
3	Carer	3 <input type="checkbox"/>
4	Other-please state	4 <input type="checkbox"/>

C	Patient study number	
D	Patient hospital number	

E	Patient gender?	E
1	Male	1 <input type="checkbox"/>
2	Female	2 <input type="checkbox"/>

F	Patient age	
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G	Does the child in your care have any health related needs? I.e. visual problems, gastrostomy, NG tube, difficulty hearing/speaking/swallowing, ADHD?	G
1	Yes- if so please describe	1 <input type="checkbox"/>
2	No	2 <input type="checkbox"/>



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University Hospitals **NHS**
Coventry and Warwickshire
NHS Trust

H	What condition is the child in your care attending the hospital for today?	
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I	Does s/he suffer from any other health conditions?	I
1	Yes- if so please list:	1 <input type="checkbox"/>
2	No	2 <input type="checkbox"/>

J	How old was the child when first diagnosed with long-term condition? Give age	J
1	<1month	1 <input type="checkbox"/>
2	1m-12m	2 <input type="checkbox"/>
3	12m-12y	3 <input type="checkbox"/>
4	12y	4 <input type="checkbox"/>

1 Drug name, form, route	2 Dose and frequency	3 Problems with frequency/timing?	4 Changes to formulation
		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?
		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?
		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?
		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?

FIND OUT Data recording template sheet 2a v1.1, 23.03.10

5 How happily does the child take this medicine?	6 side effects?	7 Estimation of compliance	8 Are there any specific problems with drug?
4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n

FIND OUT Data recording template sheet 2a v1.1, 23.03.10

Drug name, form, route	Dose and frequency	Problems with frequency/timing?	Changes to formulation	How happily does the child in your care take this medicine?	Does/has the child in your care experience/d side effects?	Estimation of compliance	Are there any specific problems with drug?
OTC Medicines		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?	4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
Vitamins and minerals/fish oils/omega 3		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?	4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
Homeopathy		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?	4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
Herbal remedies		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?	4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n

FIND OUT Data recording template sheet 2b v1.1, 23.03.10

Alcohol, other		1.y/n 2.y/n 1 2 3 4 5 6 7 When?	Syringe cup spoon 3.y/n 1 2 3 4 5 How? Ideal?	4.1 2 3 4 5 5.y/n 1 2 3 4 5 6 7 When?	6.y/n ? 7.y/n	8.y/n 9.1 2 3 4 5	10 Obtaining? y/n 11 Info? y/n 12 school? y/n 13 more info? y/n
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FIND OUT Data recording template sheet 2b v1.1, 23.03.10

Do you use any reminding systems to help remember to take your medicines? i.e. pillbox, timer, calendar?

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I

FIND OUT Data recording template sheet [2c_reminding systems v1.1](#), 23.03.10



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how you can help improve children's medicines?

Please tick the correct answers to the questions below in the boxes, where there is a blank space please write in the answer to the question. Please read the questions carefully

L	Patient's first part of postcode	
----------	---	--

M	Do you mind if I ask you how would you best describe your child's ethnic background?	M
1	Yes	1 <input type="checkbox"/>
2	No- Please tick correct answer in box in the table below	2 <input type="checkbox"/>

N								
White		Asian		Black		Mixed race		5 Any other ethnic group
White British	1a <input type="checkbox"/>	Indian	2a <input type="checkbox"/>	Black British	3a <input type="checkbox"/>	Black and White	4a <input type="checkbox"/>	<input type="checkbox"/>
White any other	1b <input type="checkbox"/>	Pakistani	2b <input type="checkbox"/>	Black Caribbean	3b <input type="checkbox"/>	Asian and White	4b <input type="checkbox"/>	
		Bangladeshi	2c <input type="checkbox"/>	Black African	3c <input type="checkbox"/>	Mixed race any other	4c <input type="checkbox"/>	
		Asian any other	2d <input type="checkbox"/>	Black any other	3d <input type="checkbox"/>			



O	Is English your 1st language?	O
1	Yes	1 <input type="checkbox"/>
2	No- please state what 1 st language is:	2 <input type="checkbox"/>

P	Are you in the early stages of learning English?	P
1	Yes	1 <input type="checkbox"/>
2	No	2 <input type="checkbox"/>

FIND OUT Data recording template sheet 3 for Parent/guardian v1.2, 25.06.10





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Q	How long have you been living in the UK?	
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R	What is the occupation of the highest earner in your household?	
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S	Is your child in mainstream (non-private) school?	S
1	Yes	1 <input type="checkbox"/>
2	No	2 <input type="checkbox"/>

T	Does s/he have additional help at school or any special educational needs?	T
1	Yes-please describe	1 <input type="checkbox"/>
2	No	2 <input type="checkbox"/>

U	Do YOU have any health related needs? I.e. visual problems/hearing	U
1	Yes- if so please describe	1 <input type="checkbox"/>
2	No	2 <input type="checkbox"/>

Thank you for your time and cooperation. If you have any other comments that you would like to make related to administering medicines to children, please enter them below.

Additional Comments:

Appendix 19 List of drug therapeutic groups featuring in BNFC chapters

BNFC Chapter number	Classification of medicines to BNFC Chapters
1	Gastro-intestinal system
2	Cardiovascular system
3	Respiratory system
4	Central nervous system
5	Infections
6	Endocrine system
7	Obstetrics, gynaecology, and urinary-tract disorders
8	Malignant disease and immunosuppression
9	Nutrition and blood
10	Musculoskeletal and joint diseases

Appendix 20 Results of univariable analysis

	Medicines refusal (p value)	Medicines refusal in previous 6 months (p value)	Forgetting to administer medicines (p value)	Forgetting to administer medicines in previous 6 months (p value)	Medicines manipulation (p value)
Age band of patient at time of interview	0.003	0.016	<0.001	0.003	0.003
Type of patient	0.223	0.724	0.061	0.053	0.618
Gender	0.757	0.898	0.925	0.961	0.606
Health-related need of guardian	0.291	0.901	0.879	0.557	0.294
English first language	0.691	NC	0.699	0.721	0.017
Additional educational needs of child	0.105	NC	0.847	0.036	0.934
Attendance at mainstream school	0.888	0.874	0.961	0.329	0.242
Ethnicity	0.373	0.496	0.557	0.917	0.478
Age band at diagnosis	0.652	0.027	0.129	0.060	0.626
No of current prescribed oral medicines	0.139	0.842	<0.001	0.009	0.368
Multiple health conditions	0.811	0.811	0.545	0.783	0.478
Other health-related need of patient	0.180	0.489	0.106	0.045	0.497
Patient had PEG/NG tube fitted	0.833	NC	0.088	0.314	0.760
Who is responsible for administering medicines	0.979	0.411	0.002	0.002	0.025
IMD 2010 score	0.026	0.229	0.385	0.538	0.806
Formulation, type of medicine	0.036	0.328	0.238	0.522	<0.001
BNFC Chapter (missing chap 7)	0.101	NC	0.132	0.048	<0.001
Specials medicine	0.680	0.488	0.946	0.661	0.809
Size or aversion to/difficulty swallowing	0.326	0.946	0.202	0.101	0.048
Taste	<0.001	0.023	0.574	0.334	0.293
Texture	<0.001	0.012	0.887	0.882	<0.001
Volume or quantity	<0.001	0.014	0.949	0.466	0.004
Colour/appearance	0.455	NC	0.621	0.244	NC
Smell	0.049	0.287	0.846	0.299	0.582
Other formulation and administration problems	0.142	0.203	0.889	0.198	<0.001
Frequency of dosing	0.165	0.556	0.149	0.191	0.037

NC= Not calculable as there were insufficient numbers of positive and negative outcomes to calculate an odds ratio.

Appendix 21 Quotations of parents, carers and young people participating in semi-structured interviews

Taste:

'Tinney' 'like a rusty nail' 'bitter' 'sour' 'acid taste' 'salty' 'like beer' 'like leaves' 'burnt throat' 'horrible' 'foul' 'yacky' 'yucky' 'horrid' 'disgusting.'

Texture:

'Foams up' 'gloopy' 'chalky' 'clumps' 'too thick' 'all bits makes her gag' 'like grit' 'thick gelatinous texture' 'oily' 'powdery' 'goeey paste' 'fizzy' 'weird texture' 'crystallises, bitty texture.'

Quantity/volume:

'Large volume' 'too many tablets' 'quantity' 'taste is worse when more sachets' 'large volume - issue if doesn't finish milk' 'volume when on 13 soluble tablets' 'large quantity when lower strength capsules taken' 'if higher volume vomits.'

Size or aversion to/difficulty swallowing:

'huge tablet' 'swallowing' 'too large' 'too big' 'size too big' 'big, got stuck in throat' 'hard to swallow' 'difficult to swallow' 'doesn't like to swallow it.'

Colour:

'Off-putting as bright red' 'colour red is alarming' 'bright orange, alarming colour and stains' 'yellow turns green if put in liquid' 'doesn't like yellow coloured liquid.'

Smell:

'Sickly smell' 'strong aniseed smell' 'smells bad' 'smells horrible' 'smells of acid.'

Appendix 22 Recoded variable factors for multivariable analysis models

Medicines manipulation:

Variable	Categories
BNFC Chapter	7 and 10 (smallest numbers of medicines in these chapters) and also formulations not featuring in any of the BNFC chapters were grouped into a chapter labelled 'other'.

Forgetting to administer medicines in the six months prior to interview:

Variable	Categories
BNFC Chapter	7 and 10 (smallest numbers of medicines in these chapters) and also formulations not featuring in any of the BNFC chapters were grouped into a chapter labelled 'other'.
Additional educational help	The N/A response for the question was included in this analysis in order to decrease the number of cases omitted from the model. The results were not greatly affected with the inclusion of the N/A category.

Appendix 23 Direct patient benefit of interviews

Counselling points were provided to parents and young people with regard to helping remembering medicines, these included: using alarms, calendars, diaries, daily medication organisers for those who reported struggling with multiple medicines and a drug chart for one particular patient with a complex medication regime.

Additional counselling points were provided to parents, carers and young people to optimise patient care (clinical benefit and/or safety). Advice that was provided to participants included: avoiding administering milk at the same time as levothyroxine tablets (due to pharmacokinetic effects reducing levothyroxine absorption), omitting ibuprofen doses on the day that methotrexate is administered if child is experiencing nausea (to minimise risk of increasing the levels of methotrexate, thus to avoid drug toxicity) and avoiding hot drinks (to avoid altering drug pharmacokinetics). RV also advised patients to discuss alternative formulations commercially available in BNF for Children (2011-2012) where difficulties with specific medicine formulations arose. One example of this was the recommendation of mycophenolate mofetil 250mg capsules to a parent struggling to halve 500mg tablets accurately.

One parent was encountering difficulties when administering omeprazole Losec Mups to an infant. RV used guidance from BNF for Children (2011-2012) and advised the parent to mix the dosage form in a small amount of yoghurt and administer immediately. However, it should be noted that no reference to scientific evidence was provided in BNFC to support this administration technique (BNF for Children 2011-2012).

Signposting participants to medical professionals and alternative sources was also necessary in some circumstances. An example of a parent signposted by RV was a child prescribed sertraline, and administered regular ibuprofen over the counter by her parent. When an NSAID is administered to a patient taking an SSRI there is an increased risk of a stomach ulcer developing (BNF for Children, 2011-2012), and therefore in circumstances where an NSAID is required, this should ideally be prescribed and monitored by the medical practitioner responsible for the child's care. A parent concerned with side effects unreported

in the BNFC was directed to speak to the responsible consultant and report the adverse events via the yellow card scheme.

A parent on a paediatric ward approached RV and queried mixing Carobel thickener and other Cow and Gate products with antiepileptics. She had been advised by consultants to mix Carobel with vigabatrin liquid against the recommendations of a pharmacist. RV advised the mother to contact Cow and Gate, who said that this had not been studied and that before laboratory investigation could be carried out, instruction of the prescriber was required. The mother in question was concerned about risk of drug-thickener binding, resulting in an altered antiepileptic dose being absorbed. RV referred the mother to the consultant responsible for her daughter's care.