

**The manipulation of dosage forms of medications, with the
aim of achieving the required dose, for administration to
children**

Thesis submitted in accordance with the requirements of the University
of Liverpool for the degree of Doctor in Philosophy

by

Roberta Helen Richey

May 2013

Title: The manipulation of dosage forms of medications, with the aim of achieving the required dose, for administration to children

Author: Roberta Richey

ABSTRACT

Background:

There is a lack of commercially-available, age-appropriate formulations designed for administration to babies and children. This means that medicines may need to be manipulated to achieve the dose that is required in paediatric practice. This raises concerns about the dose accuracy and safety of the manipulated product. Though this is known and accepted as necessary, to date there has been no assessment of the evidence relating to these manipulations, the extent and nature of manipulations or of any associated practice issues.

Objective:

This thesis aimed to determine whether there is an evidence base for drug manipulations, to investigate the nature of manipulations, at the point of administration, in current clinical practice in neonatal and paediatric settings in the UK and to explore drug manipulations in the context of long-term medication administration by parents.

Methods:

Several methods were used to explore drug manipulations: a wide-ranging systematic review, an observation based study of drug manipulations in in-patient neonatal and paediatric areas, a UK wide survey of paediatric nurses and an interview based study with parents of children taking long-term medications.

Outcomes:

Manipulations to administer the required dose occur throughout practice and are not supported by evidence. Drug manipulation is intrinsic in neonatal and paediatric practice. Manipulations were identified more often in high dependency areas but

were found throughout all clinical areas. Manipulations occurred more commonly with certain dosage forms, notably with tablets, but were found involving many dosage forms. Manipulations were identified involving drugs that are commonly prescribed and for prescriptions that had been written for babies and children of all ages and with a wide variety of diagnoses. Concerns relating to drug manipulations have been raised by those working in these areas. Parents described undertaking manipulations prior to administering medications to children, though undertaking these manipulations did not appear to cause undue concern.

Conclusions:

This thesis has reviewed the limited evidence, scoped out the nature of manipulations used in practice and by parents and suggested areas where future work would be appropriate. In exploring drug manipulation this thesis has added to ongoing discussion about the need for appropriate medication for paediatric use.

ACKNOWLEDGEMENTS

Firstly and most importantly I would like to thank my supervisor Dr Mark Turner. Mark you have been great, somehow instinctively knowing when I needed encouragement and when tougher feedback was required.

For their generous provision of additional expertise and advice I'd also like to thank Professors Tony Nunn and Jim Ford and Dr Jean Craig. Additionally the support of the R&D department at Alder Hey Children's NHS Foundation Trust has been really appreciated, particularly that of Dot Lambert, the Mulberry House Research Nurses and the ADRIC team.

Sanity and support has been provided by family and friends. Special thanks go to my sisters; Moyna, Sandra and Joanne. Additionally I'd like to thank friends, particularly those who had already been through this process (Suzanne, Niall, Nika, Emily, Shelley, Janine, Donna), those who had the sense to never try it (Kirsty, Joe, Nicole, Michele, Helen, Jo) and those who are in the middle of it (Patricia, Fred).

This thesis is dedicated in memory of Norman and Anna Richey, my much loved parents.

TABLE OF CONTENTS

Chapter 1: BACKGROUND TO DRUG MANIPULATION IN PAEDIATRIC PRACTICE AND NEED FOR THE RESEARCH IN THIS THESIS	Page Nos.
1.1 PAEDIATRIC DRUG DEVELOPMENT.....	1
1.2 PAEDIATRIC DRUG PRESCRIBING	3
1.3 MEASURES TO PROMOTE PAEDIATRIC DRUG DEVELOPMENT.....	4
1.4 OFF LABEL AND UNLICENSED PRESCRIBING.....	5
1.5 DRUG MANIPUATION	7
1.6 USE OF DRUG MANIPULATION BY ADULTS	8
1.7 ALTERING DRUGS TO EASE ADMINISTRATION.....	9
1.8 MANIPULATIONS	10
1.8.1 Tablet manipulations.....	10
1.8.1.1 <i>Splitting tablets</i>	11
1.8.1.2 <i>Dispersing tablets</i>	12
1.8.1.3 <i>Crushing tablets</i>	12
1.8.2 Capsule and sachet manipulations.....	13
1.8.3 Liquid formulation manipulations.....	13
1.8.4 Intravenous manipulations.....	14
1.8.5 Other manipulations – nebuliser solutions, transdermal patches, suppositories and enemas.....	16
1.8.5.1 <i>Nebuliser solutions</i>	17
1.8.5.2 <i>Transdermal patches</i>	17
1.8.5.3 <i>Suppositories</i>	17
1.8.5.4 <i>Enemas</i>	17
1.9 VARIATION BETWEEN DIFFERING PRODUCTS.....	18
1.10 PATIENT PREFERENCE.....	18
1.11 PALATABILITY.....	18
1.12 SUMMARY OF CURRENT SITUATION.....	19
1.13 OVERVIEW AND STRUCTURE OF THIS THESIS.....	21
Chapter 2: SYSTEMATIC REVIEW	
2.1 SYSTEMATIC REVIEW.....	23
2.2 REVIEW QUESTIONS.....	23
2.3 SYSTEMATIC REVIEW PROTOCOL.....	24
2.4 METHODS.....	25
2.4.1 Eligibility criteria for study inclusion.....	25
2.4.1.1 <i>Types of drugs/participants</i>	25
2.4.1.2 <i>Types of interventions</i>	25
2.4.1.3 <i>Types of outcomes</i>	27
2.4.1.4 <i>Types of studies</i>	28
2.4.2 Search methods.....	28
2.4.2.1 <i>Resources used</i>	29
2.4.2.2 <i>Search strategy development</i>	30
2.4.2.3 <i>Additional resources</i>	33
2.4.3 Study selection and data extraction.....	34
2.4.4 Quality appraisal.....	34
2.4.5 Data synthesis.....	38
2.5 RESULTS.....	38
2.5.1 Primary outcome: dose accuracy of the manipulated medicines – weight and/or drug content outcomes.....	41
2.5.1.1 <i>Non-tablet study</i>	52
2.5.2 Secondary outcomes: bioavailability, effectiveness, patient experience, adherence/compliance, comparison between	52

	manipulation methods.....	
	2.5.2.1 <i>Bioavailability</i>	52
	2.5.2.2 <i>Evidence of safety or harms, adverse effects</i>	56
	2.5.2.3 <i>Patient experience</i>	56
	2.5.2.4 <i>Adherence</i>	57
	2.5.2.5 <i>Comparison between manipulation methods</i>	58
2.6	DISCUSSION	59
	2.6.1 Dose accuracy.....	59
	2.6.2 Manipulations of non-tablet dosage forms.....	61
	2.6.3 Bioavailability.....	62
	2.6.4 Safety.....	62
	2.6.5 Patient experience and adherence.....	63
	2.6.6 Comparison between manipulation methods.....	63
	2.6.7 Reporting in the included studies.....	63
	2.6.8 Summary of results.....	65
	2.6.9 Systematic review methods.....	65
2.7	CONCLUSIONS.....	69

Chapter 3: IDENTIFICATION AND DIRECT OBSERVATION OF DRUG MANIPULATION WITHIN WARD AREAS

3.1	BACKGROUND.....	71
3.1.1	3.1.1 Neonatal and paediatric in-patient areas included.....	72
3.1.2	3.1.2 Estimation of the requirement for manipulation.....	73
3.2	AIMS.....	74
3.3	DRUG MANIPULATION IN CLINICAL PRACTICE.....	74
3.4	OBSERVATION.....	75
	3.4.1 Previous use of observation in research.....	75
	3.4.2 Observation and drug manipulation.....	77
	3.4.3 Direct observation – in practice.....	77
	3.4.3.1 <i>Intervention in case of error</i>	77
	3.4.3.2 <i>Disguised/undisguised observation</i>	78
	3.4.3.3 <i>Observer acceptance into the field</i>	79
3.5	SELF-REPORTING.....	79
3.6	METHODS.....	80
	3.6.1 Identifying manipulations.....	80
	3.6.2 Sampling.....	81
	3.6.3 Observation units.....	82
	3.6.4 Possible drug errors.....	82
	3.6.5 Consent.....	82
	3.6.6 Observation tool development.....	83
3.7	ETHICS	85
3.8	PILOT STUDY.....	85
	3.8.1 Pilot study aims.....	85
	3.8.2 Pilot study – wards included.....	86
	3.8.3 Pilot study outcomes.....	86
	3.8.3.1 <i>Identification of manipulations</i>	86
	3.8.3.2 <i>Data collection instruments</i>	87
	3.8.3.3 <i>Preliminary data on drug manipulations in-patient areas.</i> ..	91
	3.8.3.4 <i>The acceptability of the process to those being observed.</i> ..	91
	3.8.3.5 <i>Validity</i>	91
	3.8.3.6 <i>Implications for the main study</i>	91
3.9	MAIN STUDY.....	92
3.10	RESULTS.....	93
	3.10.1 Proportions required.....	99
	3.10.2 Observed manipulations.....	101

3.10.3	Patient characteristics.....	101
3.10.4	Tablets.....	101
3.10.5	Intravenous injections.....	102
3.10.6	Other dosage forms.....	103
3.10.7	Additional comments.....	103
3.11	DISCUSSION.....	104
3.11.1	Direct observation.....	104
3.11.2	Manipulation.....	110
3.12	CONCLUSIONS.....	114

Chapter 4: QUESTIONNAIRE

4.1	INTRODUCTION.....	116
4.2	AIMS.....	118
4.3	STUDY DESIGN.....	118
4.4	QUESTIONNAIRE DESIGN.....	119
4.4.1	Overall questionnaire design.....	120
4.4.1.1	<i>Question choice.....</i>	120
4.4.1.2	<i>Question wording, question order and layout.....</i>	121
4.4.2	Response rates.....	122
4.4.3	Saliency.....	123
4.4.4	Anonymity.....	124
4.4.5	Retrospective recall of recent drug manipulations.....	125
4.5	STEERING GROUP.....	125
4.6	ETHICS.....	126
4.7	METHODS.....	126
4.7.1	Sampling.....	128
4.7.2	Pilot study.....	128
4.8	ANALYSIS.....	129
4.9	RESULTS	129
4.9.1	Drug manipulations.....	130
4.9.2	Proportions of the original dose required.	134
4.9.3	Methods of manipulating suppositories, enemas and transdermal patches.....	136
4.9.4	Reasons for the manipulation.....	137
4.9.5	Policies, guidelines, procedures or worksheets.....	139
4.9.6	Reference sources.....	140
4.9.7	Measurement of small volumes.....	141
4.9.8	Open-ended questions.....	143
4.10	DISCUSSION.....	145
4.10.1	Questionnaire design.....	145
4.10.2	Drug manipulations reported.....	146
4.10.3	Reasons for drug manipulating occurring.....	148
4.10.4	Reference documentation.....	150
4.10.5	Measurement of small volumes.....	151
4.10.6	Concerns about manipulations.....	152
4.11	CONCLUSIONS.....	153

Chapter 5: PARENT STUDY

5.1	INTRODUCTION.....	154
5.2	CHRONIC CHILDHOOD CONDITIONS.....	155
5.3	MEDICATION ADHERENCE.....	157
5.3.1	Medication adherence – general.....	157
5.3.2	Medication adherence – children.....	157
5.4	PALATABILITY.....	158
5.4.1	Palatability – general.....	158

5.4.2	Palatability – children.....	159
5.5	DRUG MANIPULATION.....	159
5.6	STUDY OBJECTIVES.....	160
5.7	PARTICIPATION AND RECRUITMENT.....	161
5.7.1	Participants.....	161
5.7.2	Sampling.....	162
5.8	METHODS.....	163
5.9	ETHICAL APPROVAL.....	164
5.10	ANALYSIS.....	165
5.10.1	Rationale for approach used.....	165
5.10.2	Approach used in this study.....	167
5.11	RESULTS.....	168
5.11.1	The overall impact of having a child requiring long-term medication.....	169
5.11.2	Issues with change.....	171
5.11.2.1	<i>Relationship with health care professionals.....</i>	173
5.11.3	Adjustment over time.....	174
5.11.4	Administration of medications.....	175
5.11.4.1	<i>'Battle'.....</i>	175
5.11.4.2	<i>Medication administration with food/drink</i>	176
5.11.4.3	<i>Palatability.....</i>	177
5.11.5	Drug manipulations.....	178
5.12	DISCUSSION.....	180
5.12.1	Impact of long-term medication.....	181
5.12.2	Issues with change and support of health care professionals.....	182
5.12.3	Administration of medications.....	183
5.12.4	Adjustment over time.....	185
5.12.5	Palatability.....	187
5.12.6	Drug manipulations.....	189
5.13	CONCLUSIONS.....	191
Chapter 6: DISCUSSION		
6.1	BACKGROUND LEADING TO THIS RESEARCH.....	192
6.2	THESIS FINDINGS – SUMMARY.....	192
6.3	INTERNATIONAL PERSPECTIVES.....	193
6.4	DRUG MANIPULATIONS – TABLETS.....	193
6.5	NON-TABLET MANIPULATIONS.....	194
6.6	INTRAVENOUS MANIPULATIONS AND MEASUREMENT OF SMALL VOLUMES.....	195
6.7	RESOURCE IMPLICATIONS.....	196
6.8	REFERENCE DOCUMENTATION AND PROFESSIONAL LIABILITY.....	197
6.9	GUIDELINES.....	198
6.10	IMPLICATIONS FOR KNOWLEDGE AND TRAINING.....	198
6.10.1	Avoidable manipulations.....	200
6.10.1.1	<i>Dosage form preferences</i>	201
6.11	MANIPULATIONS, DRUG ERRORS AND ADVERSE DRUG REACTIONS	202
6.12	IMPLICATIONS FOR PARENTS.....	203
6.12.1	Implications of long-term medication administration.....	204
6.13	LIMITATIONS	205
6.14	FUTURE CONSIDERATIONS	206
Chapter 7: FINAL CONCLUSIONS		
REFERENCES		
		211

APPENDICES

Appendix 1: PubMed search strategy

Appendix 2: Individual drug search strategy

Appendix 3: Quality assessment form

Appendix 4: Reference guide for observer data collection forms

Appendix 5: Parent/carer interview prompt guide

LIST OF TABLES AND FIGURES

TABLES		Page Nos.
Table 1	Definition of manipulation for each dosage form.....	8
Table 2	Summary of the studies that considered dose accuracy or drug content in the manipulated tablets.....	45
Table 3	Comparison between manipulation methods.....	58
Table 4	Items to be completed on the data collection forms, by type of manipulation.....	89
Table 5	Manipulations identified during the observational study, by dosage form	93
Table 6	The drugs identified as manipulated, organised by the therapeutic classification from the BNFC, and the frequency of manipulation.....	95
Table 7	Drugs that were manipulated in the form of sachets, capsules, nebuliser solutions, suppositories and transdermal patches during the observational study.....	98
Table 8	The proportions, by dosage form, of the original complete dose that was being sought by the manipulation.....	100
Table 9	Details the proportions of the original dose required for the intravenous drug manipulations.....	100
Table 10	The drugs identified as manipulated from the questionnaire using classification from the BNFC.....	132
Table 11	Availability of supportive documentation (policies, guidelines, procedures or worksheets) on measuring small volumes reported by questionnaire respondents	
Table 12	Manipulations, by dosage form, reported by questionnaire respondents in neonatal and general paediatric areas.....	134
Table 13	The proportions of the original dose of the whole dosage form required for the manipulations reported by questionnaire respondents for capsules, sachets, nebuliser solutions, transdermal patches, suppositories and enemas.....	135
Table 14	The reasons for the manipulations that they had undertaken in the previous month by questionnaire respondents, by dosage form.....	138
Table 15	Availability of supportive documentation (policies, guidelines, procedures or worksheets) on how to carry out manipulations, reported by questionnaire respondents.....	139
Table 16	Availability of supportive documentation (policies, guidelines, procedures or worksheets) on measuring small volumes, reported by questionnaire respondents.....	140
Table 17	Reference sources that would be consulted by nurses prior to undertaking a drug manipulation, reported in the questionnaire.....	140
Table 18	The drugs where volumes of <0.2mL have been measured, as reported by questionnaire respondents.....	142
Table 19	The routes of administration for small volume doses, as reported by questionnaire respondents.....	143
Table 20	Details of the diagnosis of the children of the parents interviewed.....	169
FIGURES		
Figure 1	Search strategy development in PubMed.....	32
Figure 2	Flow diagram for the identification of the included papers.....	40
Figure 3	Studies in the systematic review that considered weight or drug content	43

Figure 4	Studies in the systematic review that considered bioavailability.....	55
Figure 5	Percentage of each drug of the total tablet manipulations identified during the observational study.....	96
Figure 6	Percentage of each drug of the total number of intravenous injection manipulations identified by the observational study.....	97
Figure 7	Where manipulations were identified during the observational study, by the main clinical specialities included.....	99
Figure 8	Main speciality of the ward/clinical area that questionnaire respondents worked in.....	130

ABBREVIATIONS USED IN THIS THESIS

BNF	British National Formulary
BNFC	British National Formulary for Children
BP	British Pharmacopoeia
CRD	Centre for Reviews and Dissemination
EMA	European Medicines Agency
EP	European Pharmacopoeia
EU	European Union
EuPFI	European Paediatric Formulation Initiative
FDA	Food and Drug Administration
GP	General Practitioner
HDU	High Dependency Unit
ICH	International Conference on Harmonisation
IPA	International Pharmaceutical Abstracts
MeSH	Medical Subject Headings
NMC	Nursing and Midwifery Council
NPPG	Neonatal and Paediatric Pharmacists Group
PICO	Population, Intervention, Comparison, Outcome
PICU	Paediatric Intensive Care Unit
PIP	Paediatric Investigation Plan
PUMA	Paediatric Use Marketing Authorisation
RCT	Randomised Controlled Trial
SPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
WHO	World Health Organisation

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE WORK IN THIS THESIS

Publications:

RH. Richey, JV. Craig, UU. Shah, JL. Ford, CE. Barker, M. Peak, AJ. Nunn, MA. Turner (2012) "The manipulation of drugs to obtain the required dose: systematic review." *J Adv Nurs* **68**(9): 2103-2112.

RH. Richey, UU. Shah, M. Peak, JV. Craig, JL. Ford, CE. Barker, AJ. Nunn, MA. Turner (2013). "Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence." *BMC Pediatr* **13**(1): 81.

Conference presentations:

European Paediatric Formulation Initiative (EuPFI), 'Formulating better medicines for children', 21st-22nd September 2010, Berlin:

An investigation of drug manipulation for dose accuracy in paediatric practice

Neonatal and Paediatric Pharmacists Group (NPPG), 12th-14th November 2010, Sheffield:

An investigation of drug manipulation for dose accuracy in paediatric practice – some preliminary results

52nd Annual Meeting of the European Society for Paediatric Research (ESPR), 14th-17th October 2011, Newcastle:

An investigation of the manipulation of drugs to achieve the required dose in neonatal practice

29th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID), 7th-11th June 2011, The Hague:

Manipulations of antimicrobial dosage forms in paediatric and neonatal practice

European Society for Developmental, Perinatal and Paediatric Pharmacology (ESDPPP) Congress, 15th-17th June 2011, Oslo:

Drug manipulations to obtain the required dose identified in paediatric practice – the MODRIC study

4th Congress of the European Academy of Paediatric Societies (EAPS), 5th-9th October 2012, Istanbul:

The use of drug manipulations to obtain doses required in paediatric practice: a systematic review

Related publication:

AJ. Nunn, **RH. Richey**, UU. Shah, CE. Barker, M. Peak, JL. Ford, MA. Turner (2013)
"Estimating the requirement for manipulation of medicines to provide accurate doses for children " European Journal of Hospital Pharmacy **20**: 3-7.

CHAPTER 1: BACKGROUND TO DRUG MANIPULATION IN PAEDIATRIC PRACTICE AND NEED FOR THE RESEARCH IN THIS THESIS

1.1 PAEDIATRIC DRUG DEVELOPMENT

There is considerable use of prescribed drugs by children, it has been estimated that in a year 200 million prescriptions for children and adolescents were issued in the UK (Costello et al., 2004). Differences in age, maturity and development, alongside the possible impact of any illness they may have, mean that the types and dosage of medications appropriate for babies and children may vastly vary. However, historically clinical drug development has not included clinical trials that have investigated the safety and effectiveness of the drug in children. The reasons for this include: the cost of studies compared with the size of the potential market, difficulties in trial design, time taken to complete studies in children as compared to adults, and the unique and complex ethical issues surrounding research with child participants, such as concern about obtaining consent from children and their parents/guardians and any risk of possible effects of the trial medications on a child's development (Rocchi et al., 2010). Furthermore, for many potential treatments the small populations of children that require the medicine mean that trials can only be carried out by the recruitment of children from large numbers of centres (Waller, 2007). With most studies having been conducted with adults, pharmacokinetic and pharmacodynamics studies have produced little data on drug effectiveness and safety data relating to children. The results of studies done in adults may be extrapolated for use in children in some circumstances (Yewale and Dharmapalan, 2012). Extrapolation can be useful and avoid trials but it can be misleading if not done carefully. Age dependent changes in physiological factors make the data extrapolated from clinical studies in adults inappropriate for children and demonstrate the need for paediatric clinical trials (Hsien et al., 2008). There has not been sufficient economic incentive for pharmaceutical companies to develop and trial medicines specifically for use in children or to extend clinical trials to include children. There has also been a trend for UK companies to discontinue

licensed paediatric formulations because of low demand (Nunn, 2003). Consequently, many medicines have been licensed for use in adults but not for use in children. This can lead to situations like those described by (Conroy et al., 2003) in which some of the chemotherapy drugs used in children have been recommended for use in trials. However the manufacturers state that safety and effectiveness in children have not been established and that specific dose recommendations for children cannot be made due to insufficient use in paediatrics. The licensing process offers reassurance that medicines are safe, effective and of acceptable quality. Medicines used as unlicensed or off-label are not supported by the reassurance that this system provides (Conroy et al., 2003). Consequently evidence-based prescribing for children is compromised by a lack of satisfactory data on many drugs. Studies have reported that 50%-70% or 50-90% of medicines used in children have not been studied adequately in the paediatric population (Yewale and Dharmapalan, 2012). Specialist treatment may be at the higher end of these ranges, as it has been reported that more than 80% of prescriptions for children with cancer and 90% of those for neonates are for medicines which have not been licensed for that use (Turner et al., 1998, Paolucci et al., 2008). A review which included UK prescriptions from 2007 found that only 43% of UK prescriptions were both licensed for children and suitably formulated for children (Ragupathy et al., 2010). Accordingly many of the drugs administered to children are products which have not been designed for paediatric use. This does not only mean that the dose may not be appropriate for paediatric use. It may also mean that any impact of organoleptic properties on children may not have been considered. While an adult may be able to rationalise taking a bitter tasting medicine this may be more challenging for a child. Or a tablet that may appear to be of a reasonable size to swallow to an adult may be viewed differently by a child. There are additional consequences from this lack of development of paediatric formulations such as the non-availability to the paediatric population of therapeutic advances (Rocchi and Tomasi, 2011).

1.2 PAEDIATRIC DRUG PRESCRIBING

The provision of appropriate doses of drugs for babies and children is complicated by the considerable physiological changes associated with childhood. Virtually all pharmacokinetic parameters change with age. Dosing regimens need to take into account factors such as growth, organ development and sexual maturation; furthermore drugs may directly or indirectly affect childhood development, though this may not be apparent for decades (Sinha and Cranswick, 2007a). The frequently applied phrase is that children are not small adults and cannot be treated as such. The developmental changes throughout childhood affect the responses to medications. The way that drugs are absorbed, distributed, metabolised and eliminated in children cannot be reliably predicted from adult data (Kearns et al., 2003; Standing and Tuleu, 2005). Furthermore growth is not a linear process; age associated changes in body composition and organ function are dynamic and can be discordant during the first decade of life (Kearns et al., 2003). Therefore the size of the dose administered may need to be variable throughout childhood, often in proportion to body weight, body surface area, or age (Nunn, 2003). In addition there can be rapid and dramatic differences in a child's weight over time, necessitating frequent dose recalculations (Conroy et al., 2007). A recent review of paediatric gastrointestinal physiology data relevant to oral drug delivery noted that stated physiological values in children vary greatly within the literature and concluded that improved understanding of measurements of paediatric gastrointestinal physiology should help produce a better understanding and prediction of drug effectiveness and safety in different age groups (Kaye, 2011). All drugs have a therapeutic range below which they do not work and above which they are toxic (Yewale and Dharmapalan, 2012). The toxicity of many medicines in children is different to that seen in adults and careful consideration of the effect of excipients is important, this was demonstrated when some of the major adverse drug reactions in children were reviewed (Choonara and Rieder, 2002). As knowledge of growth and development has increased so has the recognition that developmental changes affect the responses to medications and the need for age-dependent adjustments in doses (Kearns et al., 2003).

1.3 MEASURES TO PROMOTE PAEDIATRIC DRUG DEVELOPMENT

There has been increasing global awareness of the neglect in drug development for children's medicines. Market forces alone have proved insufficient to stimulate adequate research on the specific authorisation of medicinal products for the paediatric population (Rocchi and Tomasi, 2011). Therefore regulations have been implemented by both the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) to incentivise the development and availability of medicines for children. The World Health Organisation (WHO) developed the 'Better Medicines for Children' programme to consider research and development gaps and factors limiting access and use (Finney, 2011).

EU regulations have applied since 2007 (Regulation (EC) 1901/2006 as amended) and include the early involvement of children in drug development by a pharmaceutical company via an agreement on the proposed process for a new medicinal product or measures to adapt the formulation of the medicinal product for use in paediatrics – the Paediatric Investigation Plan (PIP). This involves an agreement on the proposed paediatric clinical trials or a waiver if the drug is not appropriate for paediatric use (Rocchi et al., 2010). When a PIP is completed an extra six months patent protection will be granted, whether or not the data support a paediatric indication. The Regulation also established a new type of marketing authorisation, the paediatric use marketing authorisation (PUMA), intended to stimulate the development of off-patent products for use in children (Rocchi et al., 2010). The European Paediatric Formulation Initiative (EuPFI) group of paediatric formulation experts from industry, academia and clinical pharmacy was founded with the aim of raising awareness of paediatric formulation issues (Cram et al., 2009).

While this increased focus will encourage future paediatric drug development further, there have been some questions raised about whether the impact is addressing priority areas for paediatric medicine. Olski et al., (2011) considered the impact of three years of the European paediatric regulation, they noted that most

of the applications for PIPs or waivers were in areas of economic importance for the adult market (such as endocrinology, oncology, infectious diseases, cardiovascular disease) and that these do not necessarily match the areas of need within children's medicines. Viergever et al., (2011) reported globally on the collection of pharmacokinetic data in clinical trials in children. This report identified that of the 1081 trials researching medicines in children only a quarter were collecting pharmacokinetic data. Additionally the analysis identified supplementary gaps; notably that in trials where pharmacokinetic data was being collected only one third of the drugs included were on the EMA priority list, furthermore priority age-groups, such as neonates, were studied less (Viergever et al., 2011). These reports have established that while progress is being made, there are still considerable issues with the availability of age, dose and condition appropriate paediatric medicines. The EMA has yet to publish its experience with supporting the development of age-appropriate formulations.

1.4 OFF LABEL AND UNLICENSED PRESCRIBING

The historical and current situation is that appropriate paediatric drug doses and dosage forms are poorly available. This means that decisions have to be made on whether to prescribe and administer drugs which are unlicensed or where their use will be off-label (off label use involves prescribing outside the product license or prescribing a dose that is unlicensed). A number of situations may occur. Medicines may not be licensed for use in those under 18 years or may only be licensed for some paediatric age-groups. The route of administration required may not be one that the medicine has been approved for. It may be licensed for a different indication than that for which it is being used or may not be licensed at all (Hill, 2005; Hsien et al., 2008). Off-label or unlicensed use may be in the best interest of the child if no other treatment with a comparable benefit-risk ratio is available (Hoppu, 2008). Prescribing needs to be appropriate for the age, developmental stage and clinical condition of the child. Several studies have shown that prescribing unlicensed and/or off-label medicines is more frequent for children than for adults.

A study across children's wards in the UK, Sweden, Germany, Italy and the Netherlands found that 46% (1036/2262) of all drug prescriptions were either unlicensed or used off-label (Conroy et al., 2000). A study that considered the use of off-label drugs in a paediatric ward in Germany found that 16.4%-75% of off-label prescriptions were due to dose, 0%-40.3% were due to indication and 9%-55.8% were due to age (Hsien et al., 2008). This use of unlicensed and off label drugs has been noted to be at an even higher level within neonatal intensive care areas (Conroy et al., 1999). This applies globally. The use of unlicensed and off-label medicines in babies and children is common practice in healthcare settings in the USA, Europe and Australia (Di Paolo et al., 2006). Choonara (2009) noted that there is a growing recognition that the key issues in relation to drug therapy in children, such as whether the formulation is appropriate for the age of the patient, are similar in high income countries and low and middle income countries.

The use of off label or unlicensed prescribing may raise concerns about disciplinary or litigious action, it is legal and it is currently accepted that this prescribing in paediatric practice may be best practice when no suitable alternative is available (Conroy and Peden, 2001; Hill, 2005; Sinha and Cranswick, 2007a) . Without such prescribing effective treatment would be denied to many children (Sutcliffe, 1999). Associations have been made between the use of unlicensed drugs and dispensing and administration errors. In both neonates and children, unlicensed drugs have been shown to be significantly more likely to be associated with medication errors than licensed drugs (Conroy, 2011), and with an increased risk of adverse events (Bush, 2006).

1.5 DRUG MANIPULATION

As many of the drugs prescribed for children were designed for and tested in adults, logically they are predominantly available as single dosage units suitable for adults. Many of these are frequently larger than those required for paediatric use. This can create a situation where the drug dose is available as a tablet, capsule, sachet, suppository or enema but the dose which is required is a fraction of the whole dose

available in that single dosage unit. This lack of commercially available, age-appropriate formulations can make it difficult to administer medication to children. Medicines may require manipulation at the point of administration by opening, splitting, crushing or dispersing the tablet, capsule, sachet, suppository or enema and trying to calculate and measure a smaller dose that is a fraction of the original whole dose. Additional difficulties arise as the magnitude of doses required through childhood can vary up to 100-fold and the ability of children to cope with different dosage forms can also vary considerably (Rocchi and Tomasi, 2011). With intravenous drugs this unavailability of appropriately sized doses causes a different problem of how to accurately obtain a much smaller dose from what is available. This may require several dilutions of the original drug to obtain a volume which is sufficient to ensure that the smaller dose can be measured with an acceptable degree of accuracy. This need to manipulate drugs to obtain these paediatric sized doses has been identified both within the UK and internationally (Bourlon et al., 2006; Skwierczynski and Conroy, 2008; Kayitare et al., 2009).

A systematic review of medication errors in paediatric practice noted that there were multiple definitions of medication errors used. Within some studies definitions were either not included or were vague. This demonstrates that terminology is important as the inconsistency limited the ability to draw comparisons between studies. The authors of this review noted the importance of standardised definitions (Ghaleb et al., 2006). Recent work by (Ernest et al., 2012) on the preparation of medicines for children noted that terminology may mean different things to different stakeholders. Therefore it is important to clearly describe what is meant for the work in this thesis by a drug manipulation.

A drug manipulation can be defined as the physical alteration of a dosage form¹ for the purpose of extracting a proportion of the drug dose (manipulation with the aim of achieving the required prescribed dose). The table below (Table 1) details the

¹ A dosage form describes the physical form in which medication is administered, the drug delivery system

drug manipulations for each dosage form, these may be necessary in paediatric practice where a dose is required which is not easily available.

Table 1: Definition of manipulation for each dosage form

Dosage form	Manipulation with the aim of obtaining the required dose
Tablets	<ul style="list-style-type: none"> ▪ Split, broken or cut and a segment given ▪ Crushed and a proportion of the powder given ▪ Crushed, dispersed in liquid and a proportion of the resulting dispersion given ▪ Dispersed in liquid and a proportion of the liquid given
Capsules/ Sachets	<ul style="list-style-type: none"> ▪ Opened, dispersed in liquid and a proportion of the liquid given ▪ Opened and a proportion of the powder given
Oral liquids	<ul style="list-style-type: none"> ▪ Diluted and a proportion given (to allow measurement of a small dose)
Nebuliser solutions	<ul style="list-style-type: none"> ▪ A proportion of the vial given
Suppositories	<ul style="list-style-type: none"> ▪ Cut or split and a segment given
Enemas	<ul style="list-style-type: none"> ▪ Proportion of sachet given (the remainder discarded) ▪ Proportion of contents removed, the remainder given ▪ Proportion of contents removed and administered
Intravenous	<ul style="list-style-type: none"> ▪ Reconstituted or ready prepared solution, further diluted to allow a smaller dose to be measured ▪ Volume of fluid removed from IV bag, drug added for infusion (to obtain accurate concentration for infusion) ▪ Drug added to infusion bag, portion with smaller dose removed and infused

1.6 USE OF DRUG MANIPULATION BY ADULTS

Drug manipulation is performed frequently by and for adult patients (Verrue et al., 2011). The need for manipulations can arise due to impaired ability to take medicines or the need for individualised dosing. In some cases, however the manipulation may not be necessary on clinical grounds. The driver for the manipulations may be economic factors, for example to help control drug prescription costs and rising healthcare costs (Quinzler et al., 2006; Berg and Ekedahl, 2010). There may be little cost difference between tablets of different doses of the same drug; for example, the halving of a tablet of twice the strength required to obtain two doses means that half of the total number of tablets is needed and therefore drug costs may be lower. This has been described by groups

such as the Veterans Administration in the USA (Flynn, 2000) and in Sweden (Berg and Ekedahl, 2010). Manipulations to achieve a proportion of the original dose has also been noted in adult practice, such as in elderly care, in intensive care or those receiving enteral feeds (Paradiso et al., 2002; Gerber et al., 2008; Berg and Ekedahl, 2010; Verrue et al., 2011). Those writing in this area have expressed concerns about this practice, such as the difficulties of splitting tablets or the possibility that the obtaining of tablet segments may result in unacceptably large deviations from the intended dose (Berg and Ekedahl, 2010; Verrue et al., 2011). Although there may be some issues which are similar across all age-groups drug manipulations will be investigated here solely within clinical neonatal and paediatric practice. As has been noted (Section 1.1) assumptions cannot be made about children using adult data (or vice versa). Thus the use of manipulations in medicines prescribed for children requires dedicated study.

1.7 ALTERING DRUGS TO EASE ADMINISTRATION

In defining drug manipulations it was evident that similar processes may be used to assist with drug administration. For example, tablets may still be split, crushed, or dispersed to assist with administration, that is where the whole dose of the tablet is given, such as for administration through a nasogastric tube. In 2001 an audit at Great Ormond Street Hospital revealed that manipulations such as tablet cutting, tablet crushing and opening capsules were necessary to administer 26% of oral doses given to inpatients (data unpublished)(Standing and Tuleu, 2005). An Australian survey of adult and paediatric solid medication dosage form modification (tablets crushed, dispersed or split, capsules opened) found that for children on 60 (82%) of occasions the inability to swallow the solid dosage form was the reason for the modification, on 10 (14%), modification was because the correct dose was not commercially available (Nissen et al., 2009). These split, crushed or dispersed dosage forms may also be mixed with food or beverages where palatability or the ability or willingness of a child to take the drug is an issue. Studies have considered the palatability of crushed angiotensin II receptor blockers (Meier et al., 2007) and

calcium channel blockers (Milani et al., 2010). The impetus which led to both of these studies was the knowledge that, in order to get their children to take their prescribed medicines, parents were crushing the tablets and administering them with food or beverages. This is not just an issue for younger children. Skwierczynski and Conroy (2008) considered manipulation to obtain the required dose and/or to help with drug administration and noted that there were similar age ranges of children being given manipulated and non-manipulated drugs, suggesting that the issues do not solely relate to babies and younger children but span the whole of childhood. There are substantial issues relating to the potential impact of altering dosage forms to assist with their administration. Standing and Tuleu (2005) noted that one important area where research is needed is into children's ability to swallow and their preferences. However, key to the administration of any drug must be that the intended dose is given. Therefore, in this thesis, priority is given to the consideration of drug manipulation to achieve the required dose, where over or under dose and the possible consequences of this, are a concern.

1.8 MANIPULATIONS

Drugs are designed to enter the body via various routes and using differing mechanisms of drug release. While the predominant concerns about efficacy and adverse effects are universal to all drug manipulations, the processes of manipulating and possible subsequent effects are specific to particular dosage forms. Therefore it is important to reflect on the potential issues regarding the manipulation of different dosage forms (see Table 1).

1.8.1 Tablet manipulations

Tablets can be manipulated using different methods; splitting, crushing or dispersing. Some potential difficulties with splitting, crushing or dispersing tablets have been recognised. There does not appear to have been a systematic attempt to scrutinise the relevant literature. Furthermore, it is not known if manipulations are

relevant in paediatric practice, which drugs are manipulated, or the clinical areas in which they are used.

1.8.1.1 Splitting tablets

Where drug manipulations have been previously considered this has predominantly been focused on splitting tablets. A number of concerns relating to the tablet segments following tablet splitting have been noted. These include differences between the halved tablets in weight, drug content and drug stability (Nissen et al., 2009; Shah et al., 2010). Unequal segmentation may increase the variability of the concentration-time profile. This may be particularly relevant for drugs with narrow therapeutic ranges, drugs with closely spaced multiple strengths (as even slight dose variability may affect clinical outcomes) and those with relatively short half-lives with respect to the dosing interval (Quinzler et al., 2006; Nissen et al., 2009; Shah et al., 2010). Furthermore splitting extended release ((such as the cutting or crushing and dispersing of nifedipine modified-release tablets as described by (Tuleu et al., 2005) or other formulations with special drug-release characteristics may risk toxicity or a lack of effect. An unintended alteration in the formulation can lead to an uncontrolled release of the active ingredient or its degradation (Breitkreutz et al., 1999; Quinzler et al, 2006).

When (Verrue et al., 2011) considered the best method for tablet-splitting in nursing homes for the elderly they noted that the extant literature reports findings in different ways (such as by one splitting method or by type of drug, or by different methods of splitting of different tablets), or reported tablet outcomes differently (such as by theoretical weight, mean deviations or maximum losses). The accuracy of tablet splitting may vary with different devices, users, and tablet shapes (Green et al., 2010). This makes comparisons difficult.

The splitting of tablets may be influenced by the presence or absence of scorelines on the tablets. It might be reasonable to assume that tablets which have a scoreline can be split as part of a manipulation to get the required dose, scorelines may indicate where to segment the tablet. However some tablets are scored to facilitate their administration to patients who may have difficulty swallowing them; thus

though the tablet has been scored, this is not necessarily intended to reduce the dosage of the medication that may be taken (Shah et al., 2010). A scoreline does not necessarily signify that there is an even distribution of the active ingredient throughout the tablet or that each of the halves can be assumed to contain half of this active ingredient (Sayeed et al., 2010). This can be seen in examples such as that described by (Sayeed et al., 2010) where a formulation that was initially available as un-scored tablets were subsequently marketed as scored tablets without any change in the formulation. A review of splitting scored tablets noted the potential advantages of scored tablets such as dose flexibility, ease of swallowing and cost saving (van Santen et al., 2002). This review concluded that the performance of score lines needed to be defined for splitting properties (breaking ease) as well for the uniformity of mass of subdivided tablets, and the loss of mass by the subdivision (van Santen et al., 2002).

1.8.1.2 Dispersing tablets

As with splitting tablets the dispersing of tablets in liquid for the purpose of administering a proportion of the dose raises concerns about the accuracy and consistency of the doses achieved. Standing and Tuleu (2005) note that insoluble drugs are often crushed and dispersed in water to give a proportion of the dose without the use of suspending agents. This method may provide highly variable dosing, especially if the proportion of the dose volume sought is small. Broadhurst et al. (2008) identified that even where dispersible tablets are used inconsistent doses were found when sampled from different depths of the container.

1.8.1.3 Crushing tablets

As with splitting or dispersing tablets, crushing tablets may be used to obtain the required proportion of the original dose. Again there are concerns about the accuracy or variability of dosing. Crushing the tablet may make measuring a smaller dose difficult. Furthermore, crushing the tablet may leave part of the drug on the walls of the container or crushing device and the transfer of the crushed substance may also generate loss of the active drug (Best et al., 2011).

1.8.2 Capsule and sachet manipulations

Other oral single dosage forms may be manipulated, such as opening capsules or sachets with the aim of obtaining a proportion of the contents, usually by dispersing the contents in liquid and administering the proportion. One study packed and split capsules and found that when split the weight at the base of the capsule was consistently more than the weight of the top portion (Caldwell et al., 2010). Overall manipulating capsules and sachets appear to have been little discussed in the literature. It is not known whether this is because this is not a widely used practice or if it is one that has not been investigated. Where the contents of the capsule or sachet are dispersed then it will raise similar issues with potentially inconsistent dosing apply as described by Broadhurst et al. (2008) for dispersing tablets.

1.8.3 Liquid formulation manipulations

Liquid formulations may be an alternative to tablets, capsules or sachets. They provide a wider possible range of doses as they can be easily adjusted by measuring the prescribed dose volume (Breitkreutz et al., 1999). However, liquid formulations come with other problems. Where designed for adult use they may be presented in a concentration which is unsuitable for measuring a small dose and administering it to babies or young children (Nunn, 2003). Stability data for many of the drugs used in children are lacking making it difficult to provide an appropriate liquid dosage form (Nahata, 1999). Oral liquids often require substantially larger amounts of excipients to ensure stability and palatability than tablets (Pandit et al., 2010). Furthermore, liquid dosage forms may have physicochemical stability issues in the medium to long-term and it can be less easy to be sure of the consistent measurement of accurate doses (Nissen et al., 2009). Nunn (2003) noted that in an unpublished survey of 112 paediatric extemporaneous formulations 54% had inadequate data on shelf life. The lack of safety and stability data and inclusion of excipients with elevated toxicological risks might hinder the advantages of liquid formulations (Pandit et al., 2010). Where a liquid formulation is not readily

available, it may be procured from a 'specials' manufacturer. 'Specials' are special-order unlicensed medicines which are made to meet the needs of an individual patient, they have not been assessed by the regulatory authority for safety, quality and efficacy in the same way as licensed medicines (National Prescribing Centre, 2011). Most 'special' liquids are expensive and have short shelf-lives (Standing and Tuleu, 2005). The use of 'specials' means that there may be little consistency in the products used. This can be exemplified by a study by (Mulla et al., 2007) who considered the variations in captopril formulations used to treat children, with licensed captopril formulations available only in tablet form. This study surveyed 26 hospitals, in the UK, and found that a variety of unlicensed liquid captopril formulations were used interchangeably and that in four of the hospitals, tablets were crushed and dispersed. The authors of this study noted that no bioequivalence data exists for the liquid formulations identified, so it was not possible to be confident that the rate and extent of captopril absorption did not vary according to its formulation. This raised concerns about optimal dosing and potential toxicity as therapeutic equivalence between differing formulations should not be assumed (Mulla et al., 2007).

Where oral liquids are being used that have not been designed for children or are being used off-label there may be issues with achieving the required dose. This may necessitate manipulation through dilution of the oral liquid formulation to facilitate the measurement and administration of a small dose.

1.8.4 Intravenous manipulations

With intravenous drugs the unavailability of appropriate dosage forms means that a dose much smaller than the dose in the vial is required. A short research report considered all of the intravenous drugs prescribed on a neonatal unit, in the UK, finding that 404 (31%) of prescriptions were for doses which were less than one tenth of the contents of the vial and 16 (4.8%) were for doses which were less than one hundredth of the contents of the vial (Chappell and Newman, 2004). Complex calculations may be required to facilitate the measurement of suitable doses from

ampoules designed for adult patients (Conroy and Peden, 2001). Furthermore there are a variety of intravenous solutions available and a lack of consensus regarding the ideal premixed solutions for paediatric patients (Sinha and Cranswick, 2007b). Dose calculation errors are the most common type of medication error in neonatal and paediatric patients (Conroy et al., 2007). A retrospective review of medication errors in a paediatric teaching hospital found that 15/195 (8%) of the medication errors identified were for intravenous drugs and involved tenfold errors (Ross et al., 2000). The risk of tenfold errors has also been highlighted by reviews (McIntyre and Choonara 2004; Sinha and Cranswick, 2007b). Neonates may be at particular risk of medication errors as they have limited reserves to buffer any errors and the potential for rapid changes in weight, making appropriate dosing difficult (McIntyre and Choonara 2004; Sinha and Cranswick, 2007a). A study by (Allegaert et al., 2006) demonstrated improved dose precision in neonates when a smaller paediatric vial (50mg) was used in preference to the larger adult vial (250mg) to achieve the required dose. McDowell et al. (2010) completed a systematic review on the preparation and administration of IV medicines which included nine European studies (one of which was in a children's hospital). This review considered 12 stages of drug preparation and administration and found that the stage which contributed the most errors was the reconstitution of the drug and diluent. Parshuram et al. (2008) reported on a direct observational study in a structured, nonclinical environment which considered the preparation of intravenous medication. This study found that the errors of the greatest magnitude were made when infusions were prepared from small volumes of stock solutions, suggesting that those requiring smaller doses, such as babies and children may be at a greater risk than larger patients for these preparation-associated errors.

The noted that the ability to accurately measure small volumes intended for newborns and young children is of particular importance. They also note that if dilution is required it must be remembered that a significant extra quantity of active drug may be contained in the hub of the syringe and that appropriate instructions are needed. The flushing of a syringe has been found to deliver more than twice the calculated amount of medication when the syringe was filled to the

0.05mL mark (Berman et al., 1978). An observational study of intravenous drug administration errors described an error identified on a neonatal unit where the drug solution contained in the hub of the syringe was also administered to the patient (Taxis and Barber, 2003a).

With intravenous drugs it may be possible to avoid further dilution (thus avoiding a manipulation). This may necessitate the measurement of very small volumes to get the dose required. A Canadian study evaluated the potential requirements for small volumes, finding that in 8% (79) of the 982 indications listed in the formulary the recommended dose would require less than 0.1mL of the stock solution (Uppal et al., 2011). These authors also completed a clinical study in ICU and found that 7.4% (5245) of the 71218 intravenous doses administered required preparation from less than 0.1mL, with 17.5% (12439) requiring preparation from less than 0.2mL. Where such small volumes are measured there may be a question of accuracy of the dose achieved. When dealing with such small doses and volumes then even small inaccuracies may represent a concerning percentage of over- or under-dosage.

This manipulation of intravenous drugs raises questions about the potential of increased drug errors relating to the calculations required, the inadvertent administration of content of the syringe hub and the measurement of small volumes.

1.8.5 Other manipulations – nebuliser solutions, transdermal patches, suppositories and enemas

Nebuliser solutions, transdermal patches, suppositories and enemas are designed for a single use of the whole drug dose in the dosage form. The lack of paediatric sized doses may also mean that these dosage forms require manipulation. With all four of these dosage forms manipulations appear to have been little discussed in the literature and, as noted with capsules and sachets, it is not known whether this is because this is not a widely used practice or if it is one that has not been investigated.

1.8.5.1 Nebuliser solutions

With inhaled drugs there are specific child related issues, the reduced motor abilities and low inspiration volume of paediatric patients often limit the proper use of drugs and dosage forms for inhalation (Breitkreutz and Boos, 2007). As nebuliser solutions are pre-packaged into dose units they may require manipulation where a smaller dose than that available in the vial is required.

1.8.5.2 Transdermal patches

Durand et al. (2012) considered transdermal drug delivery and noted that as patches are available in a limited number of dosage strengths therefore to get a different dose an alteration, such as by cutting, may be an option. These authors note that in most cases bioavailability studies to determine the effects of cutting a patch on safety and efficacy have not been conducted. Furthermore they considered that there needs to be attention given to the design of the patch e.g. reservoir or matrix system patches (Durand et al., 2012). The use of transdermal patches as a delivery route for drugs raises its own concerns for children. With transdermal drug administration the varying hydration status of the skin can effect drug permeation, in childhood the water content changes significantly due to mainly metabolic or anabolic periods during development (Breitkreutz and Boos, 2007).

1.8.5.3 Suppositories

Conroy and Peden (2001) reviewed the use of paediatric analgesia and, using diclofenac suppositories as an example, noted that fractions of suppositories may be needed to administer a dose small enough for a child. This review also noted that the distribution of the drug throughout the suppository is not known and therefore the administered dose may not be accurate.

1.8.5.4 Enemas

The possibility of manipulation of enemas does not appear to have been discussed in the literature.

1.9 VARIATION BETWEEN DIFFERING PRODUCTS

Consistency in manipulations may be further complicated as there may be variation because products from different manufacturers behave differently when they are manipulated. Sayeed et al. (2010) considered this situation and found that when tablets were split there was weight variation, demonstrating that the same tablet product from different manufacturers may behave differently. They therefore concluded that results about the manipulation of one product should not be extended to other drug products. Even within the same tablet of the same drug from the same manufacturer may show inconsistencies, van Santen et al. (2002) discussed that batch to batch differences such as in hardness, water content, or storage time may cause variability in the breakability within the same brand.

1.10 PATIENT PREFERENCE

It is possible that there may be situations where the patient preference is for a manipulated product, though one that does not require manipulation is available. Nissen et al. (2009) when considering crushing/dispersing/splitting tablets and opening capsules found that there were occasions where tablets were crushed though an alternative dosage form such as an oral suspension was available. It cannot therefore be entirely assumed that if there is an appropriate formulation and dose available that manipulations are not occurring.

1.11 PALATABILITY

Where drugs are being given orally to a child palatability is liable to have an effect, it may cause difficulties with administration to the child and consequently on medication adherence. This may be particularly relevant where medication use is long-term, such as to treat chronic conditions (Standing and Tuleu, 2005). However, palatability studies have been predominantly conducted using adult volunteers and there is a lack of formal studies considering this in children (Matsui, 2007). Manipulation may have an effect on palatability, such as where tablets which have

been coated to disguise the taste of the active ingredient and these are split or crushed, similarly where capsules have been opened.

1.12 SUMMARY OF CURRENT SITUATION

The overriding concerns relating to drug manipulation of all dosage forms are the risks of dose inaccuracy. A proportion of the original dose has been administered. This may result in subtherapeutic or toxic doses. There may also be adverse effects due to dose inaccuracy or changes that the manipulation may cause to the drug delivery mechanism.

The splitting, dispersing or crushing of tablets to obtain the prescribed dose for administration raises a number of issues. Concerns about splitting tablets such as the possibility of tablets splitting unequally or the possible effect on the drug-release characteristics of splitting modified-release tablets have been described. However, these concerns have been predominantly discussed in general terms. Therefore it is clear drugs are being manipulated, into what fractions of the original dose and how they are being manipulated in clinical practice is not known. The crushing of tablets has been less discussed than tablet splitting and this has chiefly been in relation to crushing and administering the entire dose, with the possibility of dose loss within the crushing container noted. With dispersing tablets, while one study has noted the discrepancies of taking doses of a dispersible tablet from different depths of the container involved, there does not appear to have been other studies which have considered this manipulation.

On first consideration, oral liquid formulations may appear to be the solution to avoiding the need to manipulate tablets, sachets or capsules. However there are issues with this dosage form, such as the varying use of 'specials', the larger amounts of excipients required, the possible inaccuracies of measuring small volumes and the potential rejection by patients of the large volumes and/or the taste of oral liquids.

Overall, manipulating orally administered drugs may have an impact on the palatability and therefore the acceptability of the medications.

The administration of intravenous drugs to babies or children, where the dose has been designed for adults, raises several issues about the methods of achieving the required dose, specifically in relation to the calculations of the dilutions required and the possibility of error when undertaking these dilutions. A further issue arises as to whether it is more appropriate to dilute further or to attempt to measure small dose volumes.

There are four dosage forms where manipulation does not appear to have been discussed: sachets, capsules, nebuliser solutions and enemas. The reason for this is unknown; it may be that these dosage forms are not manipulated. Or it may be that these dosage forms are being manipulated but where and how these manipulations are being undertaken is not known. With the manipulation of transdermal patches and suppositories manipulation has been mentioned as a possibility but these forms of drug manipulation have not been further explored.

Though the need to manipulate drugs to obtain the doses required for babies and children is acknowledged, it appears that this practice has not been further investigated, that there has been little research undertaken which considers it. Previous studies have identified a paucity of research about paediatric drug dosage forms, paediatric pharmacology and paediatric therapeutics (Broadhurst et al., 2008). Where medication error reduction strategies were investigated a resounding lack of paediatric-specific evidence is adduced (Miller et al., 2007). The risk of any effect of drug manipulation will be a concern for patients of all ages. The vulnerabilities of babies and children to over or under dosing, the increased probability of drug manipulations being required due to the need for drug doses to change throughout childhood and the historical lack of paediatric specific drug development make drug manipulation a particularly pertinent issue in paediatric practice.

1.13 OVERVIEW AND STRUCTURE OF THIS THESIS

In summary the literature shows that drug development and the design of medicines for children have extensively lagged behind that for adults. The developmental changes throughout childhood impact on drug absorption, distribution, metabolism and elimination therefore the lack of the availability of suitable medicines for children is a substantial concern. While the necessity of manipulating dosage forms with the aim of achieving the required dose for paediatric use is acknowledged, little is known about the practice, the extent to which it is used and which drugs are being manipulated. Despite this acknowledgement of drug manipulation there is a lack of guidance for professionals or parents/carers about undertaking manipulations.

The aim of the work in this thesis was to investigate drug manipulation in paediatric practice. This is presented in the following chapters:

Chapter 2 – systematic review of the current evidence. The extant literature has not previously been systematically reviewed and where the literature discusses manipulation results are inconsistent. This systematic review includes consideration of the design of a search where terminology is not defined and approaches used where the evidence base includes a variety of types of study design.

Chapter 3 – observational study. This chapter reports on the identification and observation of drug manipulation in inpatient hospital neonatal and paediatric settings. This includes the development of the study design, study tools and methods of identifying manipulations and reports on the differing types of manipulation, dosage forms and drugs involved.

Chapter 4 – paediatric nurse survey. This chapter reports on a UK wide survey of paediatric nurses who are currently working in neonatal and paediatric inpatient areas. The design of the questionnaire used the outcomes of the systematic review and observational study to further investigate the types and methods used to manipulate drugs and to explore the concerns of those undertaking them.

Chapter 5 – parent study. This chapter reports on interviews with parents/carers of primary school-age children who require long-term medication. This chapter reports on an investigation of how the parents/carers of these children assist them in taking their medication and within this context the impact of any drug manipulations are explored.

Chapter 6 – discussion of the outcomes of the previous chapters, implications for current practice and future research and conclusions.

Chapter 7 – final conclusions.

CHAPTER 2: SYSTEMATIC REVIEW

From Chapter One it has been noted that manipulations are a known part of clinical practice in paediatrics and that they appear not to have been substantially investigated. It was important to consider what evidence is available on manipulations. Therefore this systematic review aimed to enable the accumulation of relevant accessible information, establish the evidence base and clarify where research has been completed and where further research may be needed.

2.1 SYSTEMATIC REVIEWS

Systematic reviews have been used extensively, especially to consider drug effectiveness and safety. These reviews often focus on a single drug, or a class of drugs, and tend to draw on evidence from randomised controlled trials. Systematic review methods have evolved to encompass many other review topics. Indeed it has been argued that a systematic review should be completed as a matter of course before any new research is undertaken (Harden and Thomas, 2005). Without systematic reviews researchers may miss promising leads or may embark on studies of questions that have already been answered (Cook et al., 1997). The Evidence for Policy and Practice Information and Co-ordinating Centre (<http://eppi.ioe.ac.uk/cms/>) note that a huge variety of types of questions are being examined with synthesis of a broad range of study types and that through these the flexible nature of systematic review synthesis has been illustrated. A systematic review of any area can be carried out providing it attempts to identify and include all relevant research, is trustworthy and conclusions are based only on the findings of the studies in the review (Harden and Thomas, 2005). There have not been any previous extant systematic reviews relating to drug manipulations.

2.2 REVIEW QUESTIONS

The questions for this systematic review were:

1. What is the volume, nature and quality of the research evidence for drug manipulations at the point of administration?
2. What are the effects of manipulating drugs, using methods employed at point of drug administration, on: dose accuracy, palatability of the drug, safety (of the recipient and/or the person carrying out the manipulation), bioavailability and stability of the drug?

It should be noted that the scope of these review questions has focused on the dose accuracy of the resultant proportions of the manipulated drug. Consequently it is not specific to the drug or the dosage form involved. This systematic review has used a broad scope and aimed to locate and describe the diversity of the available evidence relating to any type of drug manipulation.

2.3 SYSTEMATIC REVIEW PROTOCOL

Within a systematic review all of the decisions used to compile the review should be explicit. This allows those who read the review to follow how the review has been conducted and consider the quality of the review process (Garg et al., 2008). Published protocols serve as a guide to research in progress. The review protocol for this systematic review has been published (Richey et al., 2012). The development of this protocol ensured that key decisions were identified and discussed prior to the review; these included defining the scope of the research question, designing the search strategy to identify diverse studies, consideration of the methods for assessing the quality of the studies of varying designs and methods for synthesising the included studies. This protocol described the process and challenges of designing and conducting a systematic review of studies that included manipulations across all types and classes of drugs. Protocol publication may reduce the likelihood of reviewers introducing bias into their review by making major changes which could otherwise remain undisclosed and undetectable (Silagy et al., 2002). It should be noted that as a systematic review is dependent on the scope and quality of the included studies, the review protocol may need some subsequent modification (Sampson et al., 2009).

2.4 METHODS

Overall the methods for the review were rooted within recognised systematic review methods and as such were informed by the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care (www.york.ac.uk/inst/crd/index_guidance.htm). These methods are well established and include; the searching of electronic databases, screening of titles and abstracts using inclusion/exclusion criteria, study selection, searching of references lists, data extraction using a review designed data extraction table, independent quality assessment by two reviewers, data analysis and narrative synthesis of the systematic review.

2.4.1 Eligibility criteria for study inclusion

2.4.1.1 Types of drugs/participants

This review considers drug manipulation and was not specific to any drug or dosage form; consequently studies of any drug could potentially be included. This research has arisen from concerns about the manipulation of drugs for paediatric use. Drug manipulation has also been highlighted within adult medicine both for economic reasons, and in specific clinical areas such as in intensive care or to assist with dose flexibility with older adults (Berg and Ekedahl, 2010; Verrue et al., 2011). Therefore studies may have been completed where drugs have been manipulated for administration to adults that involve drugs that could also be used in paediatric practice. Furthermore the outcomes, though in adults, could indicate areas for investigation in paediatric practice. Therefore it was decided not to apply age-restrictions in this systematic review.

2.4.1.2 Types of interventions

The manipulations to be investigated are defined as those that can be carried out at the point of administration and include:

- cutting, breaking or splitting into smaller segments (tablets, suppositories, transdermal patches)
- dispersing tablets or sachets with liquids and taking a proportion
- crushing tablets or opening capsules, mixing the resultant powder with liquid and taking a proportion
- taking proportions of an enema
- taking proportions of a nebuliser content
- further diluting ready prepared or reconstituted intravenous or oral solutions (usually to allow a smaller dose to be measured)

This systematic review was based on the consideration of drug manipulation as it has been defined for this research. Where drugs are altered, such as by breaking, crushing or dispersing to aid administration, for example where there are swallowing difficulties or where administration is through a naso-gastric tube, these would be excluded from this review. However modified-release formulations provide a particular issue. The design of modified release drug products intends to optimise a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval (Abdul et al., 2004). If these modified release drug products are altered in any way, such as by crushing a tablet, this may affect the mechanism of the delivery of the drug involved and could potentially impact on both the effectiveness of the drug regimen and/or the possible adverse effects associated with that product. Therefore this review allowed for the inclusion of studies where modified release formulations had been altered, though the entire dose of the original product may have been administered, as the outcomes potentially had relevance for drug manipulation.

The manipulations investigated in this review were those which would be completed at the point of administration. Therefore studies investigating extemporaneous preparations/compounding by the pharmacist were excluded. Extemporaneous preparation describes the manipulation by pharmacists of various drug and chemical ingredients using traditional compounding techniques to

produce suitable medicines when no commercial form is available (Brion et al., 2003). The use of these techniques is widespread in paediatric pharmacy practice (Brion et al., 2003).

2.4.1.3 Types of outcomes

The primary outcomes relate to the aim of drug manipulations, which is to achieve a pre-specified dose of drug which is not readily available. The secondary outcomes relate to the possible effects of drug manipulation on the medicines, those taking the manipulated drug and the person undertaking the manipulation.

Primary outcomes:

- dose accuracy of the manipulated medicine as assessed by drug content assay or other study specific methods such as weight, dissolution or dispersion
- reproducibility of manipulation assessed by variation in dose accuracy

Secondary outcomes:

- evidence of safety or harms explicitly attributed by the authors to the manipulation of medicines
- bioavailability
- tolerability/palatability/adherence (explicitly attributed to the manipulation)
- contamination of the area of the manipulation, healthcare professional, carer or patient

The effectiveness of manipulated drugs was considered, but discarded, as an outcome. There are numerous outcomes relating to the effectiveness of drugs and these are frequently condition and context specific; therefore to consider effectiveness relating to drug manipulation drug specific searches for each drug involved would be required.

2.4.1.4 Types of studies

This review aimed to explore and describe the evidence relating to drug manipulation across any drug and a range of outcomes. Systematic reviews aim to focus on the best available evidence, however where no studies of this level are found it does not mean that there is no evidence to assess and the review may appropriately consider other evidence (Counsell, 1997; Stroup et al., 2000; Hawker et al., 2002). Though systematic review methodologies were initially developed in reviews of effectiveness (focusing predominantly on randomised controlled trials), interest has been growing in the development of diverse systematic review methods to incorporate different types of evidence including other quantitative designs as well as qualitative research (Dixon-Woods et al., 2005; Goldsmith et al., 2007). Reviews in drug manipulation have not previously been completed. It was anticipated that there would not be a substantial evidence base for this. It was decided that this review would take a broad approach to explore the range of evidence available. Accordingly it would not restrict on study design except to exclude the evidence considered to be of the lowest quality that is to exclude case studies, case reports and letters.

This review considers drug manipulation across a range of outcomes. These outcomes ultimately may impact on patients. However for the primary outcomes around dose accuracy the evidence could be considered where the drug has not actually been administered. Therefore studies were included in this review, where they met the inclusion criteria, which were laboratory-based and considered weight and/or drug content but did not include bioavailability. The stated secondary outcomes of this review did require the administration of the drug to assess.

2.4.2 Search methods

The conclusions drawn by any systematic review are going to be determined by the appropriateness of the search strategy and its ability to identify relevant studies for inclusion. The design of an effective systematic search provided a particular challenge with this review. A systematic search is vital to a systematic review

(Simunovic et al., 2009). Logically, if the search strategy does not locate the eligible studies, the review risks its findings being flawed as the studies that have not been located may have provided differing results from those that were included. Within searches that, for example, consider drug effectiveness outcomes for one drug used for a particular condition, then the design of a search strategy may be more straightforward. For this review any drug or dosage form could potentially be included.

A highly sensitive search strategy will retrieve most of the relevant studies but may also retrieve many unwanted articles (Goss et al., 2007). Most searches have to balance an inevitable trade-off between a highly sensitive search which may yield an unmanageably high number of hits and a more precise search that limits the retrieval to a manageable yield (Boynton et al., 1998). This may be a particularly difficult balance in a review with a diffuse topic area. Screening references for possible inclusion within a systematic review is resource expensive. Therefore this review used a considerable iterative process where the search terms were tested and modified based on what had been retrieved and the decision as to whether or not this was a manageable yield.

The necessity of having to balance between the sensitivity and the precision of the search does raise the risk that there may be studies that have not been identified. There were a number of methods used with the aim of ensuring that this review was as complete as possible. This included searching the reference lists of included studies, contacting experts for any additional studies/grey literature and having the list of included studies reviewed by experts.

2.4.2.1 Resources used

A thorough search depends on the variety of sources searched as well as the sensitivity of the search strategy (Golder et al., 2008). A number of different databases were used to increase the coverage of journals, as the use of a wide search net increases the likelihood that the studies identified will comprise a comprehensive body of evidence (Counsell et al., 1997; Sampson et al., 2009). EMBASE is an important electronic resource for pharmacology, pharmacy,

pharmacoeconomics, pharmaceuticals and toxicology research, whilst MEDLINE (internet interface PubMed) is the automatic choice when searching the evidence base for medicine. Although overlap exists in their journal coverage, relevant information would inevitably be missed if only one of these databases were searched (Wong et al., 2006; Garg et al., 2008). Cochrane databases (the Databases of Systematic Reviews and of Abstracts of Effects and the CENTRAL Register of Controlled Trials), the Cumulative Index of Nursing and Allied Health Literature (CINAHL) and the International Pharmaceutical Abstracts (IPA) database that indexes articles about pharmaceutical practice and development and use of drugs were also searched.

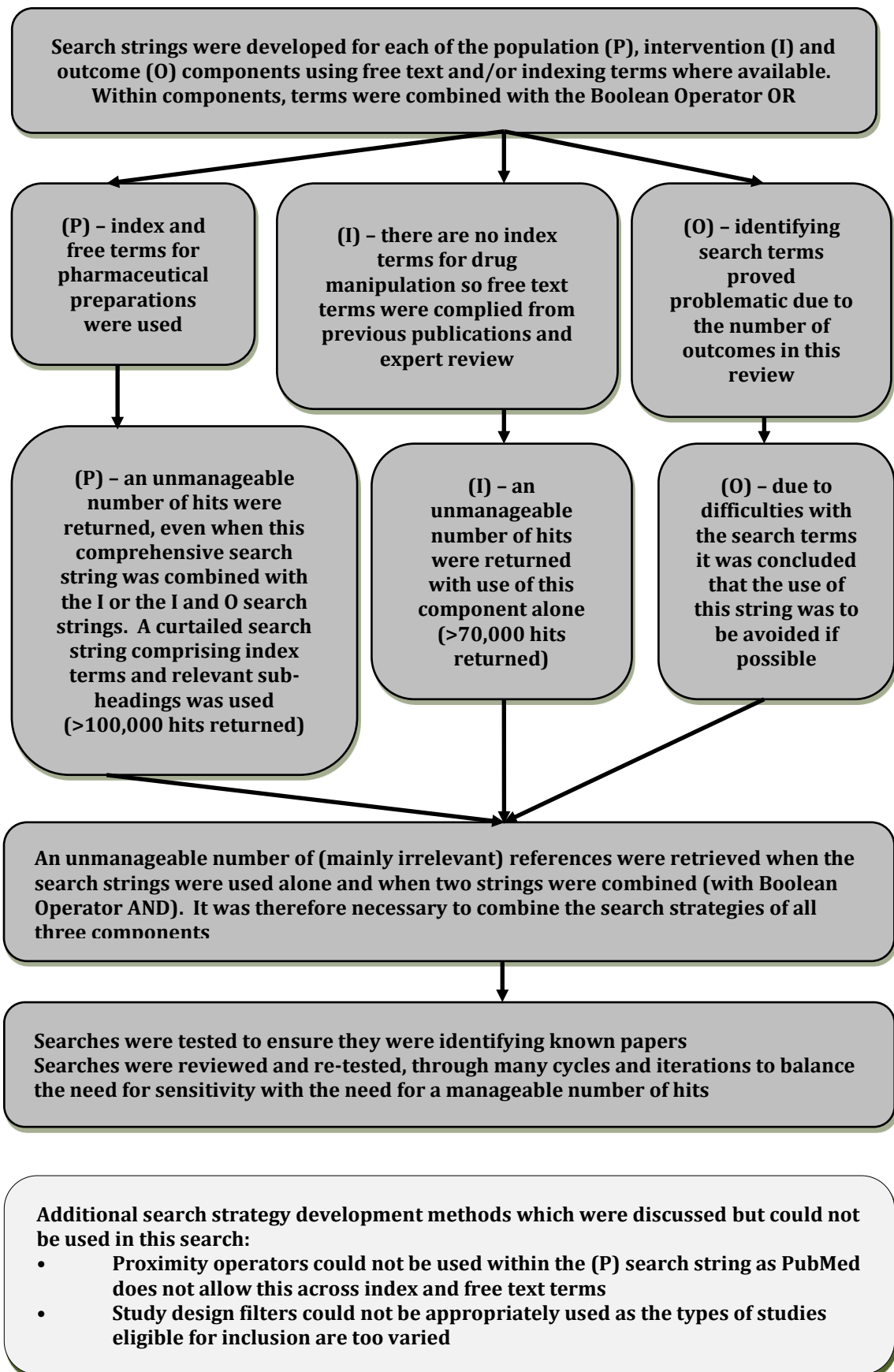
2.4.2.2 Search strategy development

In developing a search strategy, standard practice was followed and the review question was broken into the relevant sections of a PICO format (that is Participants or Population, Intervention, Comparison and Outcomes). PICO components can be both searched separately and combined where appropriate (Sampson and McGowan, 2006). For this review these components are pharmaceutical preparations (P), manipulation methods (I) and the primary and secondary outcomes (O). A comparison step was not needed as this review did not include comparison between differing drug treatments. There were several main considerations when designing the search strategy. Firstly drug manipulation is not a term which would feature in the indexing terms in the electronic search databases, such as in the MeSH (Medical Subject Headings) thesaurus in PubMed. As a result this search needed to consider the use of free text terms and MeSH subheadings which may be appropriate. Free text searches are a desirable feature because they are database neutral in the sense that they can be applied across all databases that use the same language (Goss et al., 2007). This search strategy required considerable development of the search terms as they aimed to incorporate all possible terms which could be used to describe a manipulation, such as split, cut, halve etc.. As drug manipulation does not have a defining description these terms were reviewed by pharmacy and formulations experts with the aim of

ensuring that the list was as complete as possible. This review aimed to include any drug and dosage form included in relevant studies; consequently drug or dosage form specific searches were not appropriate.

Study design filters, such as those for RCTs, can be a useful method of improving search precision (Goldsmith et al., 2007). However as the types of study potentially eligible for this review was so varied the use of study design filters was not appropriate. Throughout the design of the search strategy for this review the non-specific nature of the terms used caused difficulty in achieving the balance between sensitivity and precision. The difficulties of designing an effective, efficient search strategy where there is a multiplicity of disciplines involved in the field and the heterogeneity of terms used to describe the subject has been previously noted (Goss et al., 2007). Following the defining of the P, I and O components an iterative process followed. Searches were checked to ensure that they were identifying a small number of known papers. There was also the need to ensure that the return of the searches was producing a manageable yield of hits. These processes meant that there were many cycles and iterations of the search strategies. Due to the overarching challenges of the search strategy many successive iterations of it were required using combinations of the P, I and O components. The need to combine search terms from all three components (P, I and O) was necessary in this search though this risks reducing the recall of potentially eligible studies. This process is described in Figure 1.

Figure 1: Search strategy development in PubMed



In acknowledgement of the challenges of developing a search strategy in this subject area, the search strategy for the PubMed database was reviewed by an experienced information scientist and who considered the search strategy to be an appropriate one for this review question. The PubMed search strategy is available in Appendix 1. The PubMed search was adapted for application in other databases to take account of indexing differences and variations in the volume of the indexed references. MeSH terms were changed to appropriate indexing terms in EMBASE and CINAHL and using free text for IPA. Similarly to PubMed, the IPA search incorporated the Population, Intervention and Outcomes search strings. For EMBASE and CINAHL a manageable return was obtained using Population and Intervention search strings only.

Subsequent drug specific searches were also devised. Given the necessary iterative approach that was required in the search methods it was decided to complete a small number of drug specific searches. These were to be completed on drugs that are commonly prescribed in paediatric practice and were considered by pharmacy experts to be frequently manipulated. These additional searches, as drug specific, are more sensitive than the original search, the drug specific terms (P) combined with the (I) terms retrieved a manageable yield. If the additional searches identified studies which had not been found through the original search then further review of the search methods used and the identification of additional search terms would have been required. This approach also allowed for an in-depth consideration of frequently manipulated drugs. The three drugs selected for additional searches were omeprazole, captopril and warfarin. The search strategy for these searches is in Appendix 2.

Update searches were completed in February 2012 prior to completion of the review to ensure that the final review is as contemporary as possible.

2.4.2.3 Additional resources

Researchers, academics and health care practitioners with a special interest in medicines management were identified by a group of clinical and research experts and were contacted and asked to provide references to any additional studies or

details of any unpublished data. Reference lists of all eligible studies were also checked and any relevant studies were identified and included in the overall search yield.

2.4.3 Study selection and data extraction

Due to the considerable number of records identified with the main search strategy and with the narrower drug-specific searches the initial screen was undertaken by one reviewer, with a 5% random sample of the titles and abstracts screened by a second reviewer². The studies identified from the initial screen were independently considered by the two reviewers, these reviewers met to discuss the papers they had selected and agreed on which full text studies to obtain. A third reviewer was available for any studies where agreement on inclusion could not initially be reached. The use of this reviewer was not required.

Data from the included studies were extracted into data extraction tables by one reviewer, these were then independently assessed by the second reviewer and changes agreed.

2.4.4 Quality appraisal

The assessment of study quality is central to the methodology of systematic reviews since poor quality studies are more likely to generate inaccurate or biased results. The diversity of studies eligible for inclusion in this review posed challenges for their quality assessment. There is no widely accepted generic tool that can be applied equally across study types (Katrak et al., 2004). Traditional evidence hierarchies were developed specifically to address questions of efficacy and effectiveness and involved assessing research according to study design (Goldsmith et al., 2007). Substantial methodological guidance exists for the conduct of systematic reviews of randomised controlled trials (RCTs), and is rapidly evolving for

² Throughout the systematic review I was the first reviewer and the second reviewer was Dr Jean Craig

systematic reviews of other study designs including observational, diagnostic and qualitative research (Stroup et al., 2000; Hawker et al., 2002; CRD, 2009; Higgins and Green, 2009). Hawker et al. (2002) noted that if all evidence is to be evaluated rigorously then the traditional method of systematic review has to be modified and assessment criteria developed to encompass all the different types of material, while remaining explicit.

This review included studies that investigated outcomes of drug manipulation such as dose accuracy which were purely laboratory based. Other outcomes such as palatability, for example, were evidenced from more descriptive studies.

In general checklists tend to be specific to particular study designs, where reviews include more than one study design, separate lists can be used or a combined list selected or developed (CRD, 2009). Established quality appraisal criteria from checklists that are study design specific (e.g. RCT checklists or checklists for descriptive survey studies). Those devised by the Cochrane Collaboration and the Centre for Reviews and Dissemination (CRD) were used alongside additional criteria specific to this study to devise a customised, review specific, quality assessment form. It was important for the applicability of this review to clinical practice that this checklist included consideration of how the manipulation had been reported within the study. A previous review of paediatric trials noted that authors reporting these trials need to give complete pharmaceutical details (drug, formulation, manufacturer and administration details) to allow for the application in clinical settings (Pandit et al., 2010). What is reported in published studies can be considered in how relevant it is to the question of the review. Review specific assessments can include the relevance of focus of individual studies in relation to the review question. This approach of considering the requirements of the specific review in the assessment of the included studies has been used previously, such as in a WHO review of maternal morbidity and mortality where it was assumed that the presence of definitions of conditions and description of diagnostic methods or procedures could be regarded as an indication of higher quality (Gulmezoglu et al., 2004).

Though systematic reviews have been completed on topics such as the diagnostic value of laboratory tests (van den Bruel et al., 2011) and therapeutic drug monitoring (Touw et al., 2005), it is unusual for a systematic review to consider dose accuracy as measured by drug assays/weight/dissolution/dispersion, as used to address the primary outcomes of this review. Nonetheless it was important to consider the quality of the reported laboratory testing within these studies. In the absence of established methods for this, advice was sought from a formulations expert who used standardised tests, acceptance limits and validated analytical methods as per International Conference on Harmonisation (ICH) guidelines and assigned a quality level to this aspect of the studies. The beneficial use of experts or external consultants to provide independent appraisal of the quality and relevance of particular aspects of the review has been previously described (<http://eppi.ioe.ac.uk/cms/>). This method has been used in previous systematic reviews where critical appraisal tools for aspects of the review are not available, such as where consensus statements were reviewed (Sinha et al., 2008).

Inadequate reporting of studies can make quality assessment problematic. If insufficient detail is provided then readers are left with an incomplete picture of what was done and are not able to judge the reliability of the results (Moher et al., 2010). The customised form also drew on aspects of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (www.strobe.statement.org). While STROBE is not a tool for assessing the quality of published research it provides guidance on how to report observational research well, and does aim to make issues such as confounding, bias and generalisability more transparent (von Elm et al., 2008). This bespoke quality assessment form facilitated judgement of not only the reported quality of the study but also assessment of how it contributes to the answering of the research question underpinning this systematic review. This approach has been used previously, as the CRD note that separate lists can be used or a combined list selected or developed (CRD, 2009). While Hawker et al. (2002) considered that as there is no scoring method for the heterogeneous data it was appropriate to develop a framework to assess quality across a diverse group of studies. This bespoke quality

assessment form facilitated judgement of not only the reported quality of the study (including aspects of internal and external validity) but also assessment of how it contributes to the research question. The quality assessment form was reviewed by academic and clinical experts, tested using known papers and adjusted prior to being applied to all of the included studies. The form is available in Appendix 3.

Two reviewers independently completed quality assessments on the included studies, acknowledging the possibility of separate reviewers applying and interpreting checklist criteria in differing ways (Goldsmith et al., 2007). The reviewers met and discussed their decision-making and reached agreement on the quality level assigned to each study. A third reviewer was available if there were studies where a consensus on the assessment could not be agreed by the two reviewers, this reviewer was not required. Overall the following quality levels were assigned to the studies using the symbols ++, + and - ;

- ++ indicates studies where the reported methods and subsequent results and conclusions could be considered (with reasonable confidence) not to be biased, the process of drug manipulation was at least adequately described
- + indicates studies where there were some concerns about the reported study methods, or the methods were not reported in enough detail to permit sufficient assessment
- - indicates studies where there were considerable concerns about the reported methods or there was insufficient reporting of the methods for them to be assessed.

Six (14%) studies were assigned a ++ quality rating, 29 (67.4%) studies a + rating and 8 (18.6%) a – rating. Throughout the narrative synthesis of this review the quality assessment given to the study is included in brackets where that study is being described.

2.4.5 Data synthesis

Synthesis involves the collation, combination and summary of findings of individual studies included in the systematic review. The data from each study were extracted and tabulated by one reviewer. All of the data extraction was independently reviewed by the second reviewer. There was a diverse range of study types that could be incorporated in this review. There are challenges with the synthesis of different types of studies and data in the same review. However, there is a risk of excluding potentially valuable information where only one type of evidence is used has also been identified (Roberts et al., 2002; Thomas et al., 2004). While there has been some discussion within the systematic review literature about the use of quantitative and qualitative studies in the same systematic review, though there is little guidance available on combining different studies in reviews (Harden and Thomas, 2005). The use of laboratory-based studies in systematic reviews is more unusual and has not previously been considered. The heterogeneity of the studies included meant that the use of methods of pooling data, such as meta-analysis or meta-ethnography was not appropriate. The data was synthesised using narrative review with studies grouped using the outcomes defined for this review.

2.5 RESULTS

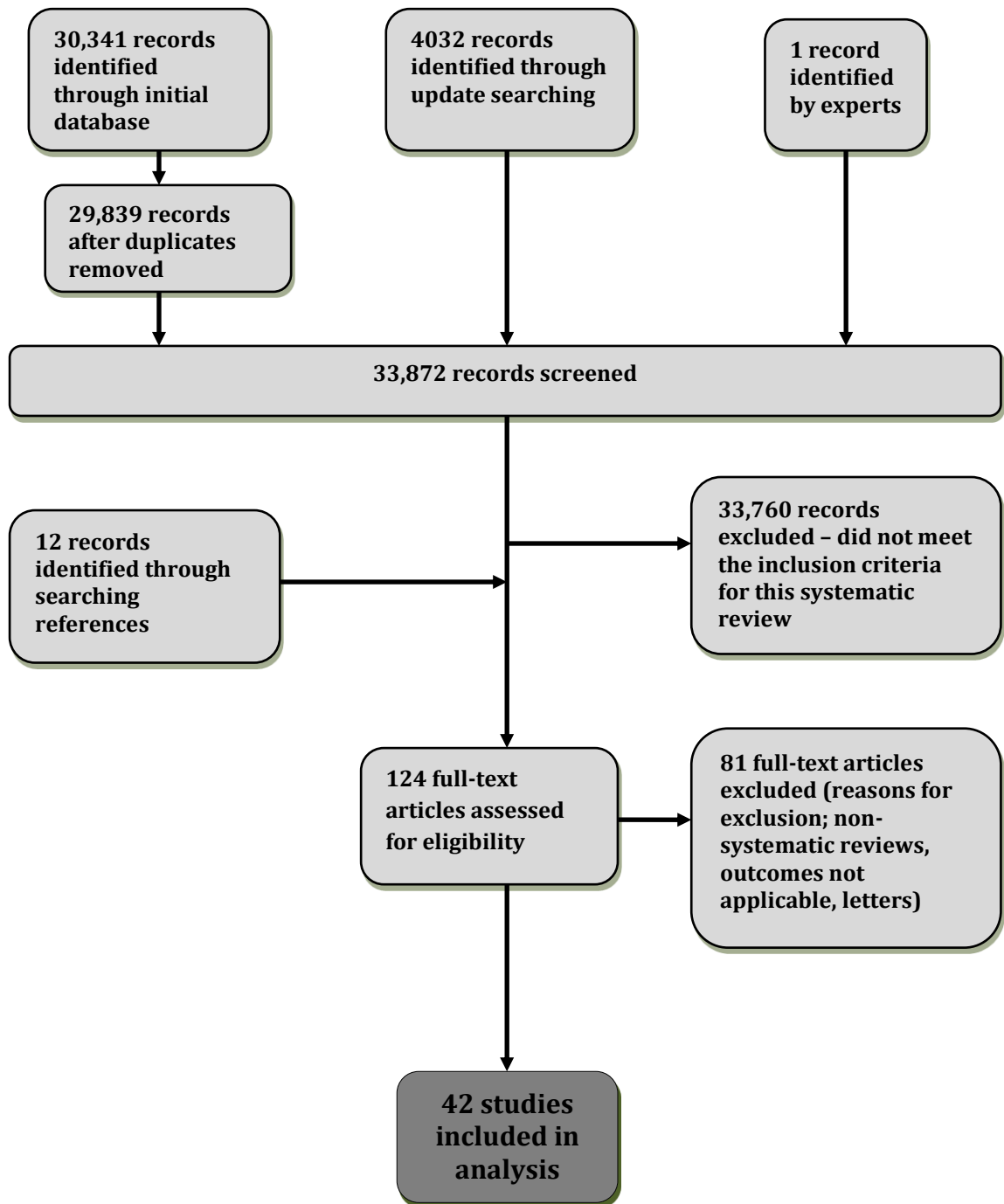
The search strategies for this review had the following yield: PubMed 15,042, EMBASE 1782, CINAHL 312 hits. Removal of duplicates from PubMed, EMBASE and CINAHL resulted in a final search of 16,633. This with the IPA search (13,119 hits), means that a total of just under 30,000 hits were screened to identify possible studies for inclusion in this systematic review. The narrower drug specific searches yielded 4535 hits, there were no additional studies identified from these searches. From the update searches an additional 4032 hits were screened for possible inclusion with two studies added to the systematic review.

Forty two studies met the inclusion criteria. The subsequent drug specific searches did not yield any additional studies. Figure 2 shows the flow diagram for the identification of the included papers. 41 of the 42 studies involved tablets, the one

remaining study involved suppositories. 16 of the 41 tablet studies investigated weight and/or drug content. There was only one bioavailability study identified where drugs were manipulated to obtain a proportion of the dosage form, and that proportion administered. Nine further studies investigated bioavailability outcomes (of which five also reported adverse effects) following the manipulations of five delayed release formulations. In these nine remaining studies all of the dosage form was administered. Eight studies reported on patient experience, adherence, taste or tolerability outcomes. Eight included a comparison of the methods used for the manipulation. Three studies considered tablet characteristics such as whether the tablets were scored or unscored.

Only two studies had child participants including the one bioavailability study where a proportion of the tablet was administered and one study which considered the taste scores of crushed tablets. No studies were identified that considered manipulation of other dosage forms known to be manipulated in practice, or that considered physical/chemical/microbial stability or contamination of the areas of manipulation. Though adverse effects were reported in five of the bioavailability studies there were no studies that specifically considered evidence of the safety or harms of manipulating medicines.

Figure 2: Flow diagram for the identification of the included papers



2.5.1 Primary outcome: dose accuracy of the manipulated medicines – weight and/or drug content outcomes

Figure 3 summarises the studies that considered weight and/or drug content. The dose accuracy of manipulated medicines was assessed by different studies through weight, dissolution profiles and/or drug content outcomes. Of the 17 studies included in this section 16 were of tablets, with 15 having segmented tablets and one study having dispersed tablets.

In the absence of pharmacopoeial standards to establish uniformity of split tablets when these studies were undertaken, authors have devised tests based on those for intact dosage forms. These studies used adapted pharmacopoeial weight and/or drug content specifications to assess whether halved tablets were truly halved (Footitt, 1983; Rosenberg et al., 2002; Teng et al., 2002; Polli et al., 2003; Rashed et al., 2003, Tuleu et al., 2005; Hill et al., 2009; Zaid and Ghosh, 2011).

These eight studies of halved tablets involved 65 products of 33 drugs and found that with 64.7% of the outcomes the product did not meet the specifications used in the study (for example the product was outwith the specified 85-115% range of target half-tablet weight). These eight studies were considered to be of reasonable quality with three assessed as ++ and five as +. One of these studies (Tuleu et al., 2005) also quartered tablets finding that there was wider variability with quarter tablet weights than with half tablet weights.

Additional studies halved and/or quartered tablets and used other weight related outcomes measures:

- One study (+) used the weight variation between tablet parts and found that 0-75% of halved tablets (of seven differing tablet products) were outwith $\pm 15\%$ of the desired weight (Horn et al., 1999). This study found that 29-74% of quartered tablets were outwith the desired weight.
- One study (+) used deviations from the theoretical weight of halved and quartered tablets (of three differing tablet products), finding that 10-32.5% of halves and 37.5-58.8% of quarters were outside the weight limit (Costa et al., 2000).

- One study (+) quartered tablets and considered them not to be of acceptable weight standards (Walker et al., 1978).

Figure 3

Three studies (all assessed as +) used dissolution profiles (Shah et al., 1987; Mandal, 1996; Erramouspe and Javi, 1997). All three considered tablets with a modified-release mechanism, and identified differences in dissolution profiles between halved and intact tablets.

Table 2 details the drugs involved in the studies above and whether when manipulated they did or did not meet the specifications defined in the study. This table also demonstrates that many of the included studies had not reported the methods of manipulation, and details on the shape, coating and presence of scoreline on the tablets. Even where these aspects were reported in many cases this reporting was incomplete and lacked detail.

Table 2: Summary of the studies that considered dose accuracy or drug content in the manipulated tablets

* G/B = generic/brand medicine

* M = manipulation (H = halved, Q = quartered),

* S = scored (Yes or No),

* Method = method of manipulation (TS = tablet splitter, Kn = knife, Ha = split by hand, Ra = split by razor blade)

++, +, - = quality assessment

Drug	Initial Strength	G/B*	Specifications	M*	Meth od*	S*	Shape (coating – where reported)	Outcomes summary	Reference [#]
Amiloride HCL & hydrochlorothiazide	5/5mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
Amlodipine	5mg	B	Weight variation	H	TS	N		77-91% halves within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
	5mg	B	Ph Eur	H	Ha	Y	Oblong (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
	5mg	B	Ph Eur	H	Ha	Y	Oblong (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
Aspirin	325mg	G	Dissolution study	H	TS			Dissolution profile similar for halved and intact tablets	(Mandal 1996) +
Aspirin (SR) (800mg matrix tablets, 650mg microencapsulated particles)	800mg	B	Dissolution study	H	TS			Dissolution profile showed higher dissolution for halved tablets than intact tablets	(Mandal 1996) +
	650mg	G	Dissolution study	H	TS			Dissolution profile showed similar drug release profile for halved and intact tablets	(Mandal 1996) +
Atenolol	25mg	B	Weight variation	H	TS	N		25-95% halves within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
	100mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
		B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
Atorvastatin	10mg	B	Ph Eur	H	Ha	Y	Oblong (film-coated)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
	20mg	B	Ph Eur	H	Ha	Y	Oblong (film-coated)	Met weight variation specifications	(Zaid and Ghosh 2011)++
	40mg	B	Adapted USP	H	TS	N	Oval	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
	20mg	B	Adapted USP	H	Ra	N	Oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
	40mg	B	Adapted USP	H	Ra	N	Oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
Buspiron	5mg	B	Adapted USP	H	TS	Y	Ovoid-rectangular	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Captopril	6.25mg	G	Adapted USP	H		Y	Capsule shaped	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	12.5mg	B	Weight variation	H, Q	TS	Y		58-100% halves, 26-55% quarters within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
	25mg		Theoretical	H, Q		Y	Round (uncoated)	25% halves, 42.5% quarters outside the weight limit	(Costa, Amaral et al. 2000) +

Table 2: Summary of the studies that considered dose accuracy or drug content in the manipulated tablets

* G/B = generic/brand medicine

* M = manipulation (H = halved, Q = quartered),

* S = scored (Yes or No),

* Method = method of manipulation (TS = tablet splitter, Kn = knife, Ha = split by hand, Ra = split by razor blade)

++, +, - = quality assessment

Drug	Initial Strength	G/B*	Specifications	M*	Meth od*	S*	Shape (coating – where reported)	Outcomes summary	Reference#
			weight					Halves met USP dissolution profiles, quarters did not	
			Theoretical weight	H, Q		Y	Round (uncoated)	10% halves, 37.5% quarters outside the weight limit	(Costa, Amaral et al. 2000) +
			Theoretical weight	H, Q		Y	Square (film coated)	Halves met USP dissolution profiles, quarters did not	
	25mg	B	Ph Eur	H	Ha	Y	Round (no coating)	32.5% halves, 58.8% quarters outside the weight limit	(Costa, Amaral et al. 2000) +
								Halves met USP dissolution profiles, quarters did not	
								Did not meet the weight variation specifications	(Zaid and Ghosh 2011)++
Carbamazepine	100mg	B	Weight variation	H	TS	Y		60-93% halves within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
Citalopram	40mg	B	Adapted USP	H	TS	Y	Oval	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
			Adapted USP	H	TS	Y	Oblong (non-coated)	Did not meet drug content specifications, met weight specifications	(Hill, Varker et al. 2009) ++
Clonidine	0.1mg	B	Weight variation	H, Q	TS	Y		81-100% halves, 44-71% quarters within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
		G	Weight variation	H, Q	TS	Y		30-79% halves, 25-49% quarters within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
Donepezil	5mg	B	Adapted USP	H		N	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002)+
Doxazosin	0.5mg	G	Adapted USP	H		Y	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	2mg	B	Adapted USP	H		Y	Oblong	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Enalapril maleate	5mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
	5mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
	10mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
	20mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
Fluvoxamine	50mg	B	Adapted USP	H		Y	Elliptical	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Furosemide	40mg	G	Adapted USP	H	TS	Y	Round	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++

Table 2: Summary of the studies that considered dose accuracy or drug content in the manipulated tablets

* G/B = generic/brand medicine

* M = manipulation (H = halved, Q = quartered),

* S = scored (Yes or No),

* Method = method of manipulation (TS = tablet splitter, Kn = knife, Ha = split by hand, Ra = split by razor blade)

++, +, - = quality assessment

Drug	Initial Strength	G/B*	Specifications	M*	Meth od*	S*	Shape (coating – where reported)	Outcomes summary	Reference [#]
Glipizide	10mg	G	Adapted USP	H	TS	Y	Round	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
	2.5mg	G	Adapted USP	H		Y	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Glyburide	5mg	B	Adapted USP	H	Ra, Ha	Y	Not oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
Hydrochlorothiazide	12.5mg	B	Adapted USP	H		Y	Round	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	50mg	B	Adapted USP	H	Ra, Ha	Y	Not oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
	25mg	B	Adapted USP	H	Ra	N	Not oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
	50mg	B	Adapted USP	H	Ra, Ha	Y	Not oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
Levodopa	500mg	B	Weight uniformity	Q	TS	Y		Quarters not of acceptable standards in uniformity of weight	(Walker, Abdulsalam et al. 1978)+
		B	Weight uniformity	Q	TS	Y		Quarters not of acceptable standards in uniformity of weight	(Walker, Abdulsalam et al. 1978)+
		B	Weight uniformity	Q	TS	Y		Quarters not of acceptable standards in uniformity of weight	(Walker, Abdulsalam et al. 1978)+
Lisinopril	40mg		Adapted USP	H	TS	N	Oval (non-coated)	Did not meet drug content or weight specifications	(Hill, Varker et al. 2009) ++
	5mg		Ph Eur	H	Ha	Y		Met the specifications for crushing strength, friability, disintegration time and mass uniformity	(Vranic and Uzunovic 2008) +
	10mg		Ph Eur	H	Ha	Y		Met the specifications for crushing strength, friability, disintegration time and mass uniformity	(Vranic and Uzunovic 2008) +
	20mg		Ph Eur	H	Ha	Y		Met the specifications for crushing strength, friability, disintegration time and mass uniformity	(Vranic and Uzunovic 2008) +
	40mg	B	Adapted USP	H	TS	N	Trapezoid	Did not meet weight uniformity specifications	(Polli, Kim et al. 2003)++
	40mg	B	Adapted USP	H	Ra	N	Not oval, not flat	Met weight variation specifications	(Teng, Song et al. 2002) +
Lisinopril/	20/		Ph Eur	H	H	Y		Met the specifications for crushing strength, friability,	(Vranic and Uzunovic 2008) +

Table 2: Summary of the studies that considered dose accuracy or drug content in the manipulated tablets

* G/B = generic/brand medicine

* M = manipulation (H = halved, Q = quartered),

* S = scored (Yes or No),

* Method = method of manipulation (TS = tablet splitter, Kn = knife, Ha = split by hand, Ra = split by razor blade)

++, +, - = quality assessment

Drug	Initial Strength	G/B*	Specifications	M*	Meth od*	S*	Shape (coating – where reported)	Outcomes summary	Reference#
hydrochlorothiazide	12.5mg							disintegration time and mass uniformity	
Lovastatin	40mg	B	Adapted USP	H	TS	N	Octagon	Did not meet weight uniformity specifications	(Polli, Kim et al. 2003) ++
Lozartan	50mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet the weight variation specifications	(Zaid and Ghosh 2011)++
Mercaptopurine	50mg	B	Adapted BP	H	Ha/Kn	Y		Did not meet uniformity of weight specifications	(Footitt 1983) +
	10mg	G	Adapted BP	H	Ha/Kn	N		Did not meet uniformity of weight specifications	(Footitt 1983) +
Methylphenidate (SR), (Ritalin-SR)	20mg	G	USP dissolution profiles	H	TS			Mean cumulative dissolution profiles showed significant differences between halved and whole tablets	(Erramouspe and Jarvi 1997) +
		B	USP dissolution profiles	H	TS			Mean cumulative dissolution profiles showed significant differences between halved and whole tablets	(Erramouspe and Jarvi 1997) +
Metformin	850mg	B	Adapted USP	H	Ra	U	Not oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
Metoprolol succinate	200mg		Adapted USP	H	TS	N	Oval (film-coated)	Did not meet drug content specifications (met when weight adjusted). Did not meet weight specifications	(Hill, Varker et al. 2009) ++
	50mg	B	Adapted USP	H		Y	Biconvex	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Metoprolol tartrate	50mg	G	Adapted USP	H	TS	Y	Oblong	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
	25mg		Adapted USP	H	TS	Y	Circular (non-coated)	Did not meet drug content specifications (met when weight adjusted). Met weight specifications	(Hill, Varker et al. 2009) ++
	25mg	G	Adapted USP	H		Y	Capsule shaped	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	25mg	G	Adapted USP	H		Y	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Nifedipine M/R	10mg	B	Ph Eur (halved tablets)	H, Q	TS			38/40halved tablets did not meet weight specifications, wide variability with halved and quartered tablets (SD 20%& 29% respectively)	(Tuleu, Grange et al. 2005) +
Oxybutynin	2.5mg	G	Adapted USP	H		Y	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Paroxetine	10mg	B	Adapted USP	H		Y	Modified oval	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +

Table 2: Summary of the studies that considered dose accuracy or drug content in the manipulated tablets

* G/B = generic/brand medicine

* M = manipulation (H = halved, Q = quartered),

* S = scored (Yes or No),

* Method = method of manipulation (TS = tablet splitter, Kn = knife, Ha = split by hand, Ra = split by razor blade)

++, +, - = quality assessment

Drug	Initial Strength	G/B*	Specifications	M*	Meth od*	S*	Shape (coating – where reported)	Outcomes summary	Reference#
	20mg	B	Adapted USP	H	TS	Y		Met weight variation specifications	(Rashed, Nolly et al. 2003) +
	40mg	B	Adapted USP	H	TS	N		Did not meet weight variation specifications	(Rashed, Nolly et al. 2003) +
	40mg	B	Adapted USP	H	TS	Y	Oval	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
	40mg	B	Adapted USP	H	Ra	U	Oval, not flat	Met weight variations specifications	(Teng, Song et al. 2002) +
Propranolol	10mg	B	Ph Eur	H	Ha	Y	Round (no coating)	Did not meet weight variation specifications	(Zaid and Ghosh 2011)++
Risperidone	2mg	B	Adapted USP	H	TS	N		Did not meet weight variation specifications	(Rashed, Nolly et al. 2003) +
	4mg	B	Adapted USP	H	TS	N		Did not meet weight variation specifications	(Rashed, Nolly et al. 2003) +
	0.25mg	B	Adapted USP	H		N	Oblong	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	1mg	B	Adapted USP	H		N	Oblong	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Rofecoxib	25mg	B	Adapted USP	H	TS	N	Round	Did not meet weight uniformity specifications	(Polli, Kim et al. 2003) ++
Sertraline	100mg	B	Adapted USP	H	TS	Y	Oblong	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
		B	Adapted USP	H	TS	Y		Did not meet weight variation specifications	(Rashed, Nolly et al. 2003) +
	25mg	B	Adapted USP	H		Y	Capsule shaped	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	50mg	B	Adapted USP	H		Y	Capsule shaped	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
		B	Adapted USP	H		Y	Capsule shaped	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
		G	Weight variation	H	TS	Y		90-100% halves within ±15% of desired weight	(Horn, Kuhn et al. 1999) +
Sertraline	100mg	B	Adapted USP	H	Ra	Y	Oval, not flat	Met weight variation specifications	(Teng, Song et al. 2002) +
Sildenafil	50mg	B	Adapted USP	H	Ra	N	Not oval, not flat	Did not meet weight variation specifications	(Teng, Song et al. 2002) +
Simvastatin	20mg	B	Adapted USP	H	TS	N	Shield-like	Did not meet weight uniformity specifications	(Polli, Kim et al. 2003) ++
	80mg		Adapted USP	H	TS	N	Oval (film-coated)	Did not meet drug content specifications (met when weight adjusted). Met weight specifications	(Hill, Varker et al. 2009) ++
Sulphamethoxy-	500mg	B	Weight	Q	TS	Y		Quarters not of acceptable standards in uniformity of	(Walker, Abdulsalam et al. 1978)+

Table 2: Summary of the studies that considered dose accuracy or drug content in the manipulated tablets

* G/B = generic/brand medicine

* M = manipulation (H = halved, Q = quartered),

* S = scored (Yes or No),

* Method = method of manipulation (TS = tablet splitter, Kn = knife, Ha = split by hand, Ra = split by razor blade)

++, +, - = quality assessment

Drug	Initial Strength	G/B*	Specifications	M*	Meth od*	S*	Shape (coating – where reported)	Outcomes summary	Reference [#]
pyridazine			uniformity					weight	
Theophylline (CR)	300mg	B	USP dissolution profiles	H				Used 8 different brands; 6/8 had significant differences in dissolution profiles for halved and whole tablets for both simulated gastrointestinal fluids used and 1/8 had significant differences for one of the fluids used	(Shah, Yamamoto et al. 1987) +
Trazodone	25mg	G	Adapted USP	H		Y	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
		G	Adapted USP	H		Y	Round	Met weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Venlafaxine	25mg	B	Adapted USP	H		Y	Shield shaped	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
Warfarin	500mcg	B	Adapted USP	H		Y	Round	Did not meet weight variation specifications	(Rosenberg, Nathan et al. 2002) +
	5mg	B	Adapted USP	H	TS	Y	Round	Met weight uniformity specifications	(Polli, Kim et al. 2003) ++
				Adapted USP	H	TS	Y	Oblong (non-coated)	Did not meet drug content or weight specifications

Overall these studies showed that halving tablets may not be reliable and that quartered tablets had substantial variation in weight and less reliably segmented than halved tablets.

Two further studies (both assessed as +) used other methods to consider dose accuracy; (Stimpel et al., 1985) split 34 brands of antihypertensive scored tablets, grouping the halved tablets into categories dependent on the weight deviation from the theoretical weight of halved tablets. Seven of the antihypertensives were considered to have excellent divisibility, eleven had good divisibility, ten had moderate divisibility and six had poor divisibility. The second study (Broadhurst et al., 2008) dispersed dispersible aspirin tablets in 10mL water and found that irrespective of dispersion time the samples taken from the base of the 30 mL container were consistently closest to the intended dose (51-95% of the intended dose) compared with those taken from the highest zone at 8mL mark of the container (23-80% of the intended dose), with a trend for the dose measured to decrease as the zones ascended up the beaker.

2.5.1.1 Non-tablet study

In the only non-tablet study (-) anaesthetists split six paracetamol suppositories of each of three different strengths into half and 2/3 doses (Kim et al., 2005). This study identified wide ranges for the resultant segments with yields of between 60-195% of the intended dose when suppositories were intended to be halved, though the authors of the study stated that there was good uniformity of paracetamol content in the intact suppository. The authors concluded that the lack of accuracy and precision was a reason to use unaltered suppositories.

2.5.2 Secondary outcomes: bioavailability, effectiveness, patient experience, adherence/compliance, comparison between manipulation methods

2.5.2.1 Bioavailability

Figure 4 summarises the studies that considered bioavailability. Bioavailability is the degree and rate to which the drug is physiologically available. While there are many

physiological and disease related mechanisms that can effect bioavailability it is also influenced by the formulation of the drug product, such as the mechanism of release (immediate, delayed), or the excipients added or manufacturing process used. The manipulation of a drug product may (or may not) have an impact on bioavailability. For example manipulation such as cutting a tablet into segments may alter the rate of the drug release or the concentration of the drug available. These possible effects of manipulation may mean that the drug dose available remains within acceptable efficacy and toxicity ranges, or they could impact negatively on both. The difficulty is that these potential effects where drug products are designed to have been administered without manipulation are not known.

There was only one bioavailability study (++) identified where a drug was manipulated to obtain a proportion of the original dosage form with this portion administered to participants and outcomes reported. This study was one of only two in this review which specifically included children, it involved 18 HIV-infected children who were banded into three weight groups and correspondingly received quartered, halved or three quartered generic tablet multiples of lamivudine (3TC) 300mg, stavudine (d4T) 80mg and nevirapine (NVP) 400mg or a generic liquid or trade liquid in a crossover study (Corbett et al., 2010). This study found that overall for all dosing groups there were no significant difference in bioavailability between the use of quartered, halved or three quartered tablets. Generally the time to maximum concentration was delayed for d4T and 3TC for the manipulated tablets compared with the liquid formulations. Overall all of the formulations were well tolerated.

There were nine studies, in adults, identified where modified-release tablets were split or crushed but the whole dose of the tablet administered. Due to the potential to alter the drug release characteristics of the formulation, the bioavailability and adverse effects outcomes of these studies are considered to be relevant to situations in which a proportion of the dosage form could, potentially, be administered. Eight of these nine eligible studies were sustained-release

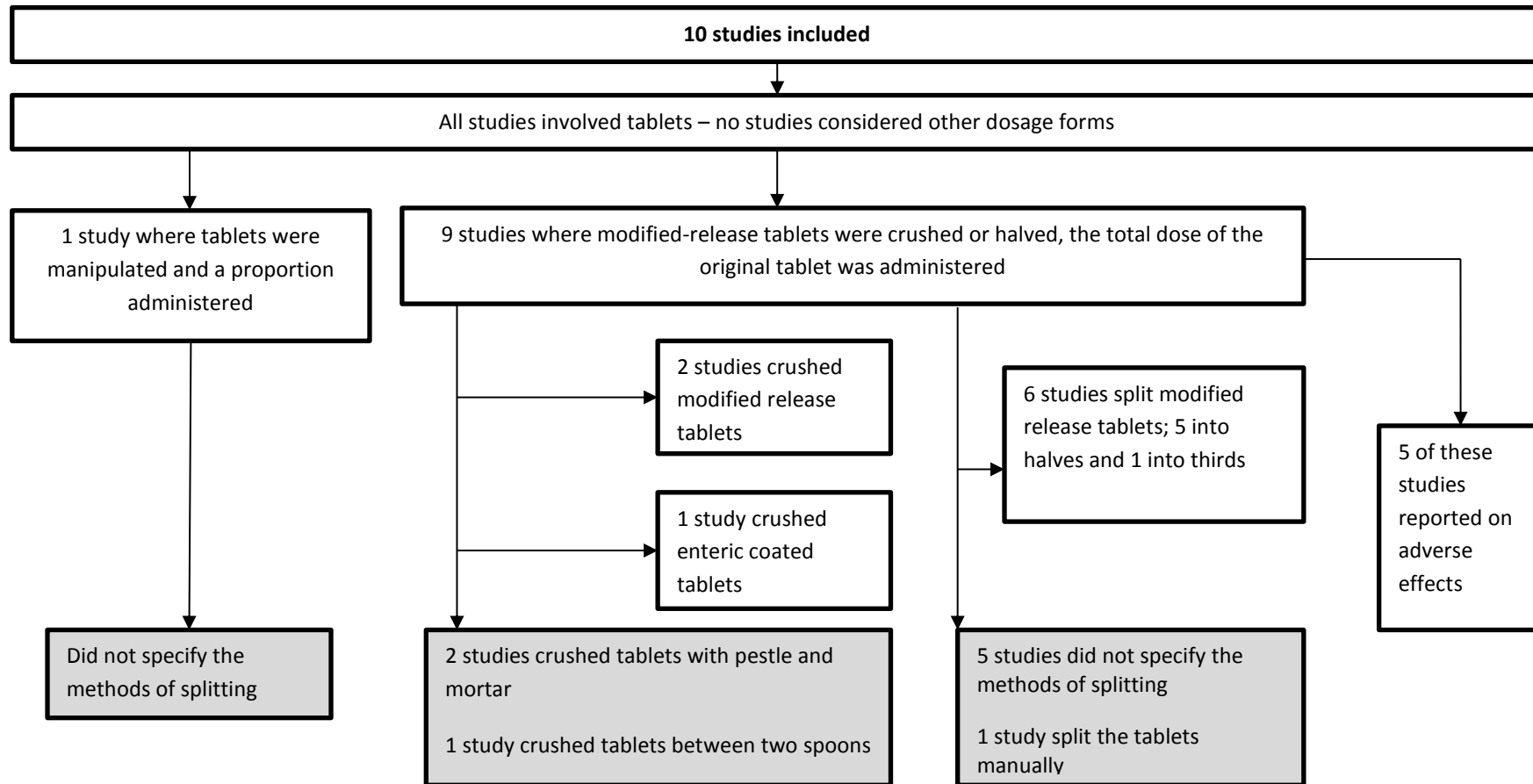
formulations and one study used an enteric-coated formulation. All of these studies had adult participants. Two studies involved crushing tablets, the crushing of pentoxifylline extended-release (Trental) 400mg and 600mg tablets (Cleary et al., 1999) (++) and theophylline matrix sustained-release (Theo-Dur) 300mg tablets (MacKintosh et al., 1985) (+) did not significantly change the bioavailability, though the time taken to reach peak concentration was shorter with crushed tablets than with intact tablets.

Five studies halved modified release tablets. No differences were found in bioavailability for halved and intact theophylline sustained-release (Theo-Dur) 100mg tablets (Simons et al., 1982) (+) and 300mg tablets (Fagerstrom, 1980) (-) tablets. One study (+) used theophylline slow-release anhydrous (Uniphyllin) 400mg tablets (Primrose et al., 1983) and peak drug levels were significantly higher with halved than with intact tablets. Two studies (both assessed as +) used verapamil sustained-release (Isoptin SR, Securon SR) 240mg matrix tablets, both studies found no differences in bioavailability for halved and intact tablets (McEwen et al., 1989; Moreland et al., 1989).

The final study including modified release tablets (+) involved cutting isosorbide-5-mononitrate (Monoket Multitab) tablets into thirds and found no significant differences in bioavailability though maximum peak concentration was higher with the trisected tablets than with intact tablets (Stockis et al., 2002).

The one study (++) that crushed enteric-coated tablets (pantoprazole 40mg) found the resultant suspension to have 25% less bioavailability than the whole tablet (Ferron et al., 2003).

Figure 4: Studies in the systematic review that considered bioavailability



2.5.2.2 Evidence of safety or harms, adverse effects

Adverse effects considered to be related to the drug manipulation were relevant to this review. There were adverse effects reported in five of the nine bioavailability studies of modified release tablets with nausea/vomiting with theophylline (Primrose et al., 1983) and pentoxifylline (Cleary et al., 1999) and headache (Primrose et al., 1983; Cleary et al., 1999) and with isosorbide-5-mononitrate (Stockis et al., 2002) featuring slightly more often with crushed or split tablets than intact tablets. One study reported excellent tolerability with both halved and intact verapamil tablets (Moreland et al., 1989). The one study which crushed enteric-coated pantoprazole tablets found both treatments to be well tolerated and considered the adverse effects reported to be related to nasogastric tube insertion rather than drug-related (Ferron et al., 2003). The number of adverse effects reported was small and reporting was not detailed.

2.5.2.3 Patient experience

One study (-) considered the experiences of children taking an oral solution compared with those taking a dispersion of crushed prednisolone tablets (Lucas-Bouwman et al., 2001). Taste assessed by visual analogue scores was significantly better for the oral solution than for the crushed tablets. Nine of the 39 children taking crushed tablets withdrew due to repeated vomiting while taking the crushed tablets compared with none from the oral solution group ($p=0.001$).

There were five surveys identified that assessed adult participants' experiences of splitting tablets. Splitting of tablets has been encouraged in some areas for economic reasons, though the dose required may be available in an intact tablet. (For example, if 5mg of a drug is required half of a 10mg tablet may be used in preference to a 5mg tablet as the 10mg tablet may be only fractionally more expensive and much cheaper than two 5mg ones.) Three studies used the same questionnaire, or an adapted version of it, for tablets split with a tablet splitter. Carr-Lopez et al. (1995) surveyed 233 patients splitting lovastatin, Gee et al. (2002) surveyed 454 patients enrolled in a statin splitting programme (both -) and Fawell et al. (1999) (+) surveyed 47 patients splitting fosinopril. Across the three studies, a

small percentage of respondents disagreed with the statement that tablet splitting had no effect on their willingness to take their medication; (4% of respondents (Fawell et al., 1999), 6.3% (Carr-Lopez et al., 1995), 7% (Gee et al., 2002). Some respondents reported missing more doses in a month when splitting tablets compared with other medicines where the tablet did not have to be halved, 7% of respondents (Gee et al., 2002) and 14% (both (Carr-Lopez et al., 1995; Fawell et al., 1999).

One study (+) surveyed 99 patients with hyperlipidaemia using a tablet splitter (55 participants received financial incentive to split tablets during the study, 54 participants did not). This study did not find differences between the groups regarding willingness to split pills, finding that 87-94% found that tablet splitting had not affected their willingness to take their medication and that 7-13% responded that they had missed more medication doses because of tablet splitting (Choe et al., 2007). In a survey (+) of 28 patients splitting lisinopril (method of splitting not reported) (Rindone, 2000) tablet splitting was bothersome 'most' of the time for 25% of participants. For 'some' of the time for 54% of participants there were more than two pieces of the tablet following splitting.

2.5.2.4 Adherence

Three of the four studies identified considered aspects of adherence; for 47 participants splitting fosinopril (Fawell et al., 1999), and 111 (Choe et al., 2007) (both +) and 3787 splitting statins (Parra et al., 2005) (-) with a tablet splitter. There were no differences in adherence between those splitting tablets and those taking whole tablets whether self-reported (Choe et al., 2007), measured by tablet counting, refill history and self-reporting (Fawell et al., 1999) or prescription refills (Parra et al., 2005). The fourth study (+) included patients with schizophrenia or schizoaffective disorder splitting risperidone. This study found that adherence increased with tablet splitting (Weissman and Dellenbaugh, 2007).

2.5.2.5 Comparison between manipulation methods

Seven studies compared different methods of manipulation when splitting tablets. In general the use of a tablet splitter was found to be better than other splitting methods such as using scissors or knives, or splitting manually (Table 3).

Table 3: Comparison between manipulation methods

Reference (quality assessment)	Manipulation	Outcomes
(Boggie et al., 2004) (+)	100 unscored tablets halved with a tablet splitter, 25 split by hand	No significant difference in weight variance between those split with a tablet splitter and those split by hand
(Cook et al., 2003) (+)	45 round, film coated, unscored tablets halved with a tablet splitter, 45 split with a kitchen knife (split by a pharmacist and 2 pharmacy doctoral students)	16% with tablet splitter and 58% with kitchen knife deviated from the theoretical segment weight by more than 15%
(McDevitt et al., 1998) (+)	51 round, scored tablets halved with tablet splitter, 876 manually halved (if tablets could not be split manually the splitter was used) (split by 94 volunteers)	40.2% of those split with a tablet splitter and 33% of those split manually were within 5% of the theoretical weight
(Teng et al., 2002) (+)	10 tablets of each of 8 formulations halved with a razor blade 10 tablets of 3 formulations where tablets were soft enough to split by hand (split by a single, trained individual)	Halved with a razor blade; 3/11 passed the specified weight criteria (2 unscored, 1 scored), 8/11 failed USP weight criteria (5 unscored, 3 scored) 3 scored drugs split by hand all failed the USP weight criteria
(Verrue et al., 2011) (+)	10 tablets of each of 8 formulations, 4 scored and 4 unscored, 6 round, 2 oblong, halved and quartered (split by 5 volunteers using each method of a tablet splitter, scissors for unscored tablets/by hand for scored tablets, or with a kitchen knife)	Those split with the tablet splitter had significantly lower deviation from theoretical weight and significantly less weight loss than those split by scissors (for unscored tablets) or by hand (for scored tablets) or with a kitchen knife. There was significantly less weight loss with the scissors/hand than with the kitchen knife, no significant difference for deviation from theoretical weight
(Williams et al., 2002) (-)	24 round, unscored tablets quartered with a tablet splitter or cut freehand with a razor blade (split by an experienced pharmacy technician)	No significant difference in weight and a significantly greater variance with the tablet splitter than with the freehand split tablets
(van Vooren et al., 2002)	10 cross-scored tablets of 1 formulation manually halved and	Half tablets; the score-up break had the lowest residual variance, the score-

(-)	quartered by hand using 4 different methods or segmented with a knife whilst score side-up or score side-down (split by 3 individuals)	down break and the score-up knife had the lowest person variability. Quarter tablets; score-down break had significantly higher variability than for score-up break or score-up knife
-----	--	---

One study (+) considered methods of crushing or dispersing whole tablets (10 tablets of 1 formulation in batches of 2 crushed using pestle and mortar or between medicine cups, or dispersed in a syringe (Powers and Cascella, 1990). Suspending the drug in the syringe delivered 18% more drug for administration than crushing with medicine cups and 36% more than crushing with pestle and mortar.

2.6 DISCUSSION

This systematic review explores a known and accepted feature of clinical practice. Within neonatal and paediatric areas drug manipulation has arisen from necessity, where the doses required for administration cannot be readily administered using commercially available preparations. This review has demonstrated that there is an overall dearth of evidence to support the practice of drug manipulation finding only one study where manipulated drug products had been administered. This one study (Corbett et al., 2010) reported on the bioavailability of administered quartered, halved or three quartered tablets, though it did not specify the methods of splitting used and had not completed any analysis on the drug content of the segments used. What evidence was available came from a wide-range of studies which used a variety of research methods.

2.6.1 Dose accuracy

When splitting tablets it is reasonable to expect that the weight or drug content of segments will vary no more than would be within the defined acceptable limits for the intact tablets. Pharmacopoeias such as the European Pharmacopoeia (EP) or the United States Pharmacopoeia (USP) provide a legal and scientific basis for quality assurance during the preparation of medicines. Pharmacopoeial standards

for intact tablets are well established and usually include tests to establish uniformity of weight or content. Whilst the detail of these may vary they are essentially ensuring low variability of weight and/or drug content of the tablets and the absence of outliers. Several authors adapted the pharmacopoeial specifications and methodology for testing the uniformity of intact tablets and used these adapted specifications to consider segmented tablets. The specifications used within these studies were not devised for segmented tablets but were extrapolated from those for intact ones. While this may be logical, this approach meant that they were using specifications that had not been devised for the purpose they were being applied to. There has been recognition that segmented tablets need consideration, in 2002 the EP presented pharmacopoeial standards for the subdivision of scored tablets. These standards marked the first time this type of pharmacopoeial requirement was established and have been subsequently reviewed and revised (Green et al., 2010). The use of such standards within other pharmacopoeias has been discussed and a stimuli article discussed why such standards should be included in the USP (Green et al., 2010).

Results varied but the majority of included studies indicated a lack of uniformity of segment weight or drug content when splitting tablets into halves and that this variation is even greater when splitting in to quarters. Tablet splitting did not meet the requirements used in the study in two thirds of the tablets tested. Such lack of uniformity would be considered of unacceptable quality for intact tablets. The one study where tablets were dispersed showed variability in the dose taken from different zones in the container. Although there were few comparisons available there would appear to be differences in variability of segments between different tablet strengths and between branded and generic tablets. As formulations may vary, these results can only be applied to the actual drug products involved in the study. These findings mean that where tablets are split or dispersed there cannot be confidence that the proportion of the tablet that will actually be administered contains the dose that the manipulation aimed to achieve.

When weight and drug content uniformity were both considered, it is concerning that when weight uniformity was compliant, content uniformity often was not. This suggests that there is uneven drug distribution within some tablets. Where tablets are scored there may be the assumption that they can be split. However if there is uneven drug distribution it may be that splitting is not appropriate. The presence of a scoreline does not necessarily signify that there is an even distribution of the active ingredient throughout the tablet (Sayeed et al., 2010). Tablets may be scored to facilitate administration and though the tablet is scored this is not intended to reduce the dosage of medication taken (Shah et al., 2010). The difficulty may be in knowing where tablets have been scored to allow a proportion of the total dose to be given. A Swiss study screened the Summary of Product Characteristics (SPC) and product information leaflets. They reported that the official information available to health professionals concerning the fragmenting of scored tablets is incomplete and inhomogeneous (Arnet and Hersberger, 2010). This raises the concern that for tablets with scorelines there may be insufficient information available about whether or not they may or should be segmented. This has been recognised and work is under way with the FDA and USP to scientifically define the term functional score for tablets and to use it to designate only tablets that can be reliably split into equal portions, as described by the American Society of Health-System Pharmacists in 2012 (<http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3789#>). This work will result in a chapter on functional scoring in the USP and The National formulary.

2.6.2 Manipulations of non-tablet dosage forms

The only evidence that was identified relating to other dosage forms involved suppositories where one study, which did not report the methods of manipulation, showed substantial variation in size of the segments cut from paracetamol suppositories, leading the authors to conclude that such suppositories should not be split. In a previous review on unlicensed and off label analgesic use in children

Conroy and Peden (2001) described that fractions of suppositories are used and noted that the distribution of the drug through the suppository may be unknown, raising questions about the accuracy of the administered dose.

2.6.3 Bioavailability

The outcomes from bioavailability studies relevant to this review related to situations where modified release tablets were split or crushed and the whole dose administered. There were nine studies using ten products. Four of the studies indicated that there may be an effect on the intended modified drug release mechanism and consequently on bioavailability following manipulation. The remaining five studies did not find differences in the outcomes of halved and intact tablets. The modified release mechanism is important in determining whether the release characteristics will be altered upon splitting. Reduction in the time to reach peak concentration was the outcome predominantly affected by the tablet being halved or crushed prior to administration. The clinical impact of manipulating modified-release tablets is unknown. It has previously been advised that the mechanism of the modified-release and the potential impact of crushing a tablet or opening a capsule should be considered prior to it being undertaken, though this predominantly refers to ease of administration (Williams, 2008; Gill et al, 2012). Again the differences between products mean that the results here cannot be generalised. Nevertheless, if the dose that is required for an infant or child is smaller than is available as an intact modified-release tablet then the decision may have to be made whether to manipulate the tablet or not to give the desired drug.

2.6.4 Safety

In general no adverse events relating to manipulations were reported. Where adverse events were reported in the bioavailability studies this was not in detail; conclusions cannot be drawn about whether or not manipulated drugs had more associated adverse effects.

There were no studies identified in this review that reported on the contamination of the area of the manipulation or safety of the healthcare professional, carer or patient. This supports the view of Crawford (2012) who discussed that splitting or crushing medications could be potentially harmful to staff and noted that research has not been undertaken on the health and safety aspects of nursing staff exposure to small, but repeated, inhalation of medicines.

2.6.5 Patient experience and adherence

Where adult patients were asked about their experience of splitting tablets they did not generally find it had impacted on their willingness to take their medication. There was only one study that had paediatric participants and this considered the taste and tolerance of crushed tablets, concluding that the oral solution was better tolerated than the crushed tablets (Lucas-Bouwman et al., 2001). Again in adult studies where adherence was actually measured splitting tablets did not have an effect on this.

2.6.6 Comparison between manipulation methods

Although results were inconsistent, tablets split using a tablet splitter appeared more likely to yield segments that had split more accurately than those split using other methods, such as scissors, knife or manual splitting. Similarly scored tablets tended to provide segments closer to the intended weight. While these results can only be considered applicable directly to the products in the studies involved they do nonetheless suggest that use of a commercial tablet splitter and scored tablets may be beneficial if tablets must be split.

2.6.7 Reporting in the included studies

Ultimately quality assessment helps answer the question of whether the studies are robust enough to guide treatment, prevention, diagnostic or policy decisions

www.york.ac.uk/inst/crd/index_guidance.htm). Within this review quality has been assessed through a customised review form specific to the review outcomes. This assessment revealed a considerable variety in the quality of the evidence relating to drug manipulation. Many of the included studies that considered dose accuracy or bioavailability described the use of, or adaption of, recognised pharmacopoeial or laboratory methods and as such met many of the quality assessment indicators. However often they had not included details that were specific to this review such as the methods of manipulation, details on who had carried out the manipulation or any methods of ensuring consistency. Some studies lacked complete information on the tablets involved such as shape, coating or brand name. Though there had been considerable attention given to, for example the pharmacopoeial specifications used or the methods of weighing tablets, similar attention had not been given to reporting manipulation details. This may echo issues found with the reporting of paediatric clinical trials. Pandit et al. (2010) reviewed the reporting of formulations information (including how the dose was administered) for oral medications in paediatric clinical trials and found that only 31% of publications provided adequate information. These authors reflected that this information is extremely important, particularly where a dosage form may have to be manipulated, to restrict the influence administration could have on intra- and inter-individual variations. Another marker of quality is that in the individual studies where bioavailability was reported any attendant adverse effects were either only briefly reported or not reported at all.

Comparison across studies or synthesis of these studies to suggest conclusions about manipulated tablets was made more difficult by the insufficient reporting on aspects of drug manipulation in many of the included studies. This makes these studies less clinically applicable, as not only are they restricted to the drugs involved, if the methods of manipulation have not been clearly stated then even the results for these drugs cannot be reliably reproduced.

2.6.8 Summary of results

This review has described the evidence that could be identified. This description has highlighted that there are substantial gaps in the evidence both generally relating to drug manipulation and specifically with regard to paediatric practice. Though the effect of splitting tablets has been investigated in a small number of higher quality studies, tablet splitting did not meet the requirements in two thirds of the tablets tested. The results can only be seen as specific to the drug product involved. Nonetheless this does raise substantial questions about the accuracy of the dose of manipulated tablets. These concerns are applicable to the manipulation of other tablets and drug products. The manipulated drug was not administered meaning that the impact of manipulations on efficacy and safety is not known. There remain substantial gaps within the evidence available, for tablet manipulation this has at least been explored to some degree. For other dosage forms this has not happened.

2.6.9 Systematic review methods

The use of a systematic review protocol is acknowledged as important both to help guide the review and to help reduce the possibility of introducing bias during the review process. Reviews, such as this one, which are not drug or intervention specific and which use a wide range of terms not featured in database thesauruses, provide additional challenges to their successful completion. The broad range of possible types of studies in this review required careful drafting of this protocol. This planning assisted with the completion of the review as it ensured that some of the main challenges, such as constructing and revising the search strategy, assessing the quality of studies and synthesising the data, had been anticipated.

The retrieval of a high number of irrelevant references was unavoidable given that many of the manipulation search terms are commonly used to describe activities spanning a broad range of clinical activities. The sensitivity of the searches used had to be sacrificed, to some extent, in favour of a more specific search that retrieved a manageable number of references. Searchers cannot hope to achieve 100% sensitivity while maintaining 100% precision (Boynton et al., 1998). The reliability of

the decision process is increased if all papers are independently assessed by more than one researcher (CRD, 2009). The overall retrieval of the large number of titles and abstracts to be screened meant that it was not possible for two reviewers to undertake this. A random 5% were assessed by a second reviewer. In consideration of the complexities of the search strategy, and that all abstracts were not screened by two reviewers, experts within the field were asked to review the included studies list to consider if there were studies that had not been included. One additional study was added via this expert review.

A subsequent search of a small number of specified, frequently prescribed and commonly manipulated drugs was undertaken to explore whether there is any additional evidence relating to the manipulation of these drugs. Had these narrower searches yielded many studies for inclusion then it would have raised questions about the original search strategy that may have prompted further consideration. These searches did not identify any further papers. This could be considered as reassurance about the validity of the original search strategy, it is equally reasonable to see this as further evidence of the lack of studies in this area.

Greenhalgh and Peacock (2005) audited the search method used in a review of complex evidence, where broad policy questions were addressed and the synthesis involved qualitative and quantitative evidence from disparate sources. This audit revealed that reference tracking (scanning the reference list of all full text papers) provided 44% of the 495 primary data sources identified, the highest yield of the search methods used (this included an electronic database search). With 28% of the papers included in this systematic review having been identified from scanning the reference lists of already included papers it appears that reference lists may be an important source of evidence in reviews where the development of the search strategy is complex.

The difficulties experienced in this review epitomise the importance of a consistent nomenclature. Initial work has been completed on this by (Ernest et al., 2012). These authors have discussed the confusion that relates to terminology which may mean different things to different stakeholders; they explored compounding and

manipulation terminology and proposed definitions to provide a hierarchical classification.

This study sought the evidence for an area of clinical practice that could potentially include any drug and/or dosage form and therefore may be limited by its complex nature. In order to define the scope of the existing research we had specified that the only study type restrictions were on case series/studies and letters. Consequently the included studies were heterogeneous not only in design and quality, but in terms of types of manipulations, drug types, dose forms, participants and outcomes investigated. Harden and Thomas (2005) in considering the mixing of different study types in systematic reviews noted the strength of diverse methods to obtain a more complete picture of a phenomenon and that this diversity allows the answering of different aspects of this phenomenon.

Some review topics can be systematically completed using studies of one study type. The importance of presenting evidence, and considering quality, from a diverse range of studies has been previously discussed. Lucas et al. (2007) integrated findings from systematic reviews of scientific evidence and lay perspectives and considered that the comparison of systematic reviews that incorporate studies based on scientific paradigms and studies on lay perspectives adds additional information that is useful for policy and practice. If this review had only assessed data relating solely to dose accuracy and not considered outcomes such as patient experience, different manipulation methods or adherence then the conclusions of the review, while relevant to clinical practice, would have been limited.

Using evidence from many study types raises further issues within the review, notably with quality assessment. Goldsmith et al. (2007) noted that the exact function of quality appraisal in reviews of quantitative and qualitative evidence is controversial, though it is recognised that reviewers should highlight evidence quality issues. Similarly Garg et al. (2008) reviewed the methods used in renal systematic reviews and considered that the most common methodological flaw was a failure to assess the methodological quality of the included studies. The

development of the quality assessment tool for this review allowed the incorporation of studies where drug assays were used to consider drug content through to studies where surveys considered palatability. The disparate nature of these studies provided a particular challenge both with quality assessment and with the consideration of the synthesis of the included studies into a review. This is notable where the studies involved are solely laboratory based as these do not generally feature in systematic reviews and so have not been considered within the available systematic review quality tools. This aspect of quality assessment was therefore undertaken with the expert input of a formulations expert. The development of the quality assessment tool used in this review included the use of established criteria for bioavailability, laboratory-based and more descriptive studies. It also included study specific additions as it was considered important that the process of manipulation was included in the quality assessment. The quality appraisal categories used in this review provided an indication of the strengths and weaknesses of the included studies. Though this is specific to this review the development methods will have relevance for other areas where the evidence base is likely to be disparate but where reviewing this base is pertinent to current clinical practice.

This review highlights that quality standards are needed for studies of manipulations. The combination of standard approaches to assessment of studies with the quality assessment tool described here will provide a foundation for these standards.

Where reviews are broadly focused then they may need to include methods for coping with diversity of issues and evidence being considered (<http://eppi.ioe.ac.uk/cms/>). This review has considered this through the review protocol, devising an iterative and responsive search strategy, development of the quality appraisal process and synthesis of this disparate review. This review incorporated a wide range of study types and unusually also included laboratory-based studies. The limitations of this are acknowledged. However, the methods used have been rooted within accepted systematic review methodology and as

such have aimed to have the rigour required for a systematic review. This has allowed the presentation of evidence from many study types and ensured that the evidence can be described and research gaps identified. This has the potential to influence planning for future research as clarifying the limits of information in current research can assist in defining the research agenda (Choi et al., 2001).

2.7 CONCLUSIONS

The optimum evidence to meet the aims of this systematic review would have been studies where a drug was manipulated to obtain the required dose, compared with a control where the drug was not manipulated, administered to participants and outcomes, including any adverse effects, reported (Ideally this study would also consider the dose accuracy of the manipulated product and test this). Only one of the 42 included studies administered manipulated drugs to participants. Where evidence was located it almost universally related to the manipulation of tablets for the treatment of adult patients. This review has demonstrated that there is an overall dearth of evidence to support the practice of drug manipulation. What evidence was available came from a wide-range of studies which used a variety of research methods. Many questions in healthcare have complex evidence bases and are not easily evaluated solely by experimental methods. The studies included in this review often investigated the drugs and patient groups that were conveniently available. A more planned approach considering the likelihood of the need to manipulate and the possible impact of this of dose accuracy, bioavailability, safety and patient acceptability would result in more appropriate studies that would have direct clinical applicability.

There is little published information and further work is needed to support what is a common practice. All but one of the included studies related to tablets. It is difficult to draw generalisable conclusions as the products and method of manipulation varied considerably. Different formulations of each drug may provide different results when manipulated. Most segmented tablets did not meet standards for variability derived from those for intact tablets. In practical terms, a

tablet that has been halved may not result in half of the dose of the whole tablet. A consistent nomenclature should be developed and used to facilitate identification of data relating to manipulations. Further work should take account of the lessons for synthesizing data relating to manipulations that can be drawn from this systematic review. Quality standards are needed for studies of manipulations which need to report fully on the drug products and methods of manipulation. In conclusion, considerable work needs to be done to support what Chapters 3 and 4 show is a common practice.

CHAPTER 3: IDENTIFICATION AND DIRECT OBSERVATION OF DRUG MANIPULATION WITHIN WARD AREAS

3.1 BACKGROUND

Within hospitals the manipulation of drugs with the aim of obtaining the required dose prior to administration is predominantly undertaken by nursing staff. In order to investigate drug manipulation accurately, the processes that occur in practice need to be explored. There is no substantive evidence base underpinning drug manipulation (Chapter 2) and it is important to not make assumptions about what happens in practice. Zeitz (2005) considered postoperative observation, an area where there is a lack of evidence and a variety of practice recommendations. This author noted that in endeavouring to achieve best practice it is important to know what constitutes current practice.

With an area that has not been investigated previously decisions need to be made about the most appropriate methods to use. The absence of previous data can mean that it is not feasible to undertake a study using rigorous sampling methods. This is relevant in this case as the absence of information relating to manipulations would make designing such a sample difficult. One study by Skwierczynski and Conroy (2008) considered how long it took to administer oral medicines to children. This study observed 198 administrations of which six had been manipulated. This study included only oral administrations and had been designed to time administrations, nonetheless it did provide evidence that manipulations could be identified and observed in practice. The initial investigations in an area where what is occurring in practice is unclear (such as here with drug manipulations) seek out as many different aspects as possible so that the data available for future research is as rich as possible and the implications for practice can be seen as widely as possible. Thus throughout this observational study, the survey of paediatric nurses (Chapter 4) and the exploration of parents' perceptions (Chapter 5) purposive sampling was used with the aim of achieving maximum variation and detailed description of all aspects of drug manipulation.

Consideration of any area of practice requires careful planning to determine how to identify and record relevant data, particularly within busy in-patient ward environments. Within this study of drug manipulations data needed to be recorded on where manipulations are occurring, which drugs and dosage forms are manipulated, how the manipulation is achieved and the reasons that a manipulation is required. The study completed by Skiwierczynski and Conroy (2008) in investigating the time taken to administer oral medicines had indicated that manipulations could be identified and observed. This study used long periods of observation within ward areas to observe administrations. Methods used to describe the details of the mechanism of manipulations occurring *in situ* has not been previously investigated. Though there were no previous studies specifically relating to drug manipulations, guidance was sought from studies which had observed and recorded prescribing errors, the time taken to administer medicines or drug administration errors.

3.1.1 Neonatal and paediatric in-patient areas included

Previous studies have identified that off-label and unlicensed use of drugs in paediatrics may be more pronounced in specialist paediatric areas and that different types of manipulations may occur in different clinical areas (Conroy et al., 1999; Conroy et al., 2003). While it may have been reasonable to speculate that manipulations may occur more frequently in the more specialist areas, this could not be assumed. Therefore all of the in-patient neonatal and paediatric clinical areas in the hospital sites were included. A children's hospital with a catchment area of >7.5 million with care for >200,000 children annually and a regional neonatal unit with 54 cots that cares for >1000 babies annually were selected for inclusion. A systematic review of medication errors in paediatric areas noted that little research had been conducted in nonpaediatric hospitals (hospitals that predominantly have adult patients but have a small number of paediatric wards) and they speculated that the type, nature and incidence of paediatric medication errors may differ between paediatric and nonpaediatric hospitals due to differences

in patient population and expertise (Ghaleb et al., 2006). It has been suggested that there may be enhanced insight and awareness in prescribing when a service is designed to care only for children (Crawford, 2012). Therefore this study also included a neonatal (16 cots, 3 ICU cots) and a paediatric ward (30 beds, 2 HDU beds) in a district general hospital to allow for possible differences in patient population, expertise and access to paediatric sized drug doses that may occur between paediatric specialist settings and paediatric care which is delivered in a predominantly adult setting.

3.1.2 Estimation of the requirement for manipulation

Concurrent to this study, a review of all of the in-patient prescriptions, over a 5-day period, within the clinical areas used in this study was undertaken (Nunn et al., 2013). I collected the data (assisted by a research nurse) which I collated for review by an experienced paediatric pharmacist (Professor AJ Nunn). This study estimated the requirement for the manipulation of medicines (including the measurement of small volumes). An experienced paediatric clinical pharmacist assessed the prescription data, finding that 10.1% (542/5375) drug administrations required either manipulation or the measurement of a small volume (<0.2mL). Of these 41.7% (226 administrations) involved either the manipulation of intravenous drugs or the measurement of a volume of <0.2mL (it was not possible without observing the administration to know which had been undertaken), 22.1% (63 administrations) involved the manipulation of tablets, 3.9% (21 administrations) manipulations of nebulisers, 1.1% (6 administrations) manipulations of enemas and 0.7% (4 administrations) manipulations of suppositories. (29.5%, 160 administrations, involved the measurement of <0.2mL of an oral liquid – though it should be noted that one type of administration (oral dose 0.1 to <0.2mL) accounted for 107 of these administrations).

3.2 AIMS

This observational study aimed to:

- identify the type and nature of drug manipulations occurring in paediatric clinical practice
- where possible, observe manipulations in practice and to describe the observed manipulations
- identify which drugs and which dosage forms are manipulated and in which clinical areas

As there has not been previous research which has considered drug manipulation in practice, therefore additionally this study also aimed to:

- consider the most appropriate methods of describing an aspect of clinical practice
- describe the methodological issues with a direct observation study in clinical in-patient settings

3.3 DRUG MANIPULATION IN CLINICAL PRACTICE

Clinical practice can be difficult to identify, to record and to describe. All of the considerations that contributed to a particular action may not be clear to observers. Hospital in-patient wards are busy areas, with many health care personnel involved in what can, to the outsider, appear to be a chaotic workspace. Therefore any data collection within a clinical area needs to consider how to achieve optimum data collection while causing minimum disruption. Research that requires high levels of input from already stretched clinical staff is liable to be unsuccessful. Therefore how to identify and record the manipulations and how to do this while obtaining and retaining the collaboration of clinical staff was fundamental to the design of this study.

The initial consideration had to be how drug manipulations were going to be identified in practice. This required the development of methods that could effectively do this but did not require large observation time periods spent in each clinical area. As this study aimed to consider manipulation throughout 21 different clinical areas it was not feasible to spend prolonged time periods observing drug preparation. Nurses within these clinical areas are responsible for the drug administration to the patients in their direct care. As such there could be several drug preparation and administration episodes occurring in one clinical area at the same time, this becomes even more marked in the higher dependency areas such as intensive care or the neonatal unit.

It is possible to predict when some manipulations will occur. Manipulations will be necessary where the dose of drug that had been prescribed could not be achieved without a manipulation e.g. 5mg of a drug has been prescribed that is solely available in a 10mg tablet. This can be predicted from prospective prescription review. However there are also likely to be occasions where the drug manipulation cannot be predicted. These include where the required dose is temporarily not available on the ward, where it may not be evident how the small dose is achieved, such as for an intravenous injection, or where patient preference requires an individualised manipulation. These episodes cannot be predicted from prospective prescription review. Therefore any methods to record data on drug manipulations need to be able to identify manipulations both those that were predictable and those that may not be.

3.4 OBSERVATION

3.4.1 Previous use of observation in research

Observation has been substantially used within ethnographic research to observe and record human cultures. Time is spent in the field to gain a comprehensive understanding of those being studied (Carthey 2003, Baker, 2006). Structured observation assigns the behaviour observed to predefined categories (Barker 1980).

In sampling and recording data the researcher uses at least one of four basic behavioural measures; frequency, duration, percentage of time spent in the activity, sequence of activities (Barner-Barry, 1986). This type of observation is not subjective as the data are not dependent on the perceptions of those being observed or of those recording the data. Barker (1980) noted observation should be free of the selective perception of the subject. With any study where behaviour is being observed, decisions need to be made about what is to be recorded. This will be vital to the validity of the outcomes. Observation is selective, purposive and involves decisions about what should be noticed and what should be ignored (McCall, 1984).

While collecting data the observer may be a participant in the field which they are studying. Alternatively they can be entirely separate, non-participant from the situation being observed and present solely in the field for the purpose of collecting data. Non-participant observational research is primarily used for descriptive research as it enables the researcher to address the question; what did the research subjects do? It allows for the study of behaviour in natural settings with the only artificially introduced factor being the presence of the data-gatherer (Barner-Barry, 1986). Barker et al. (2002a) reviewed studies that had evaluated the observation method, they considered that the observation technique produced results that were more valid and reliable than where self-reporting methods had been used. As observation is not retrospective it avoids the potential limitations of methods that are dependent on a subject's memory or willingness to report. Non-participant observation is best suited where it is important to study actual behaviour patterns of research subjects functioning in settings that are their natural habitats. This method also clearly defines the role of the observer to those who are observed. However, direct observation is time-intensive. Meyer-Masseti et al. (2011) considered that, due to its labour-intensive nature, direct observation must be performed over a relatively short period of time which inevitably results only in a brief snapshot of what could be observed.

3.4.2 Observation and drug manipulation

Studies have considered how to identify and record medication-related errors in practice, these were used as a resource in the development of this observation based study. It has been noted that there are three basic methods of identifying errors made by people: observation, self-report and study of existing records (Barker and McConnell, 1962). Studies of medication errors in paediatric settings have compared different methods of collecting the data, such as incident report review, chart review and direct observation and the advantages and disadvantages of these methods (Flynn et al., 2002; Ghaleb et al., 2006). These studies found that, while all of these methods could describe errors, direct observation of clinical practice tended to be the most effective. Observation has been used to detect and record drug errors since the 1960s and is considered to have demonstrated that it is the most valid, efficient and accurate method for this (Barker et al, 2002a; Chua et al., 2010).

3.4.3 Direct observation – in practice

Reviewing previous use of direct observation to investigate medication errors demonstrated that it was an appropriate and applicable method for considering drug manipulation. Nonetheless there were aspects of how to use this method within the settings for this study that required further consideration. How these have been developed previously and the methods used within this study are described below.

3.4.3.1 Intervention in case of error

During the observations of drug preparation and manipulation it was possible that medication errors would also be inadvertently observed. The observers were aiming to be as unobtrusive as possible while data collecting. Nonetheless there is both a professional and ethical obligation to intervene should an error be identified. An error should not be ignored to maximise the study's validity (Dean and Barber,

2001). In studies where medication errors were detected or observed this was also a consideration; those devising these studies had agreed methods of intervening where an error was occurring (Dean and Barber, 2001; Taxis and Barber, 2003a; Taxis and Barber, 2003b; Cousins et al., 2005; Ghaleb et al., 2006; Haw et al., 2007).

3.4.3.2 Disguised/undisguised observation

When disguised observation is used, those being observed are misled regarding the purpose of the observer. The argument is made that if those who were being observed were aware of the true focus of the study then their behaviour would change. Disguised observational techniques have been substantially used in studies considering drug errors. A systematic review on intravenous drug errors included nine studies all of which used disguised observation (McDowell et al., 2010). Studies of medication errors, such as by Dean and Barber (2001), stated that nurses were given a partial explanation of the purpose of the observation and that verbal consent was obtained from them. This kind of observation raises ethical questions as subjects may be consenting to being observed in the belief that the data being recorded are different to those which are actually being recorded. Therefore can their consent be considered to be truly informed? Due to the arguments noted above describing the concern that observation may alter behaviour if nurses were fully aware of the purposes of the observation, approval from ethics committees has been gained for disguised observation studies, such as in Turnock and Gibson (2001). Alongside the ethical concerns, disguising the real reason for the observation may risk the completion of the study. If the true purpose of disguised observation is discovered the researcher may lose the opportunity to continue the study (Barker, 1980). This may further pose complications for future research if those who are being asked to participate feel that they cannot trust researchers. This possible effect that the observer may have on the behaviour of the person being observed (the Hawthorne effect) is one of the apprehensions expressed about the validity of undisguised, direct observation (Dean and Barber, 2001; Chua et al., 2010). The validity of the outcomes of this current study are reliant on recording manipulations being carried out in the same way as they would be if the

observers were not present. The importance of being unobtrusive in observing and not asking the subject to change normal activities for the convenience of the researcher has been highlighted as important in ensuring accurate data capture (Barker, 1980).

3.4.3.3 Observer acceptance into the field

Direct observation is an effective data collection method but it can raise concerns about individual privacy (Baker, 2006). To use direct, structured observation in any area requires the accepted entry of a researcher into someone else's personal or professional area. The presence of researchers as observers meant that the support of nursing staff for this study was vital to its accomplishment. Several approaches were used both prior to and during the study. I and the research nurse assisting with the observations attended meetings with senior nurses, nurse prescribers and medicines champions during the planning of the observational study. The proposed study was outlined to them, any questions were answered and their opinion sought on aspects of collecting data in the ward areas.

Though the observers in this study were non-participant, the support of nurses was vital when manipulations were actually being recorded. To ensure the validity of the data recorded it was important that the drug manipulation processes recorded were true to those that would happen if the observers were not present. The potential consequences of mistakes when preparing or administering drugs are ingrained in the consciousness of nurses and as such there may be understandable apprehension about being observed. There may be some concern about the implications for the nurse of undertaking the manipulation. Throughout this study it was made clear to nurses that the details of the manipulation were the only data being recorded and no details about the nurse undertaking the manipulation were recorded.

3.5 SELF-REPORTING

The self-reporting of manipulations represents the optimum method of identifying unpredictable manipulations, as these would be reported via the nurses

undertaking them and reporting all of the incidents as they occur. When used in detecting medication errors a number of advantages with self-reporting methods were noted. These included the rarity of false positive reports; in addition the clinical significance of the errors detected was likely to be high (Flynn et al., 2002). However the under-reporting of incidents is a substantial limitation with this method. It is not possible using self-reporting to make any estimation of frequencies (Flynn et al., 2002) or total number of activities.

3.6 METHODS

3.6.1 Identifying manipulations

The potentially but not wholly predictable nature of drug manipulations meant that a multimodal approach was required to obtain a comprehensive description of the range and type of drug manipulations occurring. Self reporting was considered a useful approach as it can reveal occurrences which are difficult to predict or identify in any other way. However, a lack of awareness or understanding of the research study may cause under-reporting when self-reporting methods are used. Therefore on each ward, in the week immediately prior to the study (on that ward), time was spent during handover periods introducing the study to nursing staff and providing the opportunity for questions. A one-page laminated sheet summarising the definitions of drug manipulations for each dosage form (and with researcher contact details) was also provided and placed on or beside drug preparation areas. Researchers (I and the research nurse who supported this study) were frequently on the wards throughout the study periods collecting prescription review data and the self-report alert cards; they reminded nurses about the study and were available to answer any questions. Alert cards were to be completed by nurses when they undertook a manipulation. These cards were designed so that they were able to provide sufficient information for researchers to further investigate the possible drug manipulations but also needed to be brief and easy to complete to ensure that they did not impact on nurses' time. Prior to their use in the pilot study these cards were reviewed and discussed by a group of nurses who work within the

children's hospital and form a medicines champions group who provide expertise and medicines advice to other nurses.

Furthermore a second method was used to identify drug manipulations. The use of self-report alert cards was supplemented by prescription review. The research nurse and I undertook daily prescription reviews throughout the study period on each ward to prospectively identify any predictable manipulations.

3.6.2 Sampling

This study did not aim to obtain definitive numbers of manipulations occurring but rather to explore the scope and nature of the manipulations that were being undertaken. The only method which could have been used to definitively identify unpredictable manipulations would be continual observation of practice. This would require a considerable amount of time to be spent on the wards and to use this method would have substantially restricted the number of clinical areas which could be included; it was considered unfeasible. Studies which investigated drug errors have frequently used time sampling methods with the selection of precise time periods during which observations occur (Barner-Barry, 1986; Polit and Beck, 2008). Event sampling uses the behavioural unit of interest to determine the data collection. This is not dependent on the time this lasts or the intervals at which it occurs (Barner-Barry, 1986). Event sampling is considered to be preferable if events are infrequent and are at risk of being missed if time sampling is used (Polit and Beck, 2008). As drug manipulations do not occur at specific times (though will obviously occur more often at time periods when drugs are frequently given) the use of time-sampling would have risked missing the observing of manipulations where they did not occur during the time periods specified. Therefore purposive event sampling was the most appropriate method for use in this study. Manipulations identified through the prescription review and alert cards were followed up to see if it was possible to observe and record them. If two manipulations were prescribed to be administered at the same time but in different

clinical areas and one was of a drug or dosage form that had been previously observed then the manipulation not previously recorded would be observed.

3.6.3 Observation units

The molecular approach to observation uses small, highly specific behaviours as observational units and models behaviour as closely as possible to what actually occurs. This approach contrasts with a molar approach that involves the observation of large units of behaviour which are treated as a whole (Nolan et al., 1995; Polit and Beck, 2008). The molecular observer records only what is seen and no more; as such the interpretation of the observer should be removed from the observational picture (Barker, 1980). As drug manipulations are specific, short, measured events the molecular approach was used to record what had been observed with review and further analysis subsequently completed on the data recorded.

3.6.4 Possible drug errors

Consideration was given to the most appropriate response should a drug error be observed. Methods used in studies of drug errors were reviewed and discussed with nursing, medical and pharmacy personnel. It was agreed that if an error was identified during data collection the observers would ask the nurses involved to check their calculation, or measurement, again. If the error was repeated then they would identify it to the nurses involved. Should an error be identified during data analysis or review, the ward involved would be contacted, made aware of the error and advised to ensure that the appropriate hospital procedure and documentation for the error was completed.

3.6.5 Consent

Consideration was given as to the most appropriate form of gaining consent for this study. Written consent was liable to be too disruptive within busy clinical areas.

Due to the numbers of nurses involved it would not have been feasible to obtain this written consent in advance (within the ward areas there are around 15 whole time equivalent nurses, often with higher actual numbers of staff when those who work part-time hours are included, in the high dependency areas such as in PICU in the children's hospital there are >100 whole time equivalent nurses). Verbal consent was sought from all of those who were observed prior to any observation taking place. The process of obtaining this verbal consent was;

- checking if those potentially being observed knew the aims of the study, had any questions about it and the purposes of the observation,
- a reminder that the process of drug manipulation was what was being observed not the individuals involved,
- that no details about the individual undertaking the manipulation were recorded,
- reassurance that the observation and data recording could be stopped at any point, and finally
- the seeking of verbal permission to observe the process of the nurses undertaking drug manipulations.

3.6.6 Observation tool development

This work aimed to observe and capture the details of the practice of drug manipulations that are used to obtain the dose required for administration to paediatric patients. The observational tools used in this study had to be devised and validated.

The observation forms were designed with the aim of categorising each type of manipulation that may occur for each dosage form, into recordable sections which would provide a standardised description of the process of the drug manipulation. Long and Johnson (2000) noted the need for consistency and the importance of standardising data collection instruments to ensure that data collection is

undertaken in a manner that is free from undue variation. The design of the tools for this study aimed to use predominantly closed categories to remove the possibility of bias from observer interpretation of what was being recorded. This would help to avoid the threat to the validity of observational research from researcher bias that may result from selective observation, selected recording of information, or the subjective interpretation of situations as described by Baker (2006). As these are new tools, it was also important not to exclude the recording of categories which had not been anticipated during their design. As Barker (1980) cautions, although theoretically a high degree of reliability can be attained using small easily observed and recorded units, that this may reduce the behaviour so much that it no longer bears resemblance to what it was intended to observe, thus losing validity. Observational forms were devised for each possible dosage form which may be manipulated. Drug manipulations are known in practice and could be theoretically described. They have not previously been recorded in detail and therefore there remained the possibility that the designed tools may not capture all available data. Skiwierczynski and Conroy (2008) had observed oral administrations but other dosage forms had not been included. Therefore several open categories were added; these were marked as 'other' and were available for the recording of additional unpredicted data.

Measures of validity frequently involve the comparison of the results with those obtained from an independent measure (Barker, 1980). With no previous in-depth investigation in this area there are no established reference standards for the procedures involved in drug manipulation and therefore a comparison with previously used tools was not possible. Content validity depends largely on the sampling and careful construction of the instrument and refers to the degree to which the entirety of the phenomenon under investigation is addressed (Long and Johnson, 2000). Therefore the data collection tools within this study needed meticulous construction to ensure that there is consistency, completeness and reliability in the data collected and that the outcomes can be considered valid. This

would provide confidence that the tools were meeting the goal of measuring what they are intended to measure. The data collection tools were drafted, reviewed and revised by clinical, academic and research experts on several occasions prior to their use in the pilot study.

3.7 ETHICS

The Director of Research at Alder Hey NHS Children's Trust presented the study outline for review to the Liverpool Local Research Ethics Committee. This Committee considered that the study met their criteria as a service evaluation project involving NHS staff only. This body considered that this study did not require review by a NHS Research Ethics Committee. The appropriate permissions were obtained from the research committees of the included hospitals.

3.8 PILOT STUDY

3.8.1 Pilot study aims

A pilot study was undertaken to ascertain the feasibility of this study and the data collection tools. This pilot study aimed to:

- consider the methods of identifying drug manipulations in clinical in-patient areas,
- test the feasibility of data collection tools for observations of drug manipulations,
- generate preliminary data about the nature of drug manipulations conducted on paediatric wards,
- consider the validity of data obtained with the data collection tools,
- provide an indication of inter-observer reliability (between the two observers, myself and a research nurse) using the data collection instruments, and
- determine the acceptability of the process to those being observed.

3.8.2 Pilot study – wards included

The pilot study was conducted in the paediatric hospital and included five ward areas so that the feasibility of the study methods could be investigated in different clinical areas. Four general wards (two medical, two surgical) and one specialist ward (paediatric intensive care unit – PICU) were included in the pilot study.

During the pilot study the two researchers attended the included wards, initially at 8am to review prescriptions, remind nurses about the study, answer any questions that may have arisen and, where possible, to observe the morning medications being prepared for administration. All data collection throughout the pilot and main observational study were undertaken by myself or a research nurse who had been designated to the study. The researchers visited the clinical areas throughout the day (including weekends) to review prescriptions, collect completed alert cards and discuss any queries from nursing staff. This also gave the opportunity to plan when researchers would return to observe the drug manipulations that had been identified.

3.8.3 Pilot study outcomes

3.8.3.1 Identification of manipulations

76 nurse alert cards were returned by nurses during this two week pilot study. A review of these found that 42 (55%) correctly reported drug manipulations. The remaining 45% of alert cards had reported situations where drugs had been altered which were outwith the definition of manipulation, such as where dosage forms had been crushed, dissolved etc. to assist with administration of the drug and the entire dose had been administered, or had reported the reconstitution of intravenous drugs as a manipulation. All of these alert cards had been completed within the medical and surgical wards (where there are around 15 full-time equivalent nurses). None had been completed in PICU (where there are >100 full-time equivalent nurses). Informal feedback was sought from nurses who had completed alert cards which found that nurses considered them quick and easy to

complete and as such they did not impact negatively on their time. Furthermore the nurses considered that the use of these cards would be acceptable to nurses in a larger study. Overall the alert cards were effective in identifying manipulations and provided sufficient information that these could be followed up to plan for possible observation of the manipulation. Following their use in this pilot study small changes were made to ensure that the information required in the various boxes of the alert card was entirely unambiguous to those completing them; otherwise the alert cards were not changed prior to the main study.

It was evident from the pilot study that attending the wards during periods where there tend to be drugs prescribed (such as 8am) would require considerable time input by researchers. Although observing drug preparation during these time periods did identify manipulations, these could have been found by the use of prescription review or via reporting by nurses on the alert cards. It was not possible to observe all of the drugs being prepared or administered during these periods as there were often several nurses undertaking this role at the same time for different patients. This was not an efficient or particularly effective method of identifying manipulations. The identification of predictable manipulations via drug prescription review was effective. During the study pilot an experienced clinical paediatric pharmacist also completed a duplicate prescription review on the wards and in PICU. This review did not find any further possible manipulations which had not been found through the initial prescription review.

3.8.3.2 Data collection instruments

Both intra and inter-observer reliability in data collection needed to be optimised. Reviewing the reliability of data collection instruments Long and Johnson (2000) noted the importance of ensuring that data collection is consistent and free from undue variation as this may unknowingly exert an effect on the nature of the data. There are methods of increasing inter-observer agreement such as sufficient training, using clearly defined and non-overlapping categories, classifying the behaviour at the time of observation, demanding little inference from the

observers, using a small number of categories, or making certain the investigators are observing the behaviour at the same time (Barner-Barry, 1986). Several of these methods were used within this current study, notably during the design of the data collection tools.

The data collection forms required the completion of 24 to 34 items, depending on the manipulation, as detailed in Table 4.

Table 4: Items to be completed on the data collection forms, by type of manipulation

Section on data collection form	Number of items to be recorded	Total number of items to be recorded for each type of manipulation
Demographic data	7 items	
Drug and prescription details	8 items	
Additional data	4 items	
Tablet cut or broken	15 items	34 items
Tablet crushed	7 items	26 items
Tablet dispersed	15 items	34 items
Capsule dispersed	13 items	32 items
Oral liquid	12 items	31 items
Transdermal patch	9 items	28 items
Suppository	11 items	30 items
Enema	5 items	24 items
Nebuliser solutions	9 items	28 items
Intravenous bolus	13 items	32 items
Intravenous infusion	11 items	30 items

During the design of the data collection form, boxes were designed so that the data to be recorded was unambiguous, where possible tick boxes or score through responses (such as Yes/No) were used with the aim of ensuring that the data collection was consistent. I undertook the data collection and observation of manipulations assisted by a research nurse; both of us had spent time on the wards while discussing the study with the ward nurses and had previous observation experience.

There were seven manipulations during the pilot study observed by the two researchers (a further two were observed by the research nurse alone); four were tablets which were cut with a tablet splitter, two were tablets dispersed in water, and one was a capsule dispersed in water. It became clear during the pilot study that with two observers and all drug preparation checked by two nurses it is difficult to ensure that the observers have an unimpeded view without disrupting the process. During these seven manipulations, 236 items were recorded. Of these, both observers recorded the same data for 196, 83%, of the data collection form items. The remaining 40 items were reviewed further. For 13/236 items, 5.5%, the

observers had recorded different data as the form was not sufficiently clear. For example, one observer recorded the child's date-of-birth and the other recorded their age or one observer recording the child's weight from the prescription chart and the other taking a slightly different weight which had been recorded in the patient notes. For 17/236 items, 7.2%, data had not been recorded by one or both observers. For nine items, 3.8%, there were errors in what had been recorded and for the remaining one item, 0.4%, there had been a difference in what the observers had perceived. As 75% of the items where there were differences between the observers were due to either missing data or data which had been recorded differently by the observers as they had interpreted differently the data to be recorded; these were areas where data collection could potentially be improved. Changes were made to the data collection forms with the aim of making it clear which data were to be recorded and that all items on the form for that manipulation were to have data entered. Furthermore, in consideration of these outcomes a guide was devised to ensure that it was clear what was to be recorded in each section of the form, this provided a reference source for observers with the aim of optimising reliability. Similar guides have been used in previous observational studies such that by Barber et al. (2009). This guide to the data collection was developed into a detailed reference document (Appendix 4) which was taken with the observation forms and could be referred to in the clinical areas if there was any uncertainty about the data that were to be recorded. While data collection errors cannot be eradicated from any study increasing familiarity with the recording tools, improved clarity in the data recording forms and the development of a detailed reference document should minimise data recording errors.

Following comments made by nurses during the pilot study about the manipulation that they were being observed completing; an additional response box was added to the observation forms to allow for the recording of any such comments. Nurses were not asked for any views or opinions on manipulations. Observers did not make any remarks or ask questions while observing manipulations, but any comments

that nurses did make could then be recorded. These unsolicited comments could provide some insight into how nurses view manipulations.

Similarly to the alert cards changes were made to the observation forms to ensure clarity and consistency in the data recorded but there were no major changes were made to the observational tools.

3.8.3.3 Preliminary data on drug manipulations in in-patient areas

Data on drug manipulation were recorded in this pilot study. There were few changes made in the data collection tools and experts reviewed the collected manipulation data and considered the results to be valid. Therefore the data on drug manipulations collected in both the pilot and main studies are presented together in the results.

3.8.3.4 The acceptability of the process to those being observed

Verbal consent was obtained from all nurses involved in the pilot study. Informal feedback was sought from nurses who had been observed and they were asked how they found the process. During the pilot study set-up period when nurses were being introduced to the study they were enthusiastic about the need for the study and many provided anecdotes relating to drug manipulations. Nurses who were observed undertaking manipulations described that with the knowledge of the study objectives they were comfortable being observed.

3.8.3.5 Validity

This study was supported by a steering group comprising of nursing, medical, pharmacy, research and academic experts. This group reviewed the manipulations recorded during the pilot and main studies and considered that the data recorded did appropriately describe the drug manipulations occurring in practice.

3.8.3.6 Implications for the main study

The pilot study demonstrated that drug manipulations could be identified in practice. The use of the two methods of identification was shown to be fit for purpose. The daily prescription review yielded predictable manipulations and expert review did not find any additional data that had not been found in the

original review. The use of alert cards was not onerous to nurses and within the medical and surgical wards a number were completed. However in the PICU no cards were completed. With such a high number of nurses on each shift effective communication and reminding nurses about the alert cards was more difficult. There are limitations to the use of alert cards and there was a tailing off of their return towards the end of the two week pilot. Nevertheless the potential of the use of alert cards to identify otherwise undetectable manipulations and thus add to the scope of the manipulations described meant that their use in the main study was justifiable. The observation of manipulations in practice was feasible and the nurses who were observed during the pilot study did not find the process intrusive, were not anxious and all approached consented to their practice being observed. During the two-week period of the pilot study there were manipulations of some dosage forms that were not identified, therefore not all of the observation data collection forms were used. For the dosage forms that were observed (tablets, capsules) the forms allowed for comprehensive collection of detail on manipulations. The devising of a reference guide to support the forms for all dosage forms aimed to ensure the clarity of what was to be recorded in the main study. Overall the pilot study provided evidence that drug manipulations can both be identified and observed in practice and that this is not prohibitively intrusive on the clinical areas involved.

3.9 MAIN STUDY

The main study included 22 different in-patient areas. Data collection was conducted in blocks of two weeks over a 6-7month period. Each block was dedicated to a ward or small numbers of wards in the neonatal and paediatric in-patients areas included. Data was collected in each of the wards once, for this two-week block, during the study. During each two-week block potential manipulations for observation were identified prospectively on the relevant ward(s). This study used the methods that had been developed and refined during the pilot study. That is that time was spent on each ward area prior to the study introducing the study

and data collection tools to the nursing staff and responding to any queries. Prescription review, collection of completed alert cards and arrangement to observe any available manipulations were undertaken daily within each ward during the two weeks of data collection. I undertook this data collection aided by the research nurse who had participated in the pilot study.

3.10 RESULTS

There were 310 manipulations that were identified, involving 53 different drugs³. The highest proportion of manipulations involved tablets which represented 191 (61.6%) of those reported. The breakdown of the manipulations by dosage form is reported in Table 5.

Table 5 : Manipulations identified during the observational study, by dosage form

Dosage form	Frequency reported as manipulated	Percentage
<i>Tablets</i>	191	61.6%
<i>Sachets</i>	30	9.7%
<i>Capsules</i>	4	1.3%
<i>Oral liquids</i>	0	0%
<i>Intravenous</i>	65	21.0%
<i>Nebuliser solutions</i>	4	1.3%
<i>Transdermal patches</i>	10	3.2%
<i>Suppositories</i>	6	1.9%
<i>Enemas</i>	0	0%

The drugs which were identified crossed the spectrum of possible indications as can be seen in Table 6 which shows the manipulated drugs organised on the therapeutic classification described in the British National Formulary for Children. Though it should be noted that while these classifications indicate a reason for prescribing drugs they may not be the reason that the drug has been prescribed (for example amitriptyline is classed as an antidepressant but may be prescribed for

³ Some drugs were found to be manipulated in more than one dosage form e.g. tablet and intravenous manipulations of hydrocortisone, or tablet and suppository manipulations of paracetamol

neuropathic pain). Of the 53 different drugs manipulated during this study 13.2% (7/53) were identified only once.

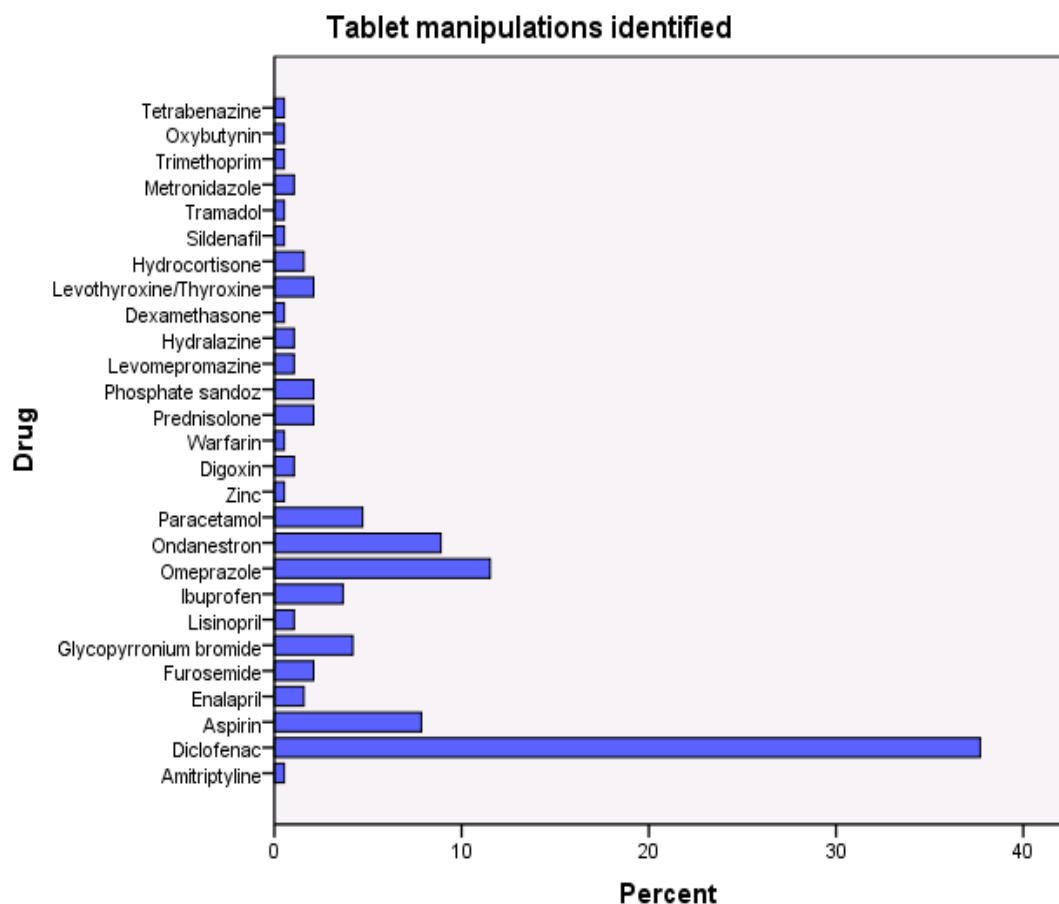
Table 6: The drugs identified as manipulated, organised by the therapeutic classification from the BNFC, and frequency of manipulation

BNFC classification	Drugs involved	Frequency classification reported as manipulated	Percentage of manipulations identified
<i>Analgesic</i>	Paracetamol, Ibuprofen, Diclofenac	92	29.7%
<i>Proton pump inhibitor</i>	Omeprazole	24	7.7%
<i>Antimuscarinic</i>	Glycopyrronium bromide, Hyoscine hydrobromide	18	5.8%
<i>Antiemetic</i>	Ondansetron	17	5.5%
<i>Alginate preparation</i>	Gaviscon	16	5.2%
<i>Antiplatelet</i>	Aspirin	15	4.8%
<i>Opioid analgesic</i>	Fentanyl, Tramadol, MST	14	4.5%
<i>Benzodiazepine</i>	Midazolam	13	4.2%
<i>Antiepileptic</i>	Vigabatrin, Phenobarbitone	12	3.9%
<i>Antibiotic</i>	Metronidazole, Vancomycin, Teicoplanin, Trimethoprim, Rifampicin	11	3.5%
<i>Neuromuscular blocking</i>	Vecuronium, Suxamethonium	11	3.5%
<i>Steroid</i>	Hydrocortisone, Prednisolone, Dexamethasone	10	3.2%
<i>ACE inhibitor</i>	Enalapril, Lisinopril	5	1.6%
<i>Bronchodilator</i>	Salbutamol, Ipratropium	5	1.6%
<i>Minerals</i>	Phosphate Sandoz, Zinc	5	1.6%
<i>Thyroid hormone</i>	Levothyroxine, Liothyronine	5	1.6%
<i>Vasodilator</i>	Hydralazine, Dinoprostin	5	1.6%
<i>Diuretic</i>	Furosemide	4	1.3%
<i>Drugs affecting the ductus arteriosus</i>	Indomethacin	3	1.0%
<i>Insulin</i>	Insulin	3	1.0%
<i>Laxative</i>	Glycerine, Movicol	3	1.0%
<i>Antipsychotic</i>	Levomepromazine	2	0.6%
<i>Antiviral</i>	Aciclovir	2	0.6%
<i>Flu prophylaxis</i>	Oseltamivir	2	0.6%
<i>Hypothalamic & pituitary hormone</i>	Tetracosactide	2	0.6%
<i>H2 antagonist</i>	Ranitidine	2	0.6%
<i>Inotrope</i>	Digoxin	2	0.6%
<i>Anticoagulant</i>	Warfarin	1	0.3%
<i>Antidepressant</i>	Amitriptyline	1	0.3%
<i>Antihypertensive</i>	Sildenafil	1	0.3%
<i>Antimotility</i>	Loperamide	1	0.3%
<i>Pineal hormone</i>	Melatonin	1	0.3%
<i>Smooth muscle</i>	Oxybutynin	1	0.3%

<i>relaxant</i>			
<i>Not in BNFC</i>	Tetrabenazine	1	0.3%

Within the 191 tablet manipulations identified there were 27 different drugs identified, with the most frequent manipulation involving diclofenac 50mg tablets. These diclofenac tablets were dispersed and a proportion of the dose administered. Overall nine of the tablet manipulations were reported only once during the study. The percentage of each drug of the total tablet manipulations identified are represented in Figure 5.

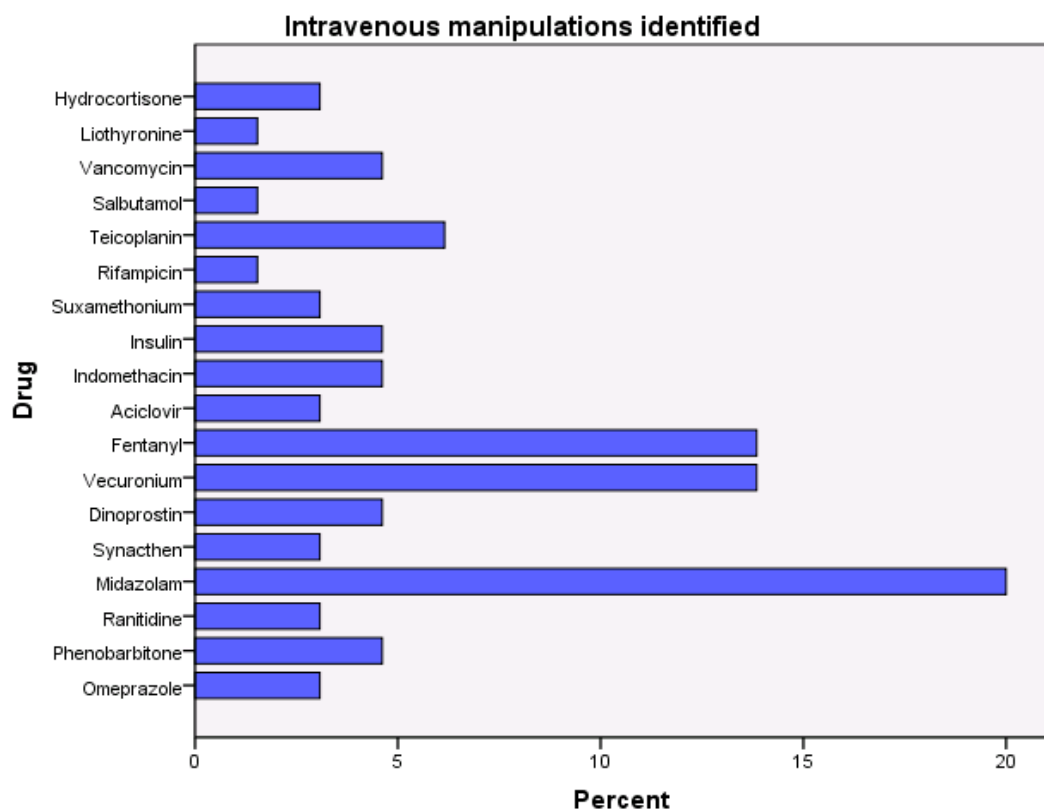
Figure 5: Percentage of each drug of the total tablet manipulations, identified during the observational study



What is also notable from Figure 5 is that several of the drugs manipulated in tablet form are available in a liquid formulation, e.g. paracetamol, ibuprofen, furosemide.

With the 65 intravenous manipulations identified there were 18 different drugs identified, the most frequent being midazolam, with three drugs reported only once during the study. The percentage of each drug of the total intravenous manipulations identified are represented in Figure 6.

Figure 6: Percentage of each drug of the total number of intravenous injection manipulations identified by the observational study



The drugs identified for the other dosage forms are detailed in Table 7.

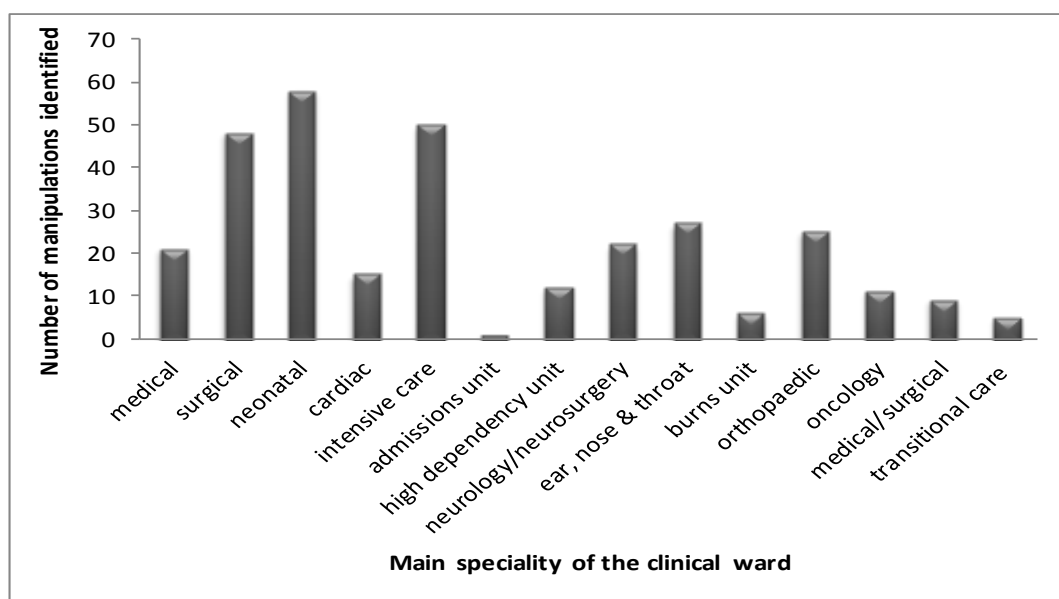
Table 7: Drugs that were manipulated in the form of sachets, capsules, nebuliser solutions, suppositories and transdermal patches during the observational study

Dosage forms	Total	Number of different drugs	Drugs involved
<i>Sachets</i>	30	4	Movicol Gaviscon MST Vigabatrin
<i>Capsules</i>	4	3	Melatonin Oseltamivir Loperamide
<i>Nebuliser solutions</i>	4	1	Ipratropium
<i>Suppositories</i>	6	3	Paracetamol Glycerol Diclofenac
<i>Transdermal patches</i>	10	1	Hyoscine hydrobromide

There were four drugs that were manipulated in two dosage forms. Diclofenac and paracetamol were manipulated in tablet and suppository forms and hydrocortisone and omeprazole were manipulated in tablet and intravenous forms.

Drug manipulations were found across all of the included clinical areas, Figure 7.

Figure 7: Where manipulations were identified, during the observational study, by the main clinical specialities included



Though manipulations were identified throughout all clinical areas, there were notable differences in the dosage forms being manipulated. Intravenous manipulations were all reported in high dependency areas, with 60% of them identified in the specialist neonatal unit, 38.5% in paediatric intensive care and the remaining 1.5% in the cardiac unit.

3.10.1 Proportions required

The predominant proportion required for administration of tablets, capsules, sachets, transdermal patches, nebuliser solutions and suppositories involved either half or a quarter/three quarters of the original dose. There were manipulations for which other proportions were required, notably with tablets, capsules and sachets

where dispersion and the subsequent measurement of differing volumes of the resultant solution was possible.

Tables 8 and 9 describe the proportions of the original dose being sought by undertaking the manipulations.

Table 8: The proportions, by dosage form, of the original complete dose that was being sought by the manipulation

Dosage form	Half of the original dose	Quarter or three quarters of the original dose	Other proportions
Tablets	58% (129/186) ^a	11.3% (21/186) ^a	30.6% (57/186) ^a
Capsules	50% (2/4) ^a	25% (1/4) ^a	25% (1/4) ^a
Sachets	46.2% (6/13) ^a	23.1% (3/13) ^a	30.8% (4/13) ^a
Transdermal patches	0%	100% (7/7) ^a	0%
Nebuliser solutions	100% (4/4) ^a	0%	0%
Suppositories	40% (2/5) ^a	0%	60% (3/5) ^{a 4}

^a Total dosage form manipulation numbers minus those where there was missing/incomplete data

Table 9: The proportions of the original dose of intravenous drugs that was being sought by the manipulations

Dosage form	<10% of the original dose	10% to <20% of the original dose	Other proportion (45% of the original dose)
Intravenous drug ampoule/vial	80% (52/65) ^a	7.7% (5/65) ^a	3.1% (2/65) ^a

^a number of the total of 65 intravenous drug manipulations identified

⁴ The suppository proportions that were not either half or a quarter/three quarters of the original dose were reviewed and discussed with a senior nurse on the ward that they had prescribed. She noted that the doses were close to either a half or a quarter/three quarters, that appropriate dose rounding would have been used to administer and prescribers would be requested to change the prescription to a more accessible dose.

3.10.2 Observed manipulations

Of these 310 manipulations 54 (17.4%) manipulations were observed in practice (I observed 12, the research nurse 27, and 15 had been observed by both of us). Of the 54 observed manipulations 49 (91%) were observed within the children's hospital and 5(9%) within the neonatal unit. 40 (74%) of the observed manipulations were of tablets reflecting the predominance of tablet manipulations. Of the remaining 14, 6 were intravenous (11%), 5 were sachets (9%), and suppositories, capsules and transdermal patches were each observed once (2%). The reasons for non-observation of identified manipulations included:

- the patient not receiving the drug at the prescribed time (for example where there had been changes in the patient's condition or the patient was in theatre),
- patient discharged from the ward,
- prescription changes, and
- difficulties with trying to anticipate when 'as required' drugs would be needed.

During the observations no drug errors were observed and therefore there were no occasions where the observers had to interrupt the drug preparation.

3.10.3 Patient characteristics

Manipulations were observed across a range of age groups, the range of patients observed went from one day to 19 years. Of the 54 manipulations observed, 6 manipulations were for patients of <1month, 18 for those 1month-<2years, 21 for those 2years-<11years and 9 for those ≥11years). As may have been expected as manipulations were found across the range of general and specialist areas there was also with a wide variety of diagnoses in the patients who were receiving manipulated drugs.

3.10.4 Tablets

Of the 40 tablet manipulations observed 25 (62.5%) were cut to get the proportion of the original dose. In all of these, where tablets were split, a tablet splitter was used. Three (12%) of these had to be repeated; in two cases the tablet crumbled while being split, while with the third the tablet was considered by the nurses to have split unevenly. There were three occasions where the tablet had been halved and the unused proportion had crumbled, the manipulations had not been repeated in these cases. With nine (36%) of these manipulations there was visible powder generated when the tablet was split.

12 (30%) of the tablets were solely dispersed in water, one (2.5%) tablet was crushed using a tablet crusher and then added to water for a dose which was three fifths of the original dose to be measured, and one (2.5%) tablet was broken by hand. For the remaining tablet observation the tablet was manipulated twice, initially being halved using a tablet splitter; a half was then dispersed in water with the aim of obtaining a quarter of the original dose for administration. In all 12 observations, where tablets were solely dispersed, the tablet appeared fully dispersed. On the one occasion where a half tablet was dispersed to get a quarter of the original dose the half tablet did not appear to fully disperse.

For 29 (72.5%) of these observed tablet manipulations, the aim/purpose of the manipulation was to acquire 50% of the original tablet dose, for 7 (17.5%) it was to acquire 25% or 75% of that original dose. The remaining four tablet manipulations that required neither a half nor a quarter/three quarters of the dose involved dispersing the tablet to allow for dose measurement.

3.10.5 Intravenous injections

Six intravenous manipulations were observed. In each of these an additional subsequent dilution was required to reconstitute or administer the drugs. This additional dilution was required to allow the measurement of the prescribed small dose. Five of these manipulations were observed in the neonatal unit, with the

remaining one on the cardiac unit. For all six manipulations there were no occasions observed where a volume of the diluent was added to the syringe containing the drug solution and this resultant solution administered, thus inadvertently including the drug dose that would have remained in the hub of the syringe. Therefore, in all observations the initially reconstituted drug was appropriately added to the diluent. With these manipulations, which were all found during the main study, it was not possible to describe adequately using the boxes on the data collection form and so the observers added a narrative account of the manipulation.

3.10.6 Other dosage forms

For sachets there were five manipulations observed, all of these involved dispersion of the sachet contents in water, with 40-80% of the original dose removed for administration. There was no visible sediment following dispersion and the dose for administration was, in all cases, taken from the bottom of the container.

For three of the dosage forms there was only one manipulation observed. A transdermal patch was cut with scissors and three quarters of the patch applied. This proportion was not measured but was judged to be three quarters of the dose. A suppository was halved longitudinally with scissors prior to administration. A capsule was opened and the contents dispersed in water and a proportion removed with the aim of obtaining an eighth of the capsule dose.

3.10.7 Additional comments

Following the pilot study the decision was made to record any relevant unsolicited comments made by nurses undertaking manipulations. These comments reported on the challenges of some manipulations with remarks having been made on the difficulty of splitting some tablets and of dispersing others or the problems of dispersing the contents of some sachets. For one intravenous manipulation the reason spontaneously stated for the manipulation was the avoidance of trying to measure a small dose (0.1mL), meaning that further dilution was used. For one

tablet manipulation the choice of the child was commented on as he preferred to take a halved tablet rather than the oral suspension that was available. There were also general comments voiced describing concerns about the accuracy of the manipulated doses being administered.

3.11 DISCUSSION

3.11.1 Direct observation

Direct observation in neonatal and paediatric clinical areas proved to be an effective method of facilitating the exploration and description of drug manipulation. The need to actually observe has been noted previously. Altmann (1974) described direct observation as playing a unique role in behavioural science, as the necessary link between laboratory science and real-world behaviour. While Zeitz (2005) noted that myths, assumptions and differing perceptions about what nurses should be and actually are doing are ever present. While we could theorise about how manipulations were being done and how they should be done in consultation with clinical and research experts, this could not substitute for the actual observations. Drug manipulations provide an exemplar of a clinical practice suitable for observation as they meet the requirements for observation specified by (Barker et al., 2002a), in that they are events that are visible, predictable, and of limited duration. Barker (1980) argues that observation becomes a scientific technique when it serves a formulated research purpose, is planned and recorded systematically, is related to more general propositions, instead of being presented as simply reflecting a set of interesting curiosities, and is subjected to checks and controls on validity and reliability. Consequentially, the success of observing and recording the resultant data is dependent on the planning of the study.

The development of the observation data collection tools that were used within this study included a substantial process of designing and refining. Decisions need to be made about what should be noticed and what should be ignored (McCall, 1984). Repeated iterations of the tools being developed were reviewed and discussed prior to their use in the pilot study. While this design and review process was time

consuming it was effective. Though there were changes made to the data collection tools from the pilot to the main study, these changes were made to improve the clarity of the tool or to the ease of completion. There were two additional alterations made to the data collection tools during the main study. A section for the manipulation of sachets had inadvertently been omitted in the initial tool and this was not a dosage form observed during the pilot. This became evident in the main study and the section on tablet dispersion was adapted for use to record sachet manipulations. It was notable that these processes were difficult to summarise into short answer boxes or tick boxes and observers had to use a narrative description for intravenous manipulation data collection. These tools had had a considerable design, review and pilot process and were fit for purpose. Nonetheless it is evident that modifications were required during the main study.

A fundamental feature of observation within clinical areas is the collaboration of clinical staff. The nurses who worked in the wards used in this study were supportive of the study. Baker (2006) considered that to get rich and in-depth information, it is important for the researcher to know when the best times to observe are and to meet with those who are actually in the area. During the planning period I consulted substantially with senior nurses prior to the pilot study. During the study when manipulations were identified the most appropriate time to observe them was discussed and agreed with the nurses involved. During these discussions it was evident that the nurses could see the relevance of the study to their practice and they discussed examples of drugs that they manipulated. All three hospital sites are very research active sites with the recruitment of patients into relevant studies embedded into the hospital ethos. This may have been an influence on the generally positive response that researchers found when asking for assistance with the study. Nurses were fundamental to aspects of this study. They were asked to both self-report on manipulations and to permit the observation of them undertaking them. I undertook substantial preparatory work within the clinical areas that were included in this study. Due to the number of different wards and sites included in this study this was resource intensive. Nonetheless it was considered vital to promoting both the identification of drugs that were being

manipulated and ensuring the validity of the recorded manipulations. Despite this preparation and my and the research nurse's regular presence on the wards, the numbers of nurses in clinical areas with changing shift patterns made achieving effective communication a challenge.

The alert cards that nurses were asked to report manipulations on were completed more in some clinical areas than others. It is reasonable to assume that there were manipulations that were not reported. The completion of the alert cards could easily be overlooked within busy hospital wards. Though this may not be the only reason, van de Mortel (2008) discusses the potential impact of socially desirable responding, the tendency for participants to present a favourable image of themselves and this is a potential source of bias that has been detected in research on many topics. Asking nurses to self-report drug manipulations may not be an obvious case where socially desirable responding may arise. However, this is rooted in the context of the high-profile that drug prescription errors and administration errors have within healthcare and the possible impact on the individuals involved that the identification of errors can have. There is a professional onus to report drug related errors or other issues that represent clinical incidents. While this has obvious patient safety benefits it can also, on occasion, have consequences for the individual involved. Donaldson and Grant-Vallone (2002) noted that self-report bias is particularly likely in organisational behaviour research where employees often believe there is at least a possibility that their employer could gain access to their responses. With the considerable organisational and professional focus on reducing drug administration related errors there may be an understandable reluctance to self-report, even for research purposes, on drug preparation and administration related data. This has been identified previously with nurses noting that they would be reluctant to report any omissions or wrong-time errors they did become aware of, unless a dangerous drug was involved (Barker, 1980). Furthermore, a systematic review of drug related issues (including adverse drug events, adverse drug reactions, medication errors) noted that with incident report review reasons for underreporting include both a perceived lack of time and a fear of the consequences (Meyer-Masseti et al., 2011). It is accepted that the numbers of alert

cards completed cannot be taken as any indication of the total numbers of manipulations occurring. Nonetheless this did find manipulations that it would not otherwise have been possible to detect. It is possible that there may have been a hesitation from some nurses about self-reporting manipulations, though this was not voiced to the researchers. It is also reasonable to assume that where alert cards were not completed, though manipulations were occurring, that the priorities of patient care took justifiable precedence. In both the pilot and main studies, despite reminders from researchers, there were fewer cards completed in the second week, suggesting that such self-report methods are unsuitable for long-term use. It should be noted that some wards had low patient turnover and this may have been an influence on the decreasing number of alert cards completed in the second week. An argument could be made that instead of having consecutive weeks that there should have been a gap between the weeks in the two-week periods spent on each ward. This would have helped to ensure that there would have been more turnover in patients, as on some wards the patient population was quite stable over the two weeks. This may have contributed to the fewer manipulations that were reported in the second week. However, taking this approach may have affected the momentum of the study on the wards and may have required further input on the wards from researchers.

This study used methods that identified predictable manipulations and followed them up for possible observation. This meant that long periods observing practice were not required and so 22 neonatal and paediatric areas could be included. This also reduced any likely impact or disruption to clinical areas, as the time episodes spent observing practice were discrete. Carthey (2003) evaluated a structured observational study in healthcare and concluded that a good observer requires interpersonal skills, the ability to keep to the stated objectives and the ability to reassure staff who may be concerned about any possible medicolegal and punitive consequences of the data. The nurses on the wards were supportive of the study and alert cards were completed, nonetheless agreement to being observed and what data was being recorded was never assumed. Many of the concerns about the effect of the observer on the observed in relation to drug preparation or

administration have been rooted in studies that considered drug errors. The concern is that the presence of observers would increase awareness, consequently fewer errors would occur. Although, the opposite effect has been discussed, that is that observation could increase the incidence of errors. The argument being that it is possible that being observed could cause unease and so make errors more likely. With drug errors it is rational to assume that those being observed do not intend to make errors. With drug manipulation the decision to manipulate is intentional. The manipulation is a reasoned response to the need to achieve the prescribed dose of a drug. Thus manipulation may be unavoidable as the prescribed dose of the drug needs to be administered. Therefore while there may potentially be an effect of the observer on the how the actual manipulation is undertaken the incidence will be unaffected.

This study used undisguised observation; all who were observed were fully informed about the purposes of the study. Nevertheless, it is reasonable to expect that a study where any aspect of drug preparation or administration is observed may cause concern in those being observed. As Barner-Barry (1986) describes, thought should be given in observational research to include the right of privacy of those being observed. Barker (1980) noted that if the observer is collecting data that has the potential to be embarrassing or damaging to the subject then every effort must be exerted to be unobtrusive, non-judgemental and not ask for any change to normal activities for the convenience of the researcher. These principles were followed and all of those approached and asked to consent verbally to being observed undertaking drug manipulations gave consent.

It may seem reasonable to assume where studies considered drug errors that the presence of an observer could decrease the error rate through increased awareness. Though it has been argued that this effect could either make the nurses more careful and error rates could decrease or could make them nervous and the rates could increase (Dean and Barber, 2001). Aspects of this study should have reduced this possible effect of the observer. Firstly undertaking a manipulation is not a choice of the nurses involved but considered necessary to fulfil the

prescription. Secondly those being observed were reminded prior to any observation that it was not about the individual involved and that no details of the individual were being recorded. Finally as drug manipulation is an accepted part of drug administration, the familiarity of the activity and the frequent presence of the observers on the wards should minimise the effect of the observers on the observation data collected. It has previously been perceived that, with the presence of an observer, there is less of a concern where the subjects are doing an activity familiar to them and when the observer is unobtrusive and non-judgemental (Barker et al., 2002a). Within drug error observational studies the effect of the observer has not been considered to have had an effect on the outcomes (Barker, 1980; Dean and Barber, 2001). Dean and Barber (2001) found no changes in omitted doses between observed and unobserved periods and no difference in the observed medication administration error rate with repeated observations. These findings, alongside those found in previous studies, led them to conclude that the concerns about the effect of the observer were unfounded and that the observational method was valid.

Barker (1980) considers that the most common reliability measure in observational studies is observer agreement. Ideally a complete assessment of inter-rater reliability would be completed where observation is undertaken. The importance of both the training of observers and the assessment of consistency has been described (Prot et al., 2005). Previous studies, such as (Nolan et al., 1995; Chua et al., 2010) using direct observation have not reported on the reliability of what has been observed. Little is known about observer agreement in the context of drug administration observation (Dean and Barber, 2001) and this has been highlighted as a methodological flaw (Carthey, 2003). One study that did attempt inter-observer reliability when observing drug errors abandoned the attempt and concluded that, due to practical issues, it was too difficult to for two observers to record the data (Dean and Barber, 2001). This was also noted within this pilot study, ensuring a clear view for the two observers with the two nurse system of checking drugs (used in many paediatric settings) while ensuring that the process is not disrupted is difficult. Within this study it was not possible to quantify inter-

observer reliability. There were a small number of manipulations which were recorded by two observers. Following the pilot study, the data from the seven manipulations which had been recorded by both observers was scrutinised. Three quarters of the differences were due to differing data being recorded as the item was not sufficiently defined, or where the data had not been recorded at all. These findings were used to improve the clarity of the data collection forms and to develop a reference document to enable enhanced data collection in the main study.

3.11.2 Manipulations

This study included a wide range of generalist and specialist neonatal and paediatric in-patient areas and included three sites within the Merseyside and Cheshire localities. This may affect the external validity of the outcomes of the study both within the UK and to wider populations. In incorporating all the of available in-patient areas with the children's hospital, a separate specialist neonatal centre and the neonatal and paediatric areas in a district general hospital this study has included both a range of general and specialist areas and given some allowance for possible differences in prescribing practice and drug availability. Many of the manipulations found involved drugs that are prescribed for indications that mean they are liable to be in common use in paediatric practice. Across the UK there may be a variety of specials⁵ ordered and so within hospitals and regions there may be differences in the drugs which require manipulation. Mulla et al. (2007) considered captopril formulations used in the UK and found that a variety of unlicensed captopril formulations are used interchangeably. Additionally there may be variance in the preferences between the dosage forms used, for example the use of suppositories in children is quite popular in western Europe but uncommon in the UK or the US (Breitzkreutz and Boos, 2007). Within Europe there may be diverse

⁵ Specials are special-order unlicensed medicines made to meet the needs of an individual patient. For children specials may be the only option for the prescriber for some conditions and in some circumstances are routinely prescribed (www.npc.nhs.uk/improving_safety/prescribing_specials/resources/5_guiding_principles.pdf)

formulations available, again meaning that there may be differences in the drugs being manipulated. Notwithstanding that there may be different drugs or drug products, methods of manipulation or dosage forms involved, the global impact of the historical lack of development in paediatric medicines and need to manipulate is acknowledged. Therefore the outcomes of this study can be considered to have relevance beyond the geographical area where data were collected.

It had been suggested that manipulations may occur more frequently in more high dependency areas. This study found that, as may have been anticipated, higher numbers of manipulations were found in areas where there are likely to be more dependent patients and therefore where more drugs are liable to be prescribed. However it was evident that manipulations are not solely occurring in these areas as they were found throughout all of the included clinical areas.

The systematic review (Chapter 2) found limited evidence relating to manipulations, what evidence there was predominately related to tablet manipulations. This current study found that 191 of the total 310 manipulations were tablet manipulations. Of the 25 observed tablet manipulations where the tablets were split 12% were repeated either due to the tablet crumbling or splitting unevenly. The numbers involved in this are small and cannot be considered to correspond to other tablet manipulations of different formulations or other drugs.

In addition, this indicates a potential for considerable waste associated with splitting tablets if regular repetition of the manipulation is needed due to the tablet crumbling or splitting unevenly.

With nine (36%) of the observed split tablets there was visible powder produced during splitting. Though this may be small and may not impact on the dose achieved, further work is needed to explore the implications of this. Even if there is insubstantial impact on the dose achieved there are other implications. If tablets are split then the dust produced will be drug-containing, this may have unknown safety implications for those splitting the tablets. Splitting tablets that contain cytotoxic, mutagenic and reproduction-toxic substances could result in the

contamination of the domestic environment with hazardous dust (Breitkreutz and Boos, 2007).

30% of the tablet manipulations involved dispersing in water and taking a proportion. In all cases the proportion taken for administration was observed to be withdrawn from the bottom of the container. The systematic review found a single study which had considered the dispersion of tablets. In this study Broadhurst et al. (2008) found that when withdrawing proportions of the dose that inconsistent doses were found when sampled from different depths of the container, though those taken from the base of the container were most consistently closest to the intended dose. This gives limited support to the observed practice that doses should be, as they were observed to be, taken from the base of the container. Though, questions about the actual dose that is contained in the proportion administered remain.

During this current study there were tablets manipulated where a liquid formulation was available. This triggers questions about why the manipulation was being done. This has been found previously, Skwierczynski and Conroy (2008) found that tablets were manipulated where they were available as a liquid; the reasons for this included cost (liquid formulation expensive compared to the tablets), availability on the ward and the volume of the liquid that was required to achieve the prescribed dose. Breitkreutz and Boos (2007) considered that the main problem with liquid formulations is the palatability of the solution. There may be practical reasons for the manipulation (such as availability on the ward). Nonetheless this raises a question about preferences, whether some children may prefer tablets (even split tablets) that are designed for them to taking large volumes of liquids of liquids that they find unpalatable.

The intravenous manipulations reported involved dilutions beyond those that would be expected for the reconstitution of the drug. These were needed to achieve a small dose which could not otherwise be measured for administration. To obtain the small dose prescribed these extra steps are a necessary addition to the drug preparation process. They do add the potential for errors in both calculation

and/or measurement. The risk of tenfold error in paediatric practice has been previously highlighted (Koren et al., 1994; Ghaleb et al., 2006; Wong et al., 2009) . Taxis and Barber (2003b) investigated intravenous drug errors and found that most preparation errors were associated with multiple step preparations. Chappell and Newman (2004) reviewed nine intravenous drugs administered at doses that were less than one tenth of the dose in the vial and four drugs administered at doses that were less than one hundredth of the dose in the vial, in a neonatal unit. They found that many of these drugs would cause considerable morbidity or mortality in 10-fold or 100-fold overdose. Of the small number of intravenous manipulations observed in this study none mistakenly added the drug dose in the hub of the syringe. Though this may be a very small dose, when considering small doses such as those prescribed in neonatal units, then this may be a substantial proportion of the prescribed dose if inadvertently administered. Taxis and Barber (2003b) found that where the volume in the syringe hub was administered on a neonatal unit the result was a 2-3 times overdosage. So although not observed in this study the administration of the dose in the syringe hub remains a risk where further dilution is required to measure the small dose prescribed.

Though other dosage forms may be manipulated less frequently it is evident that tablets are not the sole dosage form manipulated. Manipulations were found for capsules, sachets, nebuliser solutions and suppositories. There were no reported manipulations involving enemas or oral solutions. As the systematic review (Chapter 2) found only one (low quality) non-tablet study (Kim et al., 2005) there is not an evidence base to support these non-tablet manipulations.

The drugs that were manipulated in this study were not the unusual, the infrequently prescribed or those where the indication was liable to be to treat a rare condition. They were those which could be expected to be used routinely in neonatal and paediatric practice, with analgesics representing the largest group reported. Manipulations are not therefore an anomaly of clinical practice, only applicable to orphan drugs or for unusual diagnoses.

Furthermore a substantial number of the drugs being manipulated were identified only once during this study. As the aim was to investigate and where possible observe the process of drug manipulation absolute numbers of manipulations were not being sought. However, this frequent single identification does make it reasonable to surmise that there may be other drugs that are being manipulated but which were not being used on these ward during the two week data collection periods.

The comments made by nurses undertaking manipulations were unsolicited and recorded as they occurred. These comments cannot be considered representative. Nonetheless they do provide an indication of the challenges of some manipulations, with descriptions given of the difficulties of splitting some tablets and dispersing others. Nurses also expressed concern about the impact of manipulations on the accuracy of the administered, manipulated dose.

3.12 CONCLUSIONS

Observation proved to be an appropriate and valid method for considering drug manipulations in clinical practice. The limitations of this method, such as the possible observer effect on the observation and the difficulties with considering inter-rater reliability, are acknowledged. The concurrent use of self-report and prescription reviews to identify manipulations proved effective. When exploring a topic area that has not been previously investigated, such as this one, then the methods of locating manipulations and the observational data collection tools had to be designed specifically for this study. Consequently the use of research and clinical expertise review and the pilot study were an instrumental part of the process to ensure the internal validity of the outcomes.

This observation based study provides evidence of drug manipulations occurring in neonatal and paediatric in-patient areas. These manipulations were undertaken across all areas of general and specialist practice and frequently involved drugs that are in common use. Undertaking manipulations has the potential to increase medication error rates as the extra processes involved may make errors in

calculation or in measurement more likely. Aside from an increased risk of errors, questions of the dose accuracy of the manipulated product were evident from the observations. These questions about dose accuracy are raised where tablets split into unequal segments or a segment crumbles; with the potential loss of active product where there is residue left after a tablet is split, and whether tablet dispersion is sufficiently consistent, that the required dose will be accurate when a proportion is withdrawn for administration. Concerns about dose accuracy were broached by those undertaking the manipulations.

The study described in this chapter has confirmed that drug manipulation is an aspect of the administration of drugs in neonatal and paediatric in-patient areas. This study has explored and described these manipulations. The outcomes of this study were used to explore further contextual issues around this practice and the thoughts of nurses doing these manipulations in Chapter 4.

CHAPTER 4: QUESTIONNAIRE

4.1 INTRODUCTION

The observational study (Chapter 3) identified 310 drug manipulation episodes and described 54 of them through direct observation. The observational data were collected from three sites within Merseyside and Cheshire, including two specialist sites and one district hospital. The specialist children's hospital involved in the observational study has large neurosurgery and cardiac units: some of the drugs being manipulated were liable to have been specific to some of the conditions found in these specialities. Specialities at other sites may require different manipulations. Outside of the larger paediatric centres neonatal and paediatric units may represent a small number of wards in much larger adult hospitals. This may influence the availability of paediatric medicines and consequently influence the manipulations in these areas. Throughout the UK there may also be an influence from differences that may occur in prescribing practice. Porta et al. (2012) considered antibiotic use across children's hospitals in Europe and noted that there have been few studies that compare this. Within the two UK sites included they found variation in use. Therefore the data from the observational study may not have captured the scope of manipulation practice across the UK.

It is important to consider the setting in which manipulations occur. Drug manipulations may themselves be discrete actions but cannot be considered as independent actions. There are a number of contextual issues which may influence practice. These include:

- Manipulation may be an unlicensed or off-label use of the drug product. As such they will not be included in any information from the pharmaceutical companies and may not be available in other reference sources. Therefore where do those undertaking the manipulation seek information or advice relating to them from?
- Tablet manipulations were found in the observational study where a liquid formulation is available; suggesting that achieving the dose required may not be the sole reason for the manipulation, there may be other influences.

Additionally, the 5-day quantitative review showed that for both intravenous injections and/or oral liquids two methods could have been used to try and achieve the prescribed dose. That is either a manipulation in the form of a further dilution or a measurement of a small volume (<0.2mL), could have been used to obtain the final dose for administration (Nunn et al., 2013). Volumes of <0.2mL may be difficult to measure accurately. The perceptions of nurses about the need to measure very small volumes have not been described.

The observational study identified issues that could not be addressed within it. Within that study the observers aimed for impartiality and were present only to record the data of the observation. Questions were not asked except where required for clarification. Nonetheless there were spontaneous comments made by nurses doing manipulations, these were recorded. These provided some insight into the views of those undertaking manipulations, suggesting that nurses have questions and concerns relating to them.

Therefore there were several areas relating to drug manipulation where additional data would provide context for drug manipulations. In order to address these issues a further study was designed and conducted. The areas included were the variation in prescribing practice and therefore the nature and type of drug manipulations occurring, further details of manipulations that may occur less commonly, including whether they are considered to be applicable to current practice, the use of sources of supportive documentation, possible variation in the reasons why manipulations were undertaken, the use of the measurement of small volumes and any concerns that those undertaking manipulations have.

In deciding to seek this additional data there was also the opportunity to ask about the dosage forms where there had been limited data found during the observational study (Chapter 3). This specifically included suppositories and enema manipulations.

4.2 AIMS

This questionnaire study aimed to:

- Elicit complementary data (to the observational study, Chapter 3) about the nature and type of drug manipulations occurring in neonatal and paediatric in-patient areas and to investigate the process of manipulations in dosage forms that were not observed
- To consider how and where any reference materials about undertaking manipulations is located
- To explore if nurses are measuring small volumes of liquids (<0.2mL)
- To identify if nurses use any methods to avoid drug manipulations
- To elicit the views of nurses undertaking manipulations

4.3 STUDY DESIGN

On review of the study aims it was clear that questions relating to many of them could be distilled into short and direct questions, therefore fitting a questionnaire based method. Surveys are considered to be well suited to descriptive studies, but can also be used to explore further aspects of a situation or to seek explanation (Kelley et al., 2003). Furthermore a questionnaire can be appropriate if used within a mixed methodology study, such as to extend and quantify the findings of an initial exploratory phase (Boynton and Greenhalgh, 2004). Both of these aspects apply to the aims underpinning this questionnaire. The use of a survey provided the opportunity to investigate across a wider geographical area and had the potential to include many more participants than would be possible with other methods. Additional open ended questions could be used within the questionnaire to explore those questions where, either a closed question would be inappropriate, or as supplementary to a closed question to gain further insight.

4.4 QUESTIONNAIRE DESIGN

Literature on questionnaire design resonates with warnings about poorly designed questionnaires and the inherent consequences of this on the outcomes resulting from the questionnaire. With the design of this questionnaire, as with many questionnaires, a balance was required between gaining as much relevant and sufficiently robust data as possible whilst ensuring that the questionnaire is not considered too onerous by participants. Williams (2003) noted that the temptation with designing a questionnaire may be to delve into a wide range of issues which are interesting but not directly relevant to the study. The use of previously administered questionnaires in similar topic areas can help to guide the design of future questionnaires. This was not a resource available in designing this questionnaire. Questionnaire design methodologies were reviewed to ensure that this questionnaire would meet the principle described by (Gendall, 1998) of letting the respondent tell us what they mean without imposing responses on them. It is much more difficult than it seems to prevent a questionnaire becoming an instrument of the designer's perceptions, values and language, which is then inflicted on the respondent (Gendall, 1998).

Within questionnaire design the respondent defines what can be done. One of the criticisms of questionnaires is that they assume that the researcher and respondent share assumptions and interpret the wording of a statement in a similar manner (Rattray and Jones, 2007). However, a survey of a specified group can, and should, be a different proposition to a survey of the general public (Gendall, 1998). As all potential respondents were nurses, it could be assumed that potential respondents familiarity with clinically related statements and terminology existed. Nonetheless this did not diminish the importance of designing a questionnaire that ensured that the perceptions or views of the researchers were not transmitted to respondents. In tandem with this is the need to ensure the intelligibility of questions, that they are clearly comprehensible. Questionnaires have the potential for error where respondents misunderstand the question or response categories (Tourangeau, 1984; Stone, 1993). This may have a negative impact on the response rates as it has

been shown that low response rates can be due to participants being unable to read or follow the questionnaire (Boynton and Greenhalgh, 2004).

4.4.1 Overall questionnaire design

Gendall (1998) considered a questionnaire to be a structure of layers which must be integrated into an entity whose properties are greater than the individual layers (question design, question wording, and formatting or layout). Relevant aspects of this structuring were reviewed in planning and designing the questionnaire for this study.

4.4.1.1 Question choice

Many questionnaires consist of predominantly closed questions making them relatively rapid to complete and providing data that lends itself to coding and analysis. Closed questions provide the same context for all respondents, though outcomes are dependent on the answer set presented (Gendall, 1998). These questions, by their nature, restrict the pool of answers. Consequently overall the richness of potential responses is lower with closed questions (Boynton and Greenhalgh, 2004), though the questions will usually aim to include the range of possible answers. It has been proposed that within closed question design that there should always be the option for respondents to not give an opinion through, for example, the use of 'don't know' or 'not relevant' or 'other' options. It has been opined that a 'no opinion' option should be offered (Gendall, 1998). Though this is debated, as it has been argued that including the 'don't know' may lead to many non-committal responses (Williams, 2003), some respondents may choose to provide a non-committal response when they actually do have an opinionated one (Stern et al., 2012). The removal of the choice of a neutral answer forces the respondent to select a response (Rattray and Jones, 2007). Respondents have to either pick an option that they may not agree with or not complete the question. As (Stone, 1993) argued human uncertainty and indecisiveness may be an irritating inconvenience but it cannot be ignored.

The addition of open questions allows participants to express their views. The respondent must formulate an answer rather than selecting from pre-existing answers (Tourangeau, 1984). Open-ended questions allow for a large number of possible answers where it is important to capture all of the detail in the information provided (Edwards, 2010), the driver behind them is often a concern about missing an important issue (O’Cathain and Thomas, 2004). However, open-ended questions may take longer to complete meaning that they are left unanswered. Respondents may short-circuit the process, deciding to not complete the question rather than to retrieve facts from the memory or to review what they think about an issue (Tourangeau, 1984; Williams, 2003). The decision of respondents on whether or not to complete open-ended questions may mean that the views expressed may not be comprehensive. Those who choose to answer the general open questions could be different from overall respondents, either being more articulate or having a greater interest in the survey topic (O’Cathain and Thomas, 2004).

4.4.1.2 Question wording, question order and layout

For the data resulting from a questionnaire to be valid, participants must be able to correctly understand the question and what is being asked of them. The design, wording, form and order of questions can affect the responses obtained; careful design is needed to minimise bias in the outcomes (Kelley et al., 2003). The wording of questions can be an influence, in general questions should be short, simple and specific (Williams, 2003). Unfamiliar or difficult words should be avoided, as should asking two questions within one (Gendall, 1998). The aim should be to reduce the opportunity for misinterpretation with the avoidance of unambiguous words. Boynton and Greenhalgh (2004) noted that words that are often used inappropriately in closed questions are “frequently” and “regularly” and further recommends avoiding “commonly”, “usually”, “many”, “some” and “hardly ever”. Words like these are open to individual interpretation of their meaning.

There are some differences in the views on question order. Some consider that it is better to start with easy, factual, non-personal questions and that any questions that may involve some research from the respondent should come later when the

respondent will hopefully have developed an interest in the subject and feel ownership of the questionnaire (Williams, 2003). Traditionally many questionnaires have started with demographic questions though there is also a view that these questions are asking more personal information and should be placed at the end (Stone, 1993). The HTA review on the design and use of questionnaires considered that question order effects may not be ubiquitous, but that the evidence suggested that general questions should precede specific ones (McColl et al., 2001).

The importance of visual aspects of questionnaire design has been highlighted, with a caveat that researchers rarely spend sufficient time on the layout of their questionnaire (Boynton and Greenhalgh, 2004; Edwards, 2010). Visual design theory notes that even the formal visual elements of a self-administered questionnaire can be assumed by respondents to be meaningful (Stern et al., 2012). Additionally, designing a questionnaire that is easy to navigate is considered to increase response rates (Williams, 2003).

When it comes to questionnaire length there is insufficient evidence to suggest an optimal questionnaire length in terms of number of questions or pages (Nakash et al., 2006). Overall findings with respect to questionnaire length are equivocal (McCall, 1984). There is, however, an inevitable trade off between making the questionnaire comprehensive enough to answer the question adequately, and making it so long that it may have an adverse effect on response (Nakash et al., 2006).

4.4.2 Response rates

Postal questionnaires are notorious for the difficulty this method poses in attaining adequate response rates. Response rates are a potential source of bias; the potential differences between responders and non-responders should be explored and any implications discussed (Kelley et al., 2003). This study aimed to obtain participants to include a range of types of units, such as large specialist paediatric hospitals and paediatric wards based in district general hospitals, throughout the UK, and across general and specialist paediatric areas. While the individual practice

and experience of participants may differ, all participants were nurses working in paediatric in-patient areas and were asked about their professional practice, lessening the potential differences between responders and non-responders.

Cover letters have not emerged as substantial predictors of response rates. It is difficult to assess if this is because the content of the cover letter is not important or because it has been difficult to predict or measure the impact (Redline et al., 2004). Theories of individual motivation that have been used to attempt to increase response rate and have argued that the cover letter should link the survey topic and possible motivational concern of the respondent (McColl et al., 2001).

4.4.3 Saliency

It seems reasonable to infer that where potential participants are interested in the topic area then they are more likely to complete the questionnaire. Overall theory and empirical research suggests that respondents are predisposed to respond to questionnaires with more salient topics or issues that are relevant to them (Williams, 2003; Stern et al., 2012). This may even have relevance throughout the questionnaire questions. Stern et al. (2012) noted that there has been some discussion as to why certain questions show response effects while others do not and deemed item saliency⁶ to be a plausible explanation. However determining saliency is difficult. Direct measures of people's interests are difficult to obtain, so indirect measures or proxies, such as membership on a list that suggests an interest, are a logical compromise (Groves et al., 2004; Stern et al., 2012). In this situation, the selection of nurses who are currently working in neonatal and paediatric hospital areas allowed some assumption that a questionnaire that asked them to provide information on clinical practice would be salient to them. A previous survey of nurses that aimed to measure the knowledge, practice and attitudes of nurses found that many respondents were positive about participation and reported comments such as 'I welcome any means to assess my clinical

⁶ Item saliency is the degree to which any topic of any given question resonates with the respondent

effectiveness' and 'in order to be effective clinically it is important to be self-critical' (Upton and Upton, 2006). Though influential, topic is not the sole feature of a saliency. Other aspects such as the length of the survey, the sponsor of the study or poor visual design of the questionnaire may also have an effect and may need to be considered (Groves et al., 2004; Stern et al., 2012).

4.4.4 Anonymity

The argument has been made that assuring respondents of anonymity can increase response rates. The evidence from this appears to be equivocal with some concluding that stressing the anonymity of the survey could increase response rates (Williams, 2003), while a Health Technology Assessment review considered that assurances of anonymity did not improve response rates (McColl et al., 2001).

Medication errors are a particular focus within the NHS. With patient safety a paramount consideration it is understandable that medication errors are given substantial prominence. In relation to the causes of drug errors the influence of other factors is acknowledged, nonetheless attention is often focused on the individual involved in the error (Smith, 2004). As described in Chapter 3 when planning the observational study, it was necessary to be aware of the importance attached to drug errors and whether participants would be cautious due to this, and consequently reluctant to report on drug manipulations. As Crawford (2012) describes, with the administration of medicines there needs to be an ethos of transparency and responsibility, if it is felt that there is a blame culture then nurses may be less likely to report incidents.

There is the potential that a survey of nurses, which asks about their practice, may cause participants to feel constrained by their being a registered health care professional. They may be tempted to provide what they consider to be professionally acceptable responses. Edwards (2010) noted that when exploring aspects of practice of health care professionals that there may be a perception that there are responses that they should give. The use of self-administered questionnaires should mean that there is less susceptibility to response desirability

bias Edwards (2010). Akram and Mullen (2012) considered that some of the difficulty they had with getting paediatric nurses to agree to participate in the interview stage of their study was a reluctance to discuss their practice with another health colleague, that assurances of anonymity were not sufficient. The distance from researchers provided by self-administered questionnaires will help avoid any potential bias due to interviewer effects. Participants may respond more truthfully to sensitive questions, and may make more critical and less socially acceptable responses to a questionnaire than when face-to-face with an interviewer (McColl et al., 2001).

4.4.5 Retrospective recall of recent drug manipulations

Relying on the memory of questionnaire respondents provides its own complications. This retrospective approach to data collection can be prone to bias due to inaccurate recollection. Imposing a time frame in question wording can both be helpful and pose difficulties. It is considered unwise to ask about things that have happened more than six months ago (Williams, 2003). With retrospective recall it is likely that there will be episode omission, respondents may fail to recall an event that falls within the specified time-frame (McCall, 1984).

4.5 STEERING GROUP

An expert steering group was used to support the development of this questionnaire based study development. This group had initially conceived the need to investigate this area and had sourced the research funding for the Manipulation of Drugs Required in Children (MODRIC) research group. The steering group used comprised medical, pharmacist and nursing members alongside formulations and research expertise, this group were consulted with repeatedly during the questionnaire development. I completed the initial design and drafting of the questionnaire which was reviewed by this group, they provided advice for re-drafting of the questionnaire and face validity for the questionnaire.

4.6 ETHICS

This study outline was reviewed by the Liverpool Local Research Ethics Committee and met their criteria as a service evaluation project involving NHS staff only. This body considered that this study did not require review by a NHS Research Ethics Committee.

4.7 METHODS

This study used a paper based postal questionnaire. Paper based questionnaires were selected ahead of using an electronic based distribution. Consultation with ward based nurses found that there tends to be a small number of computers available in ward areas. These computers are often predominantly used for updating records and notes and access for any other purpose may be more difficult. Questionnaires were distributed via unit/ward based nurse managers.

The questionnaire used in this study was designed following a review of questionnaire design literature and in consultation with study steering group. Throughout the design of this questionnaire questions were repeatedly assessed and reviewed specifically considering their relevance, clarity and lack of ambiguity. Advice and assistance on layout and general aesthetic design was taken from a clinical audit unit with considerable experience in questionnaire administration.

In relation to issues that the review of questionnaire design had shown to be potential sources of bias the following decisions were made. Throughout the questionnaire no opinion or not applicable options were generally included. However there were a small number of questions where this option was not available. These questions asked specifically practice related questions where not having a 'no opinion' option was logical, such as when asking whether or not they take steps to avoid manipulations. Where participants were asked to retrospectively recall data this was for the time period of the previous month.

Within the design of this questionnaire supplementary open questions were used to allow respondents, if they chose to, to expand on answers given to closed questions. A small number of additional open-ended questions were used to ask about any concerns relating to manipulations and any further information that respondents may wish to give. The questions such as those relating to steps to avoid manipulations or about concerns needed to be open-ended as they aim to elucidate what the respondents think and did not want any possibility of biasing answers by using closed question categories. The aim of the cover letter sent with this questionnaire was to explain clearly the purpose of the questionnaire and to ensure that the nurses would feel that this questionnaire was salient to them, thus increasing the likelihood that the questionnaire would be completed. Nonetheless measures were taken with the aim of maximising the response rate. This included this use of several relatively easy to achieve practical suggestions which have been considered to potentially improve questionnaire response rates (Williams, 2003). These included using white stamped envelopes, pre-paid addressed envelopes for replies and using official headed paper for all correspondence.

For the outcomes of this survey to be valid the honesty of participants was necessary. With the aim of ensuring that respondents would not be concerned about providing full details questionnaires were anonymous. Participants were asked only to report the town/city that the hospital they work in is located and the type of hospital and clinical area they worked in. The provision of complete anonymity, and therefore no possibility of their responses being individually questioned, aimed to make certain that participants would not feel obliged to give professionally standard answers.

The questions that asked for retrospective recall of recently undertaken drug manipulations were placed at the end of the questionnaire following the previous 18 questions relating to manipulations, as this should assist with the recall of recent occurrences. Questionnaire respondents were asked to recall data of recent manipulations they had undertaken. A time frame of one month was used. While acknowledging the potential drawbacks, the recall by respondents of recent drug

manipulations could still supply valuable data about manipulations currently being used in clinical practice throughout the UK.

4.7.1 Sampling

This study did not aim to find a representative sample of paediatric nurses in the UK. Purposive sampling was used with the aim of ensuring both that there was a geographical spread throughout the UK and that there was a range of sizes of paediatric units included, encompassing both large specialist centres and smaller units, which are often located in larger, mainly adult, hospitals..

Neonatal/paediatric ward or unit managers in 42 neonatal and paediatric centres across the UK were contacted via email. This contact initially was made by Professor Nunn representing the MODRIC group as he is a known expert within paediatric medications related research and it was considered that this may assist with response rate. Once they had replied to him he forwarded the emails on to me and I completed all further contact including questionnaire distribution. The use of ward managers allowed questionnaires to be distributed personally within a work place environment but also preserved the anonymity of respondents. The study was described to the managers and they were asked if they would agree to distribute questionnaires to the nurses working in neonatal and/or paediatric areas. Thirty of the 42 sites responded and agreed to participate, relative to the size of the units they managed 10, 20 or 30 questionnaires were sent to the managers for distribution. All questionnaires responses were anonymous. There was no direct communication with the potential questionnaire respondents.

Reminder emails were sent to all participating managers of participating centres two weeks after the initial distribution of the questionnaires.

4.7.2 Pilot study

The questionnaire was piloted with a group of paediatric research and clinical nurses. On collating their comments a few questions were reworded to ensure that

the questions were sufficiently concise, and clear in what was being asked. Major revisions were not required. Participants in the pilot process were also asked specifically about the table used within the questionnaire to define manipulations for each dosage form to ensure that these definitions were unambiguous. Changes to this table were not considered necessary by those completing the pilot.

4.8 ANALYSIS

The data from the closed-questions were analysed descriptively. Although the data from the open questions are qualitative it can be difficult to analyse using qualitative analysis techniques. The data from open questionnaire questions often lacks some of the key strengths of qualitative research, with a lack of conceptual richness as the data often consist of a few sentences or less (O’Cathain and Thomas, 2004). The data from the open-ended questions were content analysed to report the concerns that were raised by those who chose to answer these questions. Further analyses of this was limited by the brevity of many of the responses, as these were not in-depth but were short comments or sentences.

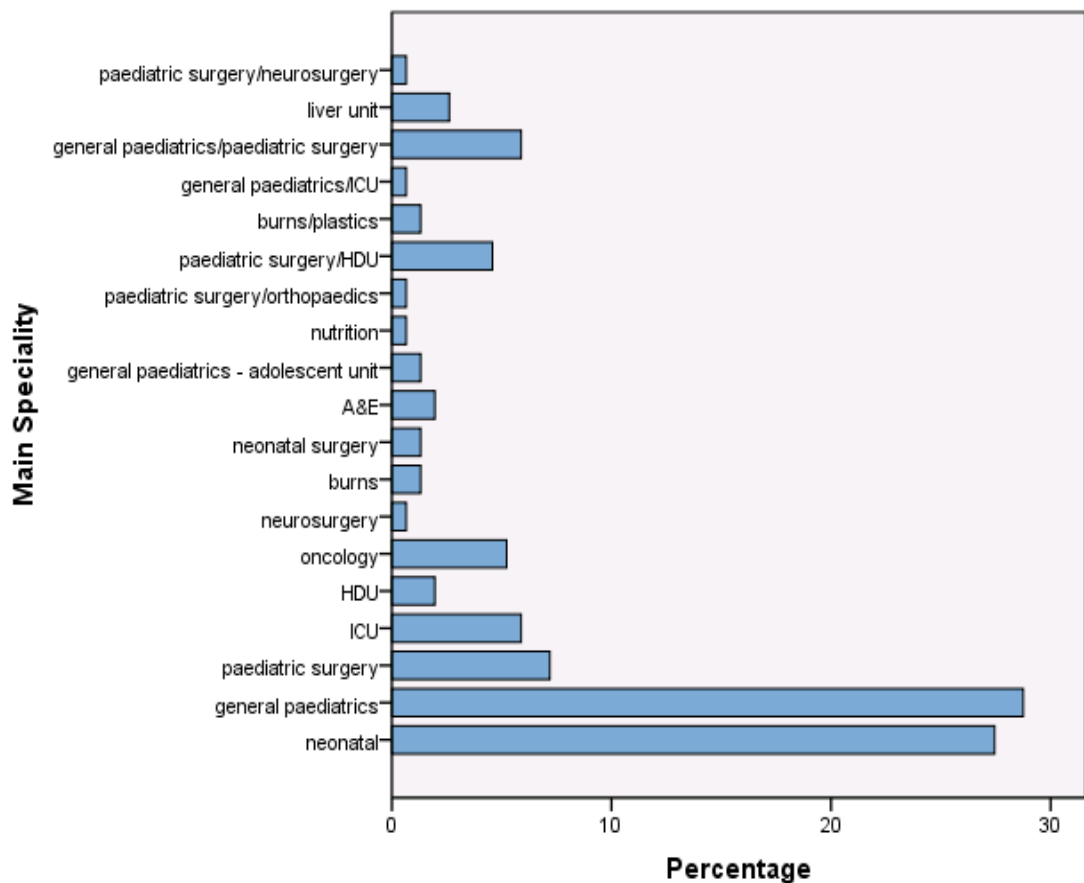
4.9 RESULTS

560 questionnaires were distributed to 30 hospital sites. Of these 153 (27%) were returned. There were respondents from 22 of the 30 hospitals where managers had agreed to distribute questionnaires. This included hospitals in Northern Ireland, England, Scotland and Wales. There was a spread of hospital types with 11.8% (18/153) of respondents working in children’s hospitals, 51.6% (79/153) in teaching hospitals with paediatric and neonatal beds and 25.5% (39/153) in district general hospitals with paediatric and/or neonatal beds. 11.2% (17/153) respondents did not specify the type of hospital where they worked.

Four respondents worked in hospitals with only neonatal cots. The number of paediatric beds in the remaining units ranged from 14 to 400 beds (mean 50 beds). Eleven respondents worked in hospitals with no neonatal beds. The number of

neonatal beds in the remaining units ranged from 6 to 60 beds (mean 20 beds). The largest groups of respondents were working in general paediatric and neonatal areas, nonetheless respondents worked across many differing specialities (Figure 8).

Figure 8: Main speciality of the ward/clinical area that questionnaire respondents worked in.



4.9.1 Drug manipulations

There were 258 manipulations reported to have been undertaken in the previous month by 68% (104/153) questionnaire respondents (within the two largest groups, 62% of those working in neonatal areas and 80% of those working in general paediatrics completed this question and reported manipulations). All of these drug manipulations were evaluated to ensure that they met the criteria to be considered a manipulation to achieve the required drug dose. This evaluation was reviewed by

an experienced paediatric clinical pharmacist. Where there was doubt as to whether the reported manipulations met the criteria, usually where the data was not complete enough (the proforma given to provide details of the manipulation was incomplete) for this to be assessed, these data were removed from any analysis. This resulted in 188 manipulations that could be considered further with 70 (27%) of the 258 reported manipulations being removed.

Table 10: The drugs identified as manipulated from the questionnaire using the classifications from the BNFC

BNFC classification	Drugs involved	Frequency this classification reported as manipulated	Percentage of manipulations identified
<i>Analgesic</i>	Paracetamol, Ibuprofen, Diclofenac	33	17.6%
<i>Proton pump inhibitor</i>	Omeprazole	24	12.8%
<i>Bronchodilator</i>	Salbutamol, Ipratropium	23	12.2%
<i>Antimuscarinic</i>	Glycopyrronium bromide, Hyoscine hydrobromide	20	10.6%
<i>Steroid</i>	Prednisolone, Hydrocortisone, Dexamethasone	12	6.4%
<i>H2 antagonist</i>	Ranitidine	8	4.3%
<i>Antibiotic</i>	Metronidazole, Amoxicillin, Gentamicin, Clindamycin, Vancomycin	7	3.7%
<i>Antiepileptic</i>	Phenobarbitone, Topiramate, Clobazam, Gabapentin, Phenytoin	6	3.2%
<i>Osmotic laxative</i>	Phosphate enema	6	3.2%
<i>Antiemetic</i>	Aprepitant, Cyclizine, Domperidone	5	2.7%
<i>Laxative</i>	Glycerine suppository	4	2.1%
<i>Immunosuppressant</i>	Tacrolimus	4	2.1%
<i>Antimotility</i>	Loperamide	3	1.6%
<i>Antiplatelet</i>	Aspirin	3	1.6%
<i>Sedation</i>	Secobarbital, Chloral hydrate	3	1.6%
<i>Benzodiazepines</i>	Diazepam, Midazolam	2	1.1%
<i>Alginate preparation</i>	Gaviscon	2	1.1%
<i>Anticoagulant</i>	Enoxaparin	2	1.1%
<i>ACE inhibitor</i>	Captopril, Lisinopril	2	1.1%
<i>Calcium channel blocker</i>	Nifedipine	2	1.1%
<i>Cytotoxic</i>	Allopurinol	2	1.1%
<i>Minerals</i>	Potassium chloride	2	1.1%
<i>Opioid analgesic</i>	Codeine, Morphine	2	1.1%
<i>Pineal hormone</i>	Melatonin	2	1.1%
<i>Vitamin</i>	Folic acid, Vitamin K	2	1.1%
<i>Antipsychotic</i>	Levomepromazine	1	0.5%
<i>Antihypertensive</i>	Sildenafil	1	0.5%
<i>Antiviral</i>	Aciclovir	1	0.5%
<i>Beta-blocker</i>	Atenolol	1	0.5%
<i>Skeletal muscle relaxant</i>	Baclofen	1	0.5%
<i>Thyroid hormone</i>	Levothyroxine	1	0.5%
<i>Vasodilator</i>	Glyceryl trinitrate	1	0.5%

Respondents were asked to identify how frequently they considered they had undertaken the manipulation that they had provided details of in the last month prior to completing the questionnaire;

- 54.8% (103/188) considered that they were undertaking the manipulation they described daily,
- 19.1% (36/188) weekly,
- 9.0% (17/188) monthly, and
- 14.4% (27/188) did not know.

Overall there were 188 manipulations identified. Manipulations reported by dosage form are described in Table 11.

Table 11: Manipulations reported by questionnaire respondents, by dosage form

Dosage form	Number of manipulations identified via questionnaire respondents	Number of different drugs involved
<i>Tablets</i>	86	30 different drugs
<i>Capsules</i>	15	8 different drugs
<i>Sachets</i>	2	1 drug
<i>Nebuliser solutions</i>	22	1 drug
<i>Transdermal patches</i>	20	2 different drugs
<i>Suppositories</i>	15	4 different drugs
<i>Enemas</i>	6	1 drug
<i>Intravenous injections</i>	22	13 different drugs

Within the largest two groups of respondents the breakdown of manipulations by dosage group can be seen in Table 12.

Table 12: Manipulations, by dosage form, reported by questionnaire respondents in neonatal and general paediatric areas

Dosage form	Manipulations, by dosage form, all manipulations reported	Manipulations, by dosage form, reported by those working in general paediatric areas	Manipulations, by dosage form, reported by those working in neonatal areas
<i>Tablets</i>	86 (45.7%)	31 (46.3%)	6 (17.6%)
<i>Capsules</i>	15 (8.0%)	5 (7.5%)	0
<i>Sachets</i>	2 (1.1%)	0	2 (5.9%)
<i>Nebuliser solutions</i>	22 (11.7%)	15 (22.4%)	0
<i>Transdermal patches</i>	20 (10.6%)	5 (7.5%)	6 (17.6%)
<i>Suppositories</i>	15 (8.0%)	4 (6.0%)	6 (17.6%)
<i>Enemas</i>	6 (3.2%)	3 (4.5%)	0
<i>Intravenous injections</i>	22 (11.7%)	4 (6.0%)	14 (41.2%)
Total	188 (100%)	67 (100%)	34 (100%)

4.9.2 Proportions of the original dose required

Of the 86 tablet manipulations, 46 (53.5%) were dispersed, 31 (36.0%) were cut and 9 (10.5%) were crushed to get a proportion of the original dose. 36% of these tablet manipulations were reported by nurses working in general paediatrics, 11.6% in oncology, 9.3% in paediatric surgery and in paediatric surgery/HDU, 8.1% in liver units, and 7.0% in neonatal areas.

For 40.7% (35/86) of overall tablet manipulations half of the original dose was required, for 14% (12/86) a quarter or three quarters of the original dose was required. For all of the reported tablet manipulations where tablets were cut or crushed the dose required was a half, quarter or three quarters. Where tablets were dispersed there was a wider range of proportions of the original dose required. For 29.1% (25/86) of all of the tablet manipulations and 54.3% of the manipulations where tablets were dispersed the proportion of the original dose of the whole tablet was not half, a quarter or three quarters of the original dose. With

these manipulations where tablets were dispersed the doses required were; 7%, 19%, 65%, 66%, 90% (one manipulation each), 20% (two manipulations), 40% (six manipulations), 60% (eight manipulations), and 80% (four manipulations). Table 13 describes the proportions of the original dose required from the manipulations of other dosage forms.

Table 13: The proportions of the original dose of the whole dosage form required for the manipulations reported by questionnaire respondents for capsules, sachets, nebuliser solutions, transdermal patches, suppositories and enemas (where the data is incomplete in this table it was missing in the questionnaire response)

Manipulations	Half of the original dose required	Quarter/three quarters of the original dose required	Other proportions of the original dose required
<i>Capsule manipulations</i>	33.3% (5/15)	13.3% (2/15)	33.3% (5/15) For each of these 5 manipulations the dose required was 6.7% (one manipulation each)
<i>Sachet manipulations</i>	50% (1/2)	None	None
<i>Nebuliser solution manipulations</i>	59.1% (13/22)	31.8% (7/22)	None
<i>Transdermal patch manipulations</i>	25.0% (5/20)	55% (11/20)	5.0% (1/20) For this manipulation the dose required was 12.5%
<i>Suppository manipulations</i>	46.7% (7/15)	6.7% (1/15)	13.3% (2/15) For each of these 2 manipulations the dose required was 66.7% (one manipulation each)
<i>Enema manipulations</i>	83.3% (5/6)	None	None

With intravenous manipulations 68.2% (15/22) were for doses of <10% of the original dose (the smallest proportion was for 0.7% of the original dose), 13.6% (3/22) were for between 10% and 20% and 13.6% (3/22) were for 40% to 70% of the original dose.

4.9.3 Methods of manipulating suppositories, enemas and transdermal patches

Within suppository and enema manipulations there had been limited opportunity to observe them during the observational study (Chapter 3). Questionnaire respondents have provided further data; the 15 suppository manipulations reported involved four different drugs (glycerine, paracetamol, diclofenac, chloral hydrate). When asked about the manipulation method for cutting a suppository, 45.4% (69/152) of those who completed this question reported that they had 'never cut a suppository'. Of 82 of those who would cut suppositories 50 (61.0%) would cut longitudinally (from the pointed end to the blunt end) while 32 (39.0%) would cut transversely across the suppository, one respondent reported that they would use either method.

With enemas there were six manipulations described by respondents all were of the same drug (phosphate enema), 47.7% considered that a question asking for details about enema manipulations were 'not applicable'. Of the 77 of those who would manipulate enemas 51(66.2%) would discard an unwanted portion from the original pack to leave the dose to be administered, 15 (19.5%) would administer the required portion from the original pack and discard the remainder and 9 (11.7%) would withdraw the required portion and administer it (the remaining two respondents said they would manipulate enemas but did not specify the method they would use).

A similar question involving transdermal patches (20 manipulations reported involving two different drugs, glycerol trinitrate and hysocine hydrobromide) found that 24.8% considered this type of manipulations 'not applicable' to them. Of the 113 who would manipulate transdermal patches 73(64.6%) would cut the patch and apply a segment, 31 (27.4%) would cover the segment of the patch not to be used and 7 (6.2%) would use either method (the remaining two respondents said they would manipulate enemas but did not specify the method they would use).

4.9.4 Reasons for the manipulation

For each manipulation for which they provided details, respondents were asked to provide the reason for the manipulation. For some manipulations respondents provided more than one reason for the manipulation:

- 75% (141/188) of respondents included no suitable preparation or strength of the drug available as a reason for manipulation
- 11.2% (21/188) of respondents included patient preference as a reason for manipulation
- 31.4% (59/188) of respondents included usual practice as a reason for manipulation

Table 14 details the reasons given for undertaking the manipulations.

Table 14: The reasons for the manipulations that they had undertaken in the previous month by questionnaire respondents, by dosage form Reasons for manipulation	All manipulations	Tablet manipulations	Capsule manipulations	Sachet manipulations	Intravenous manipulations	Transdermal patch manipulations	Nebuliser solution manipulations	Suppository manipulations	Enema manipulations
<i>No suitable preparation or strength available</i>	103 (54.8%)	46 (53.5%)	9 (60%)	0	4 (18.2%)	11 (55%)	18 (18.1%)	10 (66.7%)	5 (83.3%)
<i>Patient preference</i>	13 (6.9%)	13 (15.1%)	0	0	0	0	0	0	0
<i>Usual practice</i>	23 (12.2%)	8 (9.3%)	1 (6.7%)	1 (50%)	9 (40.9%)	3 (15%)	0	1 (6.7%)	0
<i>No suitable preparation or strength available & usual practice</i>	32 (17.0%)	7 (8.1%)	2 (13.3%)	0	1 (4.5%)	0	0	0	0
<i>No suitable preparation or strength available, usual practice & patient preference</i>	2 (1.1%)	2 (2.3%)	3 (20%)	1 (50%)	8 (36.4%)	5 (25%)	3 (13.6%)	4 (26.7%)	1 (16.7%)
<i>No suitable preparation or strength available & patient preference</i>	4 (2.1%)	4 (4.7%)	0	0	0	0	0	0	0
<i>Patient preference & usual practice</i>	2 (1.1%)	2 (2.3%)	0	0	0	0	0	0	0
<i>Other</i>	6 (3.2%)	3 (3.5%)	0	0	0	0	0	0	0
<i>Missing</i>	3 (1.6%)	1 (1.2%)	0	0	0	1 (5%)	1 (4.5%)	0	0
Total	188 (100%)	86 (100%)	15 (100%)	2 (100%)	22 (100%)	20 (100%)	22 (100%)	15 (100%)	6 (100%)

4.9.5 Policies, guidelines, procedures or worksheets

Respondents were asked if the hospital they work in has policies, guidelines, procedures or worksheets (set of instructions) on how to carry out specific manipulations. Respondents overall, and those working in general paediatric areas, gave similar answers with 58.8% and 54.5% respectively saying that there were policies, guidelines, procedures or worksheets (Table 15). Those working in neonatal areas reported higher availability of these resources with 88.1% responding that they had these forms of supportive documentation available.

Table 15: Availability of supportive documentation (policies, guidelines, procedures or worksheets) on how to carry out manipulations, reported by questionnaire respondents

	All questionnaire respondents	General paediatrics respondents	Neonatal respondents
Yes	58.8% (90/153)	54.5% (24/44)	88.1% (37/42)
No	22.2% (34/153)	25.0% (11/44)	7.1% (3/42)
Don't know	17.0% (26/153)	18.2% (8/44)	4.8% (2/42)
Missing	2.0% (3/153)	2.3% (1/44)	0
Total	153	44	42

Similarly respondents were asked when faced with measuring small volumes (i.e. less than 0.2mL) of liquid medicines for any route of administration, does the hospital they work in have policies, guidelines, procedures or worksheets. Again respondents overall and those in general paediatrics gave similar answers while those in neonatal areas reported higher availability of the supportive documentation, Table 16.

Table 16: Availability of supportive documentation (policies, guidelines, procedures or worksheets) on measuring small volumes, reported by questionnaire respondents

	All questionnaire respondents	General paediatrics respondents	Neonatal respondents
Yes	28.1 (43/153)	15.9% (7/44)	59.5% (25/42)
No	35.9% (55/153)	36.4% (16/44)	21.4% (9/42)
Don't know	33.3% (51/153)	47.7% (21/44)	14.3% (6/42)
Missing	2.6% (4/153)	0	4.8% (2/42)
Total	153	44	42

4.9.6 Reference sources

Following the question relating to supportive documentation for manipulations respondents were asked what publications and reference documents they would consult, if any, prior to manipulating a medicine. The BNF/BNFC was the most consulted reference source (Table 17).

Table 17: Reference sources that would be consulted by nurses prior to undertaking a drug manipulation, reported in the questionnaire

	All questionnaire respondents	General paediatrics respondents	Neonatal respondents
BNF/BNFC	80.6% (104/129)	86.8% (33/38)	66.7% (24/36)
Documents produced by the hospital and/or pharmacy department	62.0% (80/129)	63.2% (24/38)	75% (27/36)
Internet	6.2% (8/129)	5.3% (2/38)	5.5% (2/36)
Manufacturer instructions	11.6% (15/129)	15.8% (6/38)	2.8% (1/36)
Guidelines	4.7% (6/129)	7.9% (3/38)	2.8% (1/36)
Journals	0.8% (1/129)	0	0
Total (respondents who answered the question)	129 (24 respondents did not complete this question)	38 (6 respondents did not complete this question)	36 (6 respondents did not complete this question)

4.9.7 Measurement of small volumes

Questionnaire respondents were asked to list the drugs for which they had to measure small volumes of liquids (<0.2mL) and to indicate which route of administration they referred to. 65.4% (100/153) of respondents chose to answer this question, describing 306 cases where these small volumes were used. This question did not ask for further details; therefore the responses could not be further evaluated (as the manipulation data had been to ensure that it met the manipulation criteria). Nonetheless two small volumes responses were removed as they referred to transdermal patches. This left 304 cases of small volume measurement, details of which are found in Table 18. Of the 100 who provided answers to this question 35% worked in neonatal areas, 26% in general paediatrics, 5% in each of oncology and ICU, the remaining areas respondents worked in all represented <4%. The most frequent route of administration for drug doses that have required a small volume to be measured was intravenous. In 10.5% 32/304 drugs where a small volume is measured respondents reported that this could be for >1 route of administration (Table 19).

Table 18: The drugs where volumes of <0.2mL have been measured, as reported by questionnaire respondents

BNFC classification	Drugs involved	Frequency this classification reported as having small volumes measured >5 occasions	Percent age
<i>Vitamins</i>	Vitamin K, Folic Acid, Vitamin D	40	13.2%
<i>Opioid analgesic</i>	Morphine, Diamorphine, Oromorph, Fentanyl	34	11.2%
<i>H2 antagonist</i>	Ranitidine	30	9.9%
<i>Heparins</i>	Enoxaparin sodium, Heparin, Dalteparin sodium	26	8.6%
<i>Antibiotics</i>	Gentamicin, Erythromycin, Vancomycin, Clindamycin, Flucloxacillin, Benzylpenicillin, Cefotaxime, Trimethoprim	23	7.6%
<i>Diuretic</i>	Furosemide, Amiloride, Chlorothiazide	23	7.6%
<i>Benzodiazepine</i>	Lorazepam, Midazolam, Diazepam	19	6.3%
<i>Insulin</i>	Insulin	13	4.3%
<i>Aldosterone antagonist</i>	Spirolactone	11	3.6%
<i>Steroids</i>	Hydrocortisone, Dexamethasone	9	3.0%
<i>Immunosuppressant</i>	Tacrolimus, Ciclosporin, Mycophenolate mofetil	8	2.6%
<i>ACE inhibitor</i>	Captopril	7	2.3%
<i>Calcium channel blocker</i>	Nifedipine	7	2.3%
<i>Drugs used in neutropenia</i>	GCSF	6	2.0%
<i>Other – BNFC classification reported 5 or fewer times</i>	Ondanestron, Omeprazole, Suxamethonium, Pancuronium, Levothyroxine, Diaxoide, Octreotide, Ursodeoxycholic acid, Domperidone, Adrenaline, Dinoprostin, Sodium phosphate, Calcium supplements, Potassium supplements, Phenobarbitone, Cyclizine, Dopamine, Caffeine, Vasopressin, Desmopressin, Digoxin, Somatropin, Paracetamol, Atropine, Hyoscine hydrobromide	48	15.8%
Total		304	100%

Table 19: The routes of administration for small volume doses, as reported by questionnaire respondents

Route of administration	All questionnaire respondents	Neonatal respondents
<i>Intravenous</i>	33.2% (101/304)	43.9% (50/114)
<i>Oral</i>	29% (88/304)	27.2% (31/114)
<i>Subcutaneous</i>	9.5% (29/304)	1.8% (2/114)
<i>Intramuscular</i>	2.6% (8/304)	3.5% (4/114)
<i>Buccal</i>	2% (6/304)	0
<i>Intranasal</i>	1% (3/304)	0
<i>Intravenous or Oral</i>	5.9% (18/304)	7.9% (9/114)
<i>Intravenous or Intramuscular</i>	1.6% (5/304)	3.5% (4/114)
<i>Intravenous or Subcutaneous</i>	1.3% (4/304)	0.9% (1/114)
<i>Intravenous or Intranasal</i>	1% (3/304)	0
<i>Intravenous, Subcutaneous or Intramuscular</i>	0.3% (1/304)	0
<i>Intravenous, Oral or Subcutaneous</i>	0.3% (1/304)	0
<i>Missing</i>	12.2% (37/304)	11.4% (13/114)
Total small volume measurements reported	304	114

4.9.8 Open-ended questions

The questionnaire ended with open-ended questions, aiming to ascertain the views and opinions of the nurses undertaking the manipulations.

Participants were asked if they took steps to avoid manipulations or to make them easier to achieve. 70.6% of those who completed this question (126/153) responded yes, with 100 participants providing further details. Of these 100:

- 55% would consult with a pharmacist. The reasons given for this included to get advice, to discuss whether more appropriate preparations or doses were available, or to see if the drug could be extemporaneously prepared in pharmacy
- 21% would consider using further dilution to allow the measurement to be made
- 16% would seek changes to the prescription so that the manipulation may not be necessary, such as seeing if it is possible to prescribe a different dose

or to use dose rounding or considering if the use of another drug is appropriate

- 10% would check if the drug is available in a more appropriate dose or dosage form
- 4% would consult the BNF/BNFC
- 4% would consult hospital based documents/intranet

The second open-ended question asked respondents if they had any concerns about the manipulations to obtain the required dose. 53.6% (82/153) chose to complete this question. Of these the largest group of respondents, 31 (37.8%), were concerned about the accuracy of the manipulated dose. Other concerns mentioned by respondents included those relating to possible errors in calculations for 3.7% (3/82), difficulties with getting some products to disperse for 3.7% (3/82), and concerns about the measurement of small doses or the impact of the dead space in syringes for 4.9% (4/82). Respondents also used this question to mention other aspects of manipulation. 20.7% (17/82) noted that they used colleagues (nurses, doctors, pharmacists) to consult with and the importance of this support. The importance of documentation such as guidelines, protocols, procedures, policies as reference sources was highlighted by 7.3% (6/82) of those who answered this question.

Finally respondents were asked for any additional information that they would like to give. Ten respondents chose to add comments. These mainly echoed points found in the data from the previous question about concerns they had, with comments relating to the need for clear guidance, difficulties with dispersing tablets and the importance of consultations with pharmacists. There were two further comments from respondents who worked in district general hospital children's wards. They considered that they had difficulty in obtaining paediatric medications as they were not working in a children's hospital.

4.10 DISCUSSION

4.10.1 Questionnaire design

The use of ward/unit managers to distribute the questionnaire preserved the distance and anonymity between the researcher and participant while still allowing for personal distribution. Anonymity was assured for respondents; potential respondents were not contacted by researchers to request participation and they were asked no personal details beyond establishing the type of clinical area they worked in, their qualifications and the town/city that the hospital they worked in was based. This aimed to ensure the validity of their questionnaire responses. The administration of the questionnaire within a work place environment would help facilitate the recall of work based data. This relied on the managers to distribute the questionnaires and may have impacted on the response rate as the completion of a questionnaire may be a low priority in a busy clinical area. The 153 questionnaires returned enabled the exploration of the aims of this survey. The pilot study and steering group had been utilised to ensure that the questionnaire was both comprehensible and not onerous to complete.

The limitations associated with purposive sampling, notably the possible introduction of bias, are acknowledged. Furthermore it is acknowledged that requesting retrospective recall of data is prone to bias. While the sampling used in this approach precludes generalisation of the results it did ensure a range of neonatal and paediatric units throughout the UK were represented. Although the largest groups of respondents worked in neonatal or general paediatric areas there was a wide range of general and specialist areas represented by respondents across children's hospitals, teaching hospitals and district general hospitals with neonatal/paediatric beds.

Many of the studies and experts who have written on questionnaire design make it evident that with many aspects of questionnaire designs their impact on response rate and questionnaire outcomes are equivocal. Nonetheless some aspects that were particularly pertinent to this questionnaire were implemented. With any questionnaire it is necessary to refine what can and should be included. It is

tempting to include many aspects of the topic area; however this can have a negative effect on the outcomes. Therefore, although there were many aspects of drug manipulation that could have been explored, the priorities were distilled into a small number of main aims that were used in the process of developing this questionnaire.

4.10.2 Drug manipulations reported

There were 188 manipulations reported that were considered to provide sufficient detail or data that met the definitions of a drug manipulation. As had been found within the observational study (Chapter 3), the drugs reported as manipulated by questionnaire respondents were predominantly those which are liable to be prescribed regularly in neonatal and paediatric settings. Again it was evident that drug manipulations are not applicable solely to drugs prescribed for rare childhood conditions.

Over 50% questionnaire respondents indicated that they were undertaking the manipulation they had just provided details of, on a daily basis, with a further almost 20% considering that the manipulation was undertaken weekly. This indicates that drug manipulations are a customary part of in-patient drug preparation and administration. Yet outcomes from the systematic review chapter (Chapter 2) revealed that there are substantial evidence gaps relating to drug manipulation.

Manipulations of tablets, sachets, capsules, nebuliser solutions, transdermal patches, suppositories, enemas and intravenous drugs were reported by questionnaire respondents. As anticipated, tablets were the most frequent representing 45.7% of those reported, with 11.7% for intravenous drugs and nebuliser solutions, 10.6% transdermal patches, 8% capsules and suppositories, 3.2% enemas and 1.1% sachets.

Comparison of the drugs manipulated from the observational study and the questionnaire found that there were 24 drugs found to have been manipulated in

both studies; while 30 drugs were reported only in the questionnaire and 29 found in the observational study but not in the questionnaire. Of the 53 drugs found as manipulated in the observational study 7 were noted only once; similarly with the 54 manipulations described in the questionnaire 7 were noted only once. Six of the drugs that had been included in papers within the systematic review were manipulated in the observational study (aspirin, enalapril, furosemide, lisinopril, oxybutynin, and warfarin) and four were manipulated in the questionnaire (aspirin, captopril, lisinopril, nifedipine). Both the observational study (Chapter 3) and this questionnaire took a cross-section of the drugs that were currently prescribed in the included clinical areas. As the questionnaire responses required retrospective recall it was not expected that it would return a complete list or even complete information on individual manipulations. These studies did not aim to provide a comprehensive list of manipulated drugs but to explore the scope of drug manipulation. The number of drugs that were identified as having been manipulated on only one occasion suggests that there are likely to be other drugs that require manipulation. Nevertheless what the outcomes from both this questionnaire and the observational study show is that there are evidently a variety of drugs being manipulated in practice. Consideration is needed to decide which of these should be prioritised for future research, for example should there be a focus on those with a narrow therapeutic index or on those that are most frequently manipulated.

For many of the manipulations the doses required were either half, a quarter or three quarters of the original complete dose of the single dose unit. However, there were a number of manipulations where other proportions were required. For the intravenous manipulations proportions from 0.7% to 70% of the dose in the vial were required. Dose calculation errors have been highlighted as a substantial cause of drug errors. This combined with what appears to be piecemeal local access to supportive guidance documentation may increase the risk of drug errors occurring alongside drug manipulations. Variation in the proportions required may add to errors with differing doses being calculated from the original dose.

One suppository and no enema manipulations were observed during the observational study (Chapter 3). The one study Kim et al. (2005) included in the systematic review (Chapter 2) which considered suppositories did not stipulate how that manipulation was done. These outcomes raised the question as to whether these dosage forms are not manipulated or if they are but there is a lack of information about them. Almost half of the questionnaire participants considered that suppository and/or enema manipulations were not applicable in their practice. Thus more questionnaire respondents considered that these manipulations were applicable to their practice than did not. So although they may occur less frequently there are drugs in these dosage forms that are manipulated. There were 15 suppository and six enema manipulations reported. The results of this questionnaire suggest that there is a lack of standardisation in practice. Of the respondents who would manipulate suppositories 61% would cut them longitudinally and 39% transversely, while with those who would manipulate enemas 66% would discard a portion and administer the remainder, 20% would administer the required portion and discard the remainder and 12% would withdraw the required portion from the pack and administer. The evidence base for this practice is known to be lacking and there is an inconsistent approach to the manipulation of these dosage forms. This raises further questions both about how these manipulations should be undertaken or if they should be being carried out at all? If these dosage forms are to continue being manipulated then how they are carried out needs to be further considered, with an aim of standardising practice. Similar inconsistency was found with the manipulation of transdermal patches, with 65% reporting that they would cut a segment from the patch and 27% that they would cover a segment. Again methods of manipulating these patches need further consideration and practice standardised.

4.10.3 Reasons for drug manipulations occurring

Outcomes from the observational study (Chapter 3) found that there are occasions where manipulations may be undertaken that are not necessary. There may be an

alternative preparation available which does not require manipulation. Patient preference for a halved tablet over an oral liquid was noted. Either a lack of access to the alternative preparation when required or the usual practice being to administer the manipulated medicine were also suggested as reasons why medicines may be manipulated where alternatives are available. This questionnaire further investigated this. Patient preference was given as the only reason or among the reasons for manipulation in 11% of the manipulations described by questionnaire respondents. All of these manipulations were of tablets, representing almost a quarter of the tablet manipulations reported. With 15% of the tablet manipulations patient preference was the only reason given for the manipulation. There has been little work previously completed on the preferences of children on how they take their medicines. Palatability reviews have noted that assumptions about children have been made using adult based data or based on very limited evidence (Davies and Tuleu, 2008). Reviewing what has been previously written about the ability and age at which children can swallow tablets shows little consensus (Yeung and Wong, 2005). Liquid based preparations may be easier to swallow but these outcomes suggest that there may be a preference from some for tablets, even where a proportion of them are required. Skwierczynski and Conroy (2008) noted that though liquid preparations may be available they are not always of a useful strength. It may be that the focus on developing liquid formulations may be appropriate for many drugs and the preferences of the majority of children, or it may be that the focus should be more on the development of solid dosage forms that are acceptable to children. The production of various products of the same drug that meet the differing preferences of children may not be reasonable for many drugs. It needs to be acknowledged that drug manipulations may occur to meet patient preference. Nonetheless the lack of a suitable preparation or strength, cited by 75% of respondents, remains the predominant reason for the drug manipulation.

For 31% of the manipulations described usual practice was included as one, or the sole, reason for the manipulation. Usual practice was the sole reason given for 12% of the manipulations, this included tablet, intravenous, transdermal patch, capsule,

sachet and suppository manipulations. While usual practice may be a logical and reasonable approach to some practice it does raise the question of how much this is accepted and whether usual practice should be questioned more. Nilsen et al. (2012) reviewed the role of habit in clinical practice, they considered that much clinical practice occurs in stable healthcare contexts and can be assumed to be habitual, making it unlikely to be spontaneously reconsidered. There is a current substantial emphasis in healthcare on the use of evidence to base decision-making on. This emphasis may encourage more spontaneous questioning of clinical behaviour that may be due to usual practice, as these questionnaire responses suggest that some drug manipulations are. This further reinforces the need for the provision of and the regular revision of existing policies

4.10.4 Reference documentation

Consideration of the sources of supportive information used by nurses undertaking manipulations revealed that a substantial proportion (around 40%) either did not have access to, or did not know if they had access to, relevant local documentation (policies, guidelines, procedures or worksheets). Those working in neonatal areas had more access to supportive documentation with 88% reporting that they had access to local documentation. This may be related to the considerable use of intravenous drugs in this area as with intravenous injections there is drug policy documentation available in most hospitals.

This lack of local supportive documentation is concerning as nurses who returned this questionnaire principally reported that they access the BNF/BNFC if they consulted any reference source prior to manipulating a medicine. As described previously (Chapter 1) many of the medicines given to babies and children are unlicensed or are being used off-label. Even where the original medication may be licensed for use in children, manipulation will often not be recommended by the pharmaceutical company. Therefore sources of information available to healthcare professionals for the licensed use of medicines, for reference purposes, may not be applicable. Those who prepare the BNFC note that many drugs used in children are

used outside their licence and may not have been studied in adequate detail in children. The BNFC includes information on drugs when there is sufficient evidence for the drug to be considered relatively safe and effective in children (<http://www.bnf.org>). However for some drugs information is very scarce and their use may be limited to specialist centres, by clinicians with specialist expertise and knowledge of these drugs. In such cases, until the evidence is better established, the BNFC omits information about the drugs (<http://www.bnf.org>). Therefore for some manipulations, the BNFC may be an appropriate and useful source of reference. It is likely that for others the required information may not be available. This may mean that there is more reliance on local documentation which makes it more of a concern if such documentation is not available or when there is a lack of awareness of what is available.

4.10.5 Measurement of small volumes

This questionnaire has identified that there are a considerable number of drugs that those working in neonatal and paediatric practice consider they measure in doses of <0.2mL. This was not initially included within the investigation of the manipulations but arose during the quantitative review of prescription data that was completed concurrently with the observational study. A recent study of paediatric drug administration identified that 7.4% of 71 218 intravenous doses evaluated required less than 0.1mL of drug to be measured (Uppal et al., 2011). Previous studies have shown that the accuracy of small drug volumes drawn up by clinical staff is inconsistent (Parshuram et al., 2008; Isaac et al., 2010). Proposed reasons for this inconsistency include inaccuracies in the equipment (Bhambhani et al., 2005; Erstad et al., 2006) and human error (Taxis and Barber, 2003a;2003b). The answers to the open question asking for examples of small volume measurement indicated that this measurement may go beyond intravenous injections with several other routes of administration also mentioned. Further consideration is needed as if the measurement of these small volumes is inaccurate and/or inconsistent then

there is the risk that the dose of drug administered to a child following the measurement of a small volume may be inaccurate.

4.10.6 Concerns about manipulations

Comments were made by nurses during the observational study (Chapter 3) that had illuminated some concerns that they may have about manipulations. Although these comments had been noted, the question relating to concerns was designed as an open-ended one so that all possible responses could be represented and that there could be no risk of influencing the answers. It is accepted that those who choose to answer open questions may not represent all respondents (O’Cathain and Thomas, 2004). The chief concern reported by nurses related to the possibility that the dose that is administered following the manipulation is not accurate, that the manipulation did not successfully achieve the desired proportion of the original dose. Other concerns described included the risk of dose calculation errors, the measurement of small doses and the difficulties with dispersing some drug products. That there is awareness of possible dose inaccuracies shows that though manipulations may be an accepted feature of paediatric practice they are not instigated without thought about the outcomes. What are perhaps notable are the other possible consequences that were not mentioned, such as the effect that a manipulation could have on efficacy or any potential changes in adverse effects of a manipulated drug. A survey on off-label prescribing among GPs found that 50% of respondents were concerned about the lack of paediatric dosage information and appropriate formulations (Ekins-Daukes et al., 2005). As with the respondents to this questionnaire there was a lower rate of concern about other aspects of this with 15% reporting specific concerns about side-effects or unevaluated efficacy (Ekins-Daukes et al., 2005).

4.11 CONCLUSIONS

That drug manipulations are a feature of clinical practice has been established. This questionnaire study provides insight into the nature of drug manipulations. These do not solely involve tablets, the dosage form at least discussed if not methodically investigated in previous research, but are found across all dosage forms. Furthermore manipulations are a usual feature of practice with over half of those describing manipulations having noted that these were events that they undertake daily. However, supportive or reference documentation on conducting drug manipulations is often lacking. This questionnaire has revealed several areas for future research. These include; consistency in the practice of manipulating suppositories, enemas and transdermal patches; that manipulations may occur for reasons other than the lack of the required strength of the drug, and the measurement of small volumes.

This questionnaire study and the observation based study (Chapter 3) have described the range of the use of drug manipulation in paediatric in-patient practice. The results of these studies have been published (Richey et al., 2013).

However, for many children taking medications will be based at home. Therefore in investigating drug manipulations and identifying areas for future research it is important to consider manipulations that will be undertaken in the community setting.

CHAPTER 5: PARENT STUDY

5.1 INTRODUCTION

Through the legalisation introduced by the EMA and FDA and the development of organisations such as the European Paediatric Formulation Initiative (EuPFI) there is an increasing focus on the need for appropriate paediatric formulations to be available. Attention needs to be given to what this means to those children who are actually taking the medications. This will be particularly pertinent for those children who are likely to need to take prescribed drugs for a prolonged period, for whom there is no definite end point when they will no longer need to take medications. The incidence of chronic illness in children has increased; approximately 14% of children in Britain now have some form of chronic illness (Fisher, 2011). Not all of these children will require long-term drug treatment; nonetheless the need to administer on-going medication to a child for a chronic condition is not an unusual occurrence. Though there may be periods spent as hospital in-patients, for many of these children their predominant treatment will be as an out-patient. Furthermore there is a shift towards providing home-based care for children with chronic illness (Ziaian et al., 2006). Consequently for many children the administration of the majority of their prescribed drugs will take place at home. For these children adhering to long-term medication regimens may be challenging. Dimatteo (2004) reviewed the role of effective communication in fostering adherence to paediatric treatment regimens. This author noted that paediatric chronic disease treatment regimens can be prolonged and stressful, and can adversely affect quality of life both of paediatric patients and their families. With the administration of medications to children at home there is reliance on both the commitment and on the understanding of their parents (Breatkreutz and Boos, 2007). A lack of research has been noted relating to the understanding of parents' views about giving medicines to children. Sweis and Wong (2004) described that little is known about parental attitudes and the extent of their knowledge regarding medicines for their children. These authors further commented that the lack of knowledge is unsettling and a possible solution may be found through qualitative research with parents.

5.2 CHRONIC CHILDHOOD CONDITIONS

The impact of having a chronic condition on children has been previously researched. A systematic review of qualitative studies of children's experiences of living with juvenile idiopathic arthritis identified six themes. These were: an aversion to being different, striving for normality, stigma and understanding, suspension in uncertainty, desire for knowledge and managing treatment (Tong et al., 2012).

Furthermore, there is widespread recognition that the presence of a child with a chronic condition can be a source of stress and distress among family members (Herzer et al., 2010). The nature and process of parenting has to be restructured to raise a child with a chronic health condition and this has consequences for the entire family (Ray, 2002). Studies that have investigated this have found many aspects can be affected, such as the effect on intrapersonal and interpersonal relationships, medicalising parents, disrupting family norms, coping strategies and support structures (Tong et al., 2008). Research findings have been mixed. The literature has highlighted the variability in family functioning across chronic paediatric conditions (Herzer et al., 2010). A systematic review on the needs of parents with chronically sick children found that, following diagnosis, parents needed to regain a version of normalcy, required information regarding their child's condition, and wanted to be regarded as partners in the care of their child (Fisher, 2001). For many families living with a child with a chronic condition uncertainty is a constant, even if the disease is under control or in remission parents know this can change (Cohen, 1995).

Studies have often not addressed any medication-related issues or considered the methods used to administer medications at home to children. While many studies have considered the impact of treatment, especially in relation to the need for knowledge and information (Tong et al., 2008; 2012), they have not actually addressed administration or have reviewed administration only in the context of non-adherence (Schultz et al., 2012). A study that addressed supporting parents in

managing drugs for children with cystic fibrosis had to draw on studies with informal carers of adults to review problems that have been experienced with medication-related activities (Slatter et al., 2004). A model was developed around family-centred models of care-giving for children with chronic illness or disability and medical care was one of its six major sections (Ray, 2002). This medical care section included technical aspects (such as tracheostomy care or gastrostomy use) and symptom control but did not feature any reference to drug preparation or administration. Walsh et al. (2011) noted that there has been little attention paid to medication errors occurring in the home and they investigated this in parents of children with sickle cell disease and seizure disorders. They concluded that home visits and observation highlighted the complexity of the home medication use process and the numerous ways things can go wrong, such as medication preparation problems, and communication failures in the doctor's office and at home. This study also found that parents would sometimes alter the technique for administration from what the physician had told them to do either because they did not have the proper equipment at home or because the technique they were told to follow did not work at home (Walsh et al., 2011). These authors concluded that systems for medication use at home are complex and error prone and that indeed they may be more error prone than systems in the hospital.

Where the support needed by parents in managing drugs for children with cystic fibrosis was considered it was found that medication was described by parents as conferring a degree of 'controllability' to a disease and a certain amount of protection (Slatter et al., 2004). This was considered to be balanced with more negative views, such as concerns about side-effects, some distrust of the medication, practical problems (such as unpleasant taste), problems of obtaining supplies, sheer quantities of medications and time-consuming regimens. Overall the benefits were commonly perceived to outweigh the concerns (Slatter et al., 2004).

5.3 MEDICATION ADHERENCE

5.3.1 Medication adherence – general

Adherence involves the accurate observance by a patient of a prevention or treatment regimen set out by a health professional (Dimatteo, 2004). Medication adherence refers to the degree to which the medications taken reflect the prescriber's intention (Dean et al., 2010). Non-adherence to medicines is known as a substantial difficulty within all aspects of healthcare with an obvious potential impact on the efficacy of treatments, poorer patient outcomes and the use of scarce healthcare resources (Dean et al., 2010; Clyne et al., 2012). Poor adherence to medication regimens is considered to be a common problem with life-threatening disorders (Zindani et al., 2006). With chronic conditions the long-term maintenance of adherence is critically important as disease management maybe life-long and can pervade every aspect of daily life (Dimatteo, 2004). Reasons given for poor adherence include extended treatment duration, multiple medications, and periods of symptomatic remission (Gardiner and Dvorkin, 2006). Much of the evidence and most existing reviews on adherence has been derived in adult populations (Dean et al., 2010; WHO, 2010). In describing medicines adherence in Europe, (Clyne et al., 2012) reflected that there are numerous gaps in knowledge about reasons for non-adherence (both intentional and non-intentional) and evidence of how to reduce non-adherence remain elusive. Costello et al. (2004) noted that with the advances in medical therapeutics during the past two decades it seemed reasonable that non-adherence studies or research on effectiveness strategies would flourish. However, Gardiner and Dvorkin (2006) considered that, on the contrary, the literature concerning interventions to improve medication adherence remains surprisingly weak, and that this contrasts with the rigor applied to drug trials.

5.3.2 Medication adherence – children

Adherence to medicines in children provides particular challenges, requiring both compliance from the child and a committed parent or caregiver (WHO, 2010).

Estimates of non-adherence or non-compliance range from 25% to 60% of children or adolescents, figures considered to be greater than those reported in adults (Costello et al., 2004). Reasons suggested for non-adherence within children include an inability to swallow tablets, an aversion to taste, feeling unwell and subsequent refusal to co-operate (WHO, 2010). Other reasons that have been suggested include the influences of parents, such as parents' lack of understanding of the diagnosis, concerns about drug therapy effectiveness, and fear of medication side effects (Gardiner and Dvorkin, 2006).

Where adherence has been investigated in children studies have focused on whether or not the medication was taken. The impact of achieving adherence has not been considered. Furthermore, any actions that may mean that the medication has not been taken as it was designed to be taken have not been investigated. These actions include the use of drug manipulation, or the addition of the medication to food or drinks. Where these have been considered it has tended to be a feature of general discussion.

5.4 PALATABILITY

5.4.1 Palatability – general

Palatability is likely to have an effect on adherence to medication regimens. The ability to take medicines and/or palatability of the medicines may be particularly relevant where they are used in the treatment of long term conditions as this may impact medication adherence (Standing and Tuleu, 2005). Palatability of paediatric oral medicines is considered to be crucial in influencing adherence to therapeutic regimens and consequently therapeutic outcomes (Cram et al., 2009). Though it should be remembered palatability can be affected by more than taste as somatosensory modalities such as touch, temperature, appearance and perhaps most importantly smell may be significant (Davies and Tuleu, 2008).

5.4.2 Palatability – children

A literature review on interventions to improve the use of medicines in children found that evidence specific to paediatrics is limited and considered that available compliance and adherence studies were insufficient to allow conclusions to be drawn (Costello et al., 2004). This review noted that ensuring that the child has a convenient, palatable, easily administered medication with minimum effect on lifestyle is intuitively attractive, but the contribution of various influences on this requires further study. Furthermore, Ziaian et al. (2006) discussed that studies on health related quality of life, in patients with chronic conditions, have largely focused on the relationship with clinical status alone and have not considered the relationship with treatment time and treatment hassle.

Difficulties with the palatability of medicines and/or with the child's adherence to a medication regimen can put parents in a problematic situation. Their wish to ensure their child takes their prescribed medications may be in conflict with their sympathy for their child's preferences. Parents may deploy a range of strategies to ensure that the medication is taken. However, the practical ways that parents deal with this problem have not been described. This current study, by considering the actual process of drug administration and drug manipulation, will add to previous work relating to children and add to the discussion on methods of improving adherence.

5.5 DRUG MANIPULATION

With the manipulation of drugs to obtain the dose required for administration to children there has been a decision made to perform a manipulation. If the manipulation was not done then the child would either not get the prescribed drug, have an inappropriate (potentially either less effective or harmful) dose or have a different (possibly less appropriate for the purpose required) drug. There may be an effect on the efficacy and a risk of changing side effects with manipulating a drug, but these are balanced against the need for the child to receive the drug. It has been assumed in all of these considerations that the drug will be actually taken by

the child. What actually occurs within the home situation, where long-term medications are prescribed for children, is unknown.

There are no published reports about how parents describe manipulations, how they are supported (or not supported) by health care professionals or about the impact of manipulations.

5.6 STUDY OBJECTIVES

There is a lack of paediatric drug related research; specifically that work that has investigated children with chronic conditions has not investigated any impact of the ongoing medication regimens. Therefore, this study will be exploratory, and in considering the administration of drugs to children by their parents/carers, will help to clarify areas that may be appropriate for future research.

This study aims to explore the methods parents/carers use to assist them to administer medications that are being prescribed for long-term use to their child/children. This will include where the child may be reluctant to or has difficulty in taking the medicines and where manipulation of the medications is required to get a dose which is a proportion of the dose in the intact dosage form.

This will include exploration of the following issues relating to taking long-term medication:

- skills/methods developed to administer medicines
- issues relating to the ability of the child to take medicines, including dosage form preferences
- where manipulation is required;
 - how it is undertaken
 - the issues that parents have relating to the manipulation
 - any supportive information or advice that was helpful or would have been helpful if given

- relationships with any HCPs which may have proved beneficial, who advice is sought from, and the type of advice which proved useful
- any effect on the child/parent relationship

Approaching parents to investigate how they undertake manipulations, and their views on them, provided the opportunity to additionally explore how they administer medicines to their child. This allowed the framing of manipulations within the real-life context that occurs for children and parents, that is that if drugs are being manipulated by parents then this will be within all other medicine-related aspects of their child's condition.

5.7 PARTICIPANTS AND RECRUITMENT

5.7.1 Participants

Children cannot be treated as a homogenous group. Varying developmental capacities of children and adolescents may influence medication adherence (Dean et al., 2010). Adolescents have psychosocial and lifestyle issues, adolescent non-adherence has to be seen in the context of adolescent development (Rianthavorn and Ettenger, 2005). The differences between younger children and adolescents have been acknowledged in previous studies, such as where adherence to treatment in cystic fibrosis was considered using two groups, those less than 12 years old and those 12 and over (Zindani et al., 2006). Their analysis showed that there was a non-significant higher rate of adherence with the younger group. It has been intimated that while solid dosage forms are more accepted by older children, that younger children and their carers tend to prefer liquid formulations (Cram et al., 2009).

Previous work has suggested that drug manipulation occurs across all ages of children (Skwierczynski and Conroy, 2008) and the outcomes of the observational study (Chapter 3) have supported this. Nevertheless it was important to select the age of children to be included in this study. Adolescents were excluded in recognition of the differences between them and younger children. With the

changes that occur in this age-group adolescents, as a group, should be considered separately. Children of primary-school age were included as, at this age, the child will be able to express opinions about taking their medications but will be predominantly reliant on their parents/carers. Children's use of medicine at this age is still controlled by their parents (Hameen-Anttila et al., 2011). According to observation and previous experience the medication intake of those younger than twelve was expected to be supervised closely by their parents (Zindani et al., 2006). Studies have indicated that when considering any issues relating to the administration of medicines to younger children that parental/carer involvement within any research is imperative (Matsui, 1997). The involvement of carers in the management of medication potentially introduces a third party to the consultation who have their own, and differing views regarding the need for medication (Slatter et al., 2004). Children are in a unique situation, in that they are dependent on their parents for medication administration, but can display oppositional behaviour when medication is being delivered (Schultz et al., 2012). Therefore, the current study involved interviews with parents/carers of primary school aged children where the child (or children) requires long-term medication.

As has been used previously (Ziaian et al., 2006), to ensure the focus is on chronic rather than acute management; all children had their condition for at least one year prior to the study. Furthermore all of the children had to be taking medications orally, those having medications administered via nasogastric or gastrostomy tubes were excluded. Those who are having medications administered in this way may well require manipulated medications; however this group are liable to have their own specific manipulation related circumstances and merit their own investigation.

5.7.2 Sampling

Purposive sampling was used to identify potential participants. This study aimed to act as an initial exploration of this area; as such it does not make any claim to representativeness. Participants were selected on their ability to provide data relevant to the area under investigation. This approach to sample recruitment will

provide rich data that addresses the research objectives (Horsburgh, 2003; Shaw et al., 2006).

Potential participants were identified by the clinical teams reviewing them at rheumatology and renal out-patient clinics in a specialist tertiary children's hospital. These particular clinics were selected as they are likely to include children who have considerable medication needs and are often managed predominantly on an out-patient basis (this was confirmed following a discussion I had with a paediatric consultant). They were asked to initially approach parents/carers, describe the study to them and provide them with information leaflets. These parents were then contacted, invited to ask any questions about the study and asked if they wished to participate. Parents were offered their choice of interview location either at home or at the hospital; all chose to be interviewed in their own homes.

5.8 METHODS

This study used semi-structured interviews. This allowed for a core set of topics to be used in the interview with the flexibility for the exploration of additional topics, experiences and perceptions that may arise during the interview. I devised an interview prompt guide (Appendix 5) for the interviews that was reviewed by clinical and research experts. This guide was also reviewed during the study as part of the process of constant comparison (see section 5.10.2). This allows for the exploration of topics that arose during the analysis, as described in previous studies using this method, such as (Shilling et al., 2011a; 2011b). I completed brief field notes immediately following the conclusion of each interview. These detailed what I considered to be the key points of the interview and any overall impressions about how the parents found the interview. All interview recordings were transcribed verbatim for analysis, transcription undertaken externally.

5.9 ETHICAL APPROVAL

I applied for and obtained ethical approval for this study was provided by a UK National Health Service research ethics committee (NRES Committee West Midlands - The Black Country, Rec Reference 12/WM/0267). Written informed consent, including consent to be audio-recorded, was obtained from all participants prior to their interview. The protocol and interview prompt guide for this study were reviewed and approved by the Alder Hey NHS Children's Foundation Trust research review committee (Reference: 12/24/RE).

Participants were assured of the confidentiality of the interviews and that they could withdraw from the interview at any time. Though participants were identified through their child's attendance at out-patient clinics they were assured that the interviewer was entirely independent of the clinical team and that their interview responses would be treated confidentially.

As the interview centred around drugs prescribed for the child involved, it was possible that interviews could reveal that these were not being administered. It was agreed within the ethics approval that if the interviewer had any concerns relating to this then these would be discussed with a paediatrician, who was independent of the child's clinical team, and a judgement made about safeguarding.

Following explanation of the study and an invitation to ask any questions, participants were asked to sign an informed consent form that included consent to audio-record the interview.

Parents were provided with the choice of whether to be interviewed at home or in the hospital research unit. The hospital lone worker policy was consulted and followed for all home-based interviews. This involved ensuring that a member of hospital research staff was aware of the time of the interview and the address that it was occurring at; I then contacted this person following completion of the interview to inform them that it had been completed.

5.10 ANALYSIS

5.10.1 Rationale for the approach used

Analysis was based on the principles of the constant comparative approach. Constant comparative analysis was originally an integral part of grounded theory, of Glaser and Strauss, as part of theory development, with emergent categories forming interrelations that ultimately form the emerging theory (Thorne, 2000; Bowen, 2008). Constant comparative analysis comprises four stages; comparing incidents applicable to each theme that emerges from the data, integrating themes and their properties, delimiting the theory, and writing the theory (Bowen, 2008). The comparing and contrasting of categories to see how they cluster or connect together helps to build, densify and saturate the categories and is a vital step in forming the scaffolding in the final substantive theory (Coyne and Cowley, 2006).

Some qualitative analytic strategies have taken an approach using the principles of constant comparative analysis. Though constant comparison is associated with grounded theory, these other strategies draw from this analytic strategy to create knowledge that is generally descriptive or interpretative, this has been used in areas such as coping with cancer, or living with illness (Thorne, 2000). Studies using the constant comparison principles of analysis involve systematic coding procedures. Open codes serve to reduce textual data into manageable groupings, these are checked and rechecked across the data, codes are clustered into substantive categories that are compared across interview transcripts. There is continual comparison of newly gathered data with the codes that have been developed (Bowen, 2008). This procedure does not aim to generate theory but uses the constant comparative approach to develop categories from the data. This type of constant comparative approach has been used to continuously compare the views and experiences of respondents. Where the purpose is to generate knowledge about themes within the human experience this process compares each new interview or account until all have been compared with each other (Thorne, 2000).

The use of constant comparison goes beyond content analysis to develop nuanced descriptions of the lived experience (Hsieh and Shannon, 2005). This type of analysis has been used to explore aspects of healthcare, such as in investigating ventilator-dependent children and adults (Dybwik et al., 2011), the use of complementary therapy by patients and parents of children with asthma (Shaw et al., 2006), or the impact of treatment demands on the patients and siblings of those with cystic fibrosis (Foster et al., 2001).

Specifically in relation to children and their medicines, this method has been effectively used as part of a project that considered parents' experiences of their child's suspected adverse drug reaction (Arnott et al., 2012a) and enhancing parental participation in pharmacovigilance (Arnott et al., 2012b). This method has also been used to investigate the recruitment to randomised controlled trials involving children (Shilling et al., 2011a) and parents' experiences of their child's presence in discussions with physicians about leukaemia (Young et al., 2011).

These studies exemplify the use of constant comparison principles, the continual review of data and emerging analysis throughout the study process. This does not lead to theory development as it would where grounded theory was being used. It does however provide detailed description and analysis of the views and experiences of those involved.

Within healthcare research using a constant comparison approach through this cycling between the data and analysis through discussion can allow the developing analysis to also be judged on catalytic validity (Wright et al., 2004). Catalytic validity is that the analysis should not merely describe, but should have the potential to influence and change practice or research (Wright et al., 2004; Salmon et al., 2007; Arnott et al., 2012a). As observed by (Arnott et al., 2012a) where the aim is to inform practice and the methods applied should fit with this aim and the criterion of catalytic validity.

Within these studies the analysis followed the general principles of the constant comparative method and was informed by several steps to ensure its quality. Within this parent/carer study analysis I followed these methods with specific

reference to those studies which included interviews with parents (Arnott et al., 2012a; 2012b).

5.10.2 Approach used in this study

I entered the verbatim transcripts of the interviews and field notes recorded immediately following the interview were entered into NVivo 9, qualitative data analysis software, for analysis. Initially analysis was commenced through the repeated reading of transcripts, though I had completed the interviews this approach ensured in-depth familiarity with the interview data and assisted with the development of the coding process. Subsequently the coding process was developed. Initially through line-by-line open codes, this process provided a large numbers of initial codes that were then refined into broader more substantive categories. These codes were continually compared across each interview transcript and between interview transcripts. This comparison provided a framework for further categorisation into smaller and more specific coding categories which aimed to reflect the interview data. It ensured that similarities and differences across the transcripts could be recognised. The coding and subsequent comparison within and across categories was reflected on by clinical and research experts (Dr MA Turner and Professor AJ Nunn). A process of 'cycling' between the developing analysis and new data was used; this was refined and tested by periodic discussion with these experts. This discussion of the developing analysis helped to confirm and refine the categories. This discussion also provided the means to challenge and reform categories as new interview data was analysed. Quotes that correlate to the categories that arose through the analysis are used to illustrate these during the results. General issues relating to children requiring long-term medication were identified alongside the specific drug manipulation related issues. Though initially analysis focused on the participants' accounts this progressed to interpreting the accounts and considering what they chose to focus on in their responses. The use of an interpretative view will allow for consideration of not only the content of the data but the overall focus of what participants viewed as

significant for them. The field notes recorded following the interviews were referred to further when reflecting on the context of the interview and the areas of medication administration that the parents considered important to them.

In an area such as drug administration and manipulation for primary school aged children this exploration will provide a valuable insight both for those working within drug development and health care professionals.

5.11 RESULTS

Seven interviews were completed; all participants choose to be interviewed at home. I undertook all interviews which were between 24 and 67 minutes duration, with an average interview length of 39 minutes.

This study aimed to approach parents/carers and stated no preference as to whether mothers, fathers or both were being invited to be interviewed. Six of the seven interviews were with mothers, with one interview involving both parents. In one case the father had been the one initially approached by the clinical team but he deferred being interviewed to his wife. There were eight children involved; in one interview the parent had twins both of whom had a chronic condition. The children of the parents interviewed comprised four boys and four girls and ranged across the primary-school age spectrum (Table 20).

Table 20: Details of the diagnosis of the children of the parents interviewed

Interviews	Diagnosis (as described by parents during the interview)	Sex	Current Age	Age at diagnosis
<i>Interview 1</i>	Systemic juvenile onset arthritis	Female	10 years	5 years
<i>Interview 2</i>	Juvenile idiopathic arthritis	Female	5 years	2 years
<i>Interview 3</i>	Polyarticular juvenile rheumatoid arthritis	Female	10 years	3 years
<i>Interview 4</i>	Juvenile idiopathic arthritis	Male	8 years	5 years
<i>Interview 5</i>	Renal transplant, registered blind, thalassemia	Male	11 years	Birth
<i>Interview 6</i>	Neurological condition secondary to cardiac arrest, hemophagocytic lymphohistiocytosis (HLH)	Female	7 years	6 years
<i>Interview 7</i>	Cystinosis	Male – twins	9 years	6 years

5.11.1 The overall impact of having a child requiring long-term medication

It was evident from parents that the uncertain and probably on-going nature of their child’s condition has an impact on both their child and on them. They accepted that, in many cases, their child’s condition could be unpredictable and long-term.

“Well no-one can give us a guarantee; if anyone could give us a guarantee then we would be able to tell her exactly what’s happening” (Int 2)

“I don’t know we just take everyday as it comes to be honest. That’s just the best thing to do that’s the only way you can do it because you get things thrown at you every so often” (Int 7)

The consequences of their child’s condition and their medication requirements pervade many aspects of everyday childhood. This can be seen when parents described issues that they have had to think through and discuss with their child’s school.

“A lot of schools won’t give them medications will they while they are at school. So I was running over to the school and having to give her medications” (Int 1)

“because of her compromised immune system you have got to be very careful about being around people who have had chicken pox or measles and I am really worried that I do actually need to go to school and make sure they are fully aware” (Int 2)

Parents highlighted the additional stress that is caused by always having to consider their child’s medication, which impacts on many aspects of everyday life; such as when going on holiday, the child going to a friend’s sleepover or going out for the evening.

“Then of course we had the issue of if she went for tea at a friend’s house because you give the medication at a certain time, you don’t want to start moving times around, so if she had gone to a party that was going on all evening and was having a sleepover and then of course I had to turn up to give her the medication” (Int 6)

“So I get a bit fed up with it to be honest especially when it comes to going out for an evening and thinking, right ok have I got those with me, and holidays, when you go on holiday and you have to get all your prescriptions sorted and your letters sorted” (Int 5)

“It’s a nightmare! We went to Blackpool in July, we went in a caravan and we had to take everything!” (Int 7)

Additionally some of these parents had to collect prescriptions and drugs from the tertiary hospital pharmacy and could not access them locally. For some parents this required travelling some distance and was considered to cause extra and unnecessary frustration.

“So every eight weeks whether [child’s name] has an appointment or not somebody has got to trek to the hospital to get her prescription filled and it’s stressful.....I don’t think whoever makes these rules up really understands exactly what it is like ” (Int 1)

These persisting issues need to be managed as part of everyday life for a child and their parents where long-term medications will be needed.

Parents considered that when it comes to administering medication it is the on-going nature that can pose particular difficulties as unlike short-term prescriptions a child often cannot be told of a time when they will not need to take them.

“I think you can get away for a short period for administering any type of medicine sweet or foul tasting” (Int 6)

Parents also described how the relationship that they have with their child can be affected by the need to administer long-term medications to them. This relationship has already had to absorb and sustain the implications of their child’s condition.

“It is hard, as a parent it is hard, you don’t want to see them ill but then you don’t want to start getting them upset because they’ve got to take medication on top of everything else, that’s what’s hard” (Int 1)

“You have to be openly honest with them and just try and explain it to the best you can for them to understand why they have to do it. Because I suppose in a lot of ways of being a parent you have to be cruel to be kind don’t you!” (Int 4)

5.11.2 Issues with change

As described above there are wide-ranging effects on family and everyday life of a child taking long-term medications, often combined with uncertainties about the future of the child’s condition. Consequently, where families felt that they had achieved some stability in the current situation they found changes challenging. This wish not to disturb the *status quo* that they had reached may have caused some of the anxiety that was described when handling changes to the medications that their child is prescribed; unless there were evident benefits to the change. Parents, at times, found prescription modifications and the attendant uncertainty relating to the outcomes of this change difficult. The support of healthcare staff in effecting the change was important.

“I don’t like it when you start a new medication and then they say – this could lead to this, that and the other and because it’s not we don’t know if it will lead to this, that or the other” (Int 3)

“I was really, really upset to be honest that he had to go on another medication that would lower his immune system even further than it was” (Int 5)

“I was really, really upset about it to be honest that he had to go on another medication.....she [hospital nurse] went away and she got me loads of information, she got me print-outs, she got me leaflets, she got me all sorts of information on it and they went through it with me” (Int 6)

Parents expressed reluctance, at times, to change between dosage forms, notably where they were offered solid dosage forms like capsules or tablets in preference to oral liquids. Though, as some parents correspondingly commented on their own reticence when faced with taking tablets, this may have been a factor in their perception that their child is unable to or is very reluctant take tablets.

“If I was to be asked to give [child’s name] capsules, I know for a fact she wouldn’t be able to swallow them because of the size of them” (Int 1)

“I could just see it being sat in her mouth for ten minutes and still not being swallowed.....it’s a different battle whereas we know the battle with the oral [liquid] side of it we know how to do it quite well now” (Int 2)

“No he still hasn’t got the gist of it yet but I don’t think it helps because I’m not very good with it [swallowing tablets] either” (Int 4)

Parents expressed a need for familiarity with their child’s treatment and usual drug products. They described their uneasiness with the disruption that could be caused when the prescribed drugs were unchanged but they were faced were unanticipated (often seemingly unwarranted) changes in the dispensed drug products that they receive.

“I mean by that point she was quite used to the medicines and so the fact that it had changed and we said it was the same medicine wasn’t sitting well with her really” (Int 2)

“Then they changed the packaging and they changed how you fill it up.....I think the last one they did it was meant to be easier.....because you’ve got to mix it up and you just forget, you know I’ve slept since the last time I did it, I can’t remember how much ” (Int 3)

“When I got a prescription filled two months ago they had no liquid so they gave me tablets and I just couldn’t dissolve them.....then a week later the medicine was back” (Int 5)

5.11.2.1 Relationship with health care professionals

These interviews revealed that parents generally found both the relationship with health care professionals and the information that parents received from them to be constructive. The main source of support was the tertiary hospital and the staff who work there are most likely to be contacted. The provision of support from this centre was highly regarded by parents. Local services, such as general practitioner (GP) surgeries, were viewed as not aware enough of either their child’s condition or the medications they were prescribed.

“I’ve never been sat here waiting in limbo – are they [hospital staff] going to ring me back? They have always rung me back and they’ve always answered every question I’ve ever wanted to know” (Int 1)

“I remember having issues, it must have been a couple of months after they’d started taking it and they’d given me an emergency number for the Saturdays.....so I phoned the ward.....they were really helpful” (Int 7)

“It’s been a bit of a battle this year to get our flu shots sorted out with the GP because I’ve had to explain numerous times [child’s condition] and she’s on [drug name] for that and therefore her immune system is compromised” (Int 2)

5.11.3 Adjustment over time

The chronic nature of their child's condition provided parents with a perspective on how their child had adjusted to taking medications over time. There were positive aspects, that the difficulties with administration had become more manageable as the child has increased understanding of their condition. Consequently, they had adjusted to taking their medications. Though for some the experience was negative that as time passed, though the child was accepting they had to take medication, they were increasingly exasperated or upset by it.

"Now that she's older she's got used to having what she's got it's kind of like, she doesn't bother now, she just takes it" (Int 1)

"He gets fed up with them, he does say to me 'here we go again', and I can understand that because I feel the same" (Int 5)

"The longer he was on it, it became more of a battle and it would be like the less he would have of it" (Int 4)

Parents considered that as their child got older and therefore could better understand explanations about the reason for their medications and consequently be negotiated with, subsequent administrations became less challenging.

"She's been on a helluva lot of medicines and it has been hard, but I think we are coming to a point now that because she is older it's easier to explain it to her because she understands that bit more now" (Int 1)

"But she's at that age where we were able to try and do some negotiation.....it sounds awful doesn't it, she almost resigns herself to the fact that she has to go through all of this" (Int 6)

5.11.4 Administration of medications

5.11.4.1 'Battle'

It was evident from these interviews that parents do not, by and large, find the long-term administration of medications to their primary-school aged child a straightforward process. It was clear that this is true for both the child and their parents. Parents described that, at times, the interaction was seen as a 'battle'.

"It's just always been hard thinking how am I going to and can I be bothered having this battle with her for her to have this tablet" (Int 3)

"We had a few times when we'd have to battle with him because he's crying because he doesn't want to take them" (Int 4)

"She knew, every morning we went through this – and she'd be going – no, I don't want to take it.....it was a battle every morning" (Int 6)

Though, this challenging set of circumstances was not true for all of the children involved, or for all medications.

"It was just really the [name of the medicine] that we had trouble with, all the others were fine" (Int 4)

"He's never said to me 'Mum I'm not taking them', I don't know what I'd do if he did to be honest!" (Int 5)

In one interview the parent did note that there were occasions where the difficulties with administration had meant that the child had not had their medication⁷.

"Again sometimes with the tablets we're just right she's not having them then, because it just wasn't worth the battle with her, the fallout from it, the arguing and the upset" (Int 3)

⁷ This parent was describing a medication that her child was no longer taking so discussion with the independent paediatrician was not required

Other parents described situations with where they struggled on with administration until they reached a crunch point where they turned to medical staff and, where possible, got the prescription changed.

“We’d got to the stage where I’d had to go to [hospital name] and say – look we are having a real battle and she’s now saying that the medication is making her sick and you know, to the point where we thought well ok let’s just take her off it and see how she goes” (Int 6)

5.11.4.2 Medication administration with food/drinks

Parents described the use of food and/or drinks to try and assist with administration, either to mask the taste or to make it easier for the child to take, or both. For some this included attempting to disguise the medication and administer it without the child’s knowledge. Several parents had been advised to use food or drinks by health care professionals though others had independently decided to take this approach.

“If she knew it [the tablet in the foodstuff] was in there then there would have been no way she would have taken it. I might as well have stood there and had the argument with her about swallowing tablets” (Int1)

“We tried to hide it in her drink but she wouldn’t drink anything” (Int 3)

“It was the ward.....it was them that said to me – use a bit of blackcurrant or orange if they won’t take it” (Int 7)

“But I really think you are left to try and work out how you can give this child the medicine you know, and I don’t think at any point I even thought about saying to the nurses – well I’m mixing it with milk, do you think that’s ok? You just do anything to get that medication down your child really” (Int 6)

Though the impact of this on the foodstuffs and the possibility of making their child suspicious of foods they were given was a concern for some parents.

“She loved her yoghurts so again to put it into her yoghurts but then of course your concern is that she’s going to relate that yoghurt afterwards to a disgusting medicine” (Int 6)

“We also have an issue about trying to hide it in food and things because if she found out we were doing it we felt that she’s feel betrayed by us” (Int 2)

5.11.4.3 Palatability

When parents were asked about medication preferences or changes that would help their child, there was a strong feeling that improving the taste of medicines or more availability of liquid medicines would have the most impact.

“If the volume was twice as much, if she had to have 10ml but it tasted nice, then I don’t think we would have the same problems” (Int 2)

“I think most of the problems with medicines is that the taste is never very nice and I think that’s the main thing. The [drug name] he’ll take that so easily because it was a sweet medicine and it was easy to take” (Int 4)

“It’s got to be, make it palatable for kids hasn’t it so they don’t think – ugh, that tastes horrible” (Int 5)

Taste was frequently mentioned, though it should be noted that this was not the only sensory aspect of medications that was mentioned as onerous for some children.

“We tried different flavours and one was quite a thin liquid and another was quite a thick liquid, and that was even worse to get down because it didn’t blend with the juice very well because it was a thicker texture” (Int 4)

“She said you need the powder from the thing [capsule]so they said to put it in blackcurrant or orange if they wouldn’t drink it because it smells disgusting” (Int 7)

5.11.5 Drug manipulations

In six of the seven interviews parents were currently, or had previously, undertaken drug manipulations prior to administering medications to their child. Descriptions given by parents included splitting of tablets and dispersing tablets. Two aspects of manipulations were evident in these interviews. Firstly, the information provided by healthcare professionals to parents on how to undertake manipulations was not consistent. Secondly these parents were predominantly not concerned about undertaking manipulations, though several described situations where the manipulation could have been perceived to have been problematic, such as tablets crumbling when they were split.

“If it was like half a tablet I would cut the darn thing and pray the other one doesn’t fly away!.....We had shattered halves so we just kind of scooped it in. No we didn’t have any major problems with it” (Int 2)

“Well I had to put it in water, obviously in a cup then I’d pour it out, obviously what I didn’t need and then keep what I needed in the cup and then pour the juice in it to give to her” (Int 1)

“We just tend to use a kitchen knife, if I remember rightly they’ve got a little line in the middle so it was quite easy to cut” (Int 4)

“I had a pill cutter from the hospital which just used to cut your tablets in half.....fine no problem with it” (Int 5)

“I think the knife is better than using the tablet cutter to be honest! Although it’s handy because it stays there then, you can keep it there for the next morning the other half if it doesn’t cut straight. I cut that one yesterday and that’s this morning’s one, it’s in three bits” [asked if the tablet often crumbled this parent replied Yes!](Int 7)

It appeared that, in general, parents did not express concerns about undertaking manipulations. Although, one parent did consider the possible effect of the manipulation on the accuracy of the dose that was obtained and subsequently administered.

“I did notice on the odd occasion that you can see the edges crumbling off so you hadn’t actually got a full half, you’ve got bits and pieces. So.....it’s not very accurate” (Int 6)

This parent was also the only one who described concerns about the impact of mixing medications with foodstuffs.

“Well if I’m mixing it with something acidic is that having an effect on the medication or if she’s taking it with dairy products, again is that having an effect” (Int 6)

In all of the interviews when parents were asked about manipulations they provided brief factual answers even when asked supplementary questions. With many other questions parent provided answers that were expansive and provided topic areas for further exploration, this did not happen when they were asked about drug manipulation.

The responses that parents gave to questions about drug manipulations provided a clear contrast to the very thoughtful descriptions that parents gave about other aspects of their experiences. This is illustrated where the brief responses about drug manipulations are reviewed alongside other depictions that parents gave of the quite meticulous approach they apply to other aspects of giving their child medications, such as; the care that they take to measure doses accurately, measures that they take to ensure that their child takes all of the dose or the actions they take to ensure that their child gets their medication at the correct time.

“I’ve crushed it up and put it underneath her cereal and then stood over her shoulder – ‘now come on you’ve got to eat all that” (Int 1)

“You know as a child you are told a teaspoon is 5 ml.....teaspoons aren’t 5ml, ours are all different amounts. So I tried with a teaspoon and I was – oh there aren’t 5ml there” (Int 2)

“It’s quite a viscous medicine, very, very, thick, very difficult to get the correct measurement” (Int 6)

“You do watch the clock all the time when you have to watch don’t you; you know for 12 hours, especially with anti-rejection drugs, they have to be within certain timescales” (Int 5)

5.12 DISCUSSION

This study used semi-structured interviews with parents of children who require long-term medication. There was no preference stated as to which parent was interviewed. It was interesting to note that six of the seven interviews were solely with the child/children’s mother; the remaining interview involved both parents. Even where it was the father who had been initially approached, this father chose to pass the option of being interviewed to his wife. This has been found in previous studies that considered care-giver time for children with chronic conditions and reported that there are substantial demands on maternal time (Ziaian et al., 2006).

The situations of the parents within this study must be viewed as directly applicable only to their own unique context. Nonetheless there are many aspects of the outcomes of this study that are likely to have relevance for other parents/carers of children taking long-term medications. Many of the consequences of childhood health problems are independent of the specific diagnosis since these children and care-givers experience common challenges and life experiences (Kohen et al., 2007). It is important to establish the parental view as parents model health behaviours and coping skills that will establish behavioural norms for their children (WHO, 2010).

Using interviews meant that it was a small sample of parents that provided the data relating to drug manipulations within the context of how parents administer long-term medications to their children. However, this approach ensured that topics that arose during the interviews and the nuances of drug administration to primary-school aged children could be explored. This also aimed to safeguard the honesty and willingness of parents to provide information as they were interviewed at home and not in the presence of other parents. The interviewer had no previous relationship with the participants and was not connected in any way to the clinical

teams responsible for their child's care. This lack of a pre-existing relationship between the interviewer and interviewee, and that they were unlikely to encounter each other again, has previously been considered to enable mothers to voice fears and concerns without fear of recrimination or judgement (Hodgkinson and Lester, 2002).

The key themes arising from these interviews were around the impact of a primary-school age child requiring long-term medication

5.12.1 Impact of long-term medication

Parents in this study described adjustments that were required in their family lives to adapt to their child requiring long-term prescribed medication and the uncertain nature of their child's condition. Fisher (2001) reviewed the literature relating to parents of chronically sick children. This author noted that it is clear that a change of lifestyle occurs for parents when a diagnosis of chronic illness is made and that health care professionals should be alert to the fragile nature of the coping mechanisms developed by parents. Previous studies relating to the needs/impacts of chronic conditions on family life have often not included medication – except in the context of wider treatment needs, such as physiotherapy with cystic fibrosis.

There were a number of practical issues raised in these interviews, issues that were not directly related to medication administration. Many children who have a chronic condition will be referred to, and have their major care decisions made in, large tertiary centres. For some this will require travelling some distance to attend clinic appointments. Participants in this study expressed frustration with disjointed links from the hospital to their local healthcare provision particularly with the need to obtain the prescribed medications from the hospital pharmacy which was some distance from where they live. These practical difficulties have been previously described as disruptive by a senior nurse writing on children and anti-epileptic drugs who considered that having to travel to a distant pharmacy to fulfil a prescription may represent an important obstacle for some families (Wilmot-Lee, 2008). The continual need to plan for their child's medication needs, such as in

relation to social occasions for child or parent, or going on holiday, or in discussions with their child's school was illustrated by parents during the interviews in this study. Parents have previously described that their child's condition had to come first, that any family activities required advanced planning and there is little opportunity for spontaneous activities (Hodgkinson and Lester, 2002). This study suggests that the effect of a child requiring long-term medication goes beyond medication administration and can impact across other aspects of normal life activities.

5.12.2 Issues with change and support of health care professionals

Parents in this study appeared ambivalent where prescription changes were required or new drugs needed to be introduced into the regimen. The support of health care professionals in supporting both the medication regimen and facilitating change was considered important. This supports previous findings that parents emphasised the value of information at the commencement of new therapy (Slatter et al., 2004). These interviews revealed the importance of the availability of health care professionals from the tertiary centre; this was especially notable where parents had questions or anxieties that they wanted to discuss without delay. The use of specialist secondary care as the first point for queries, in preference to primary care, has been previously described when the stresses and coping strategies of mothers of a child with cystic fibrosis were investigated (Hodgkinson and Lester, 2002). The importance to the parents in this study of effective communication between healthcare providers and patients/families is evident. Children and their families need to fully comprehend what they are being asked to do, and should be encouraged to question both to clarify understanding and to provide feedback about their experiences (Dimatteo, 2004). This may have implications beyond ensuring that families feel well supported and able to seek reassurance when required. Yin et al. (2010) investigated parents' medication errors and described parental errors with measuring doses. These authors noted the importance of clearly informing and ensuring parental understanding. Research

evidence supports the important role of effective communication in fostering adherence to preventive and chronic disease treatment regimens in the care of children and adolescents (Dimatteo, 2004). This interview study found that parents were positive and felt that overall they were well supported and informed by the children's hospital health care professionals. Nonetheless there did appear at times to be an *ad hoc* approach to how they received information about their child's prescribed drugs. This was particularly evident when it came to information about drug manipulations and the addition of drugs to food or drinks.

Some parents did express a misgiving as to whether primary healthcare services had sufficient understanding of either their child's condition or their medication. This reliance and trust in only the tertiary centres has been previously described. Parents of children with cystic fibrosis perceived their GP had less knowledge and some regarded their GP as an irrelevance when it came to their child's condition with all queries addressed to health care professionals in the tertiary centre (Slatter et al., 2004). It would be interesting to consider whether this is related to the process of achieving diagnosis and whether parents are more trusting of the health care professionals to whom their child was referred who provided the diagnosis and possible treatment options for their child. This reliance by parents on the tertiary centres may be further influenced by the requirement for some to collect prescribed drugs only from this centre with no more localised availability.

5.12.3 Administration of medications

Parents in this study described a range of methods used to administer their child's medications, including using various food stuffs and drinks. It is not known with most of these drugs is whether this is an acceptable approach. It may be that using food or drinks to aid administration does not affect the drug and may be reasonable. The concern is that, for example, a crushed tablet or opened capsule may cause bioavailability changes either from the crushing or opening and/or from the mixing with food or drinks. The 'Use of Melatonin in Children with Neurodevelopmental Disorders and Impaired Sleep' (MENDS) trials considered

melatonin capsules mixed in water, orange juice, semi-skimmed milk, strawberry yoghurt and strawberry jam (Shah et al., 2008). This study reported a good percentage recovery of melatonin for all food products and considered that these results suggested that mixing melatonin in common beverages or foods is an acceptable method of drug administration to children, if they are unable to swallow capsules. This study considered the use of melatonin, a drug that is prescribed for children on a 'named patient only' basis, the conclusions had to be viewed with the caveat that the lowest and highest effective doses of melatonin in children have never been determined (Shah et al., 2008). Nevertheless, this study concluded the mixing of this drug into food or drinks to be acceptable, though they noted that there could be differences in bioavailability between those taking melatonin with food and those not (Shah et al., 2008).

The MENDS study had surveyed parents of children with neurological disabilities to identify the commonly used food and drink vehicles (Shah et al., 2008). Similarly, Nissen et al. (2009) found that a variety of mixers were used where crushed or split tablets or opened capsules were added to food and drinks. These were jam, patient's food, water, custard, yoghurt, thickened fluid, juice and honey. Parents reported using various types of food and drinks to assist with administration. In some cases this was done with the aim of disguising from the child that the medication was being taken, while in others it was to mask the medication and make it easier for the child to take. It may be, if it can be established that the food or drink does not have an impact, that this is a useful and viable method to assist with administration. However, this is not known as the effects on the stability and bioavailability of mixing drugs into food or beverages are mostly undetermined (Standing and Tuleu, 2005; Davies and Tuleu, 2008). If a formulation is to be mixed in beverages/food, the dose accuracy, reproducibility and physiochemical stability issues should be considered in these vehicles (Pandit et al., 2010). In this current study several parents had discussed using food or drinks and they had been informally advised to do this by health care professionals. A study that investigated paediatric nurses' practice of mixing medication into foodstuffs found little consistency amongst those interviewed in how they actually undertook this (Akram

and Mullen, 2012). If there is no consistency within in-patient clinical areas then it is unsurprising that the advice and information that parents appear to be receiving is inconsistent and delivered on an *ad hoc* basis. Where the choice is balancing the use of food or drinks to administer the medication with the likelihood of non-adherence then it is rational to take the view that ensuring the drug is taken is the priority. However, this may not be sanctioned by those producing the drug. This also raises questions relating to the liability of the health care professionals involved either in mixing drug products into food/drinks themselves or advising parents to do so.

5.12.4 Adjustment over time

Parents portrayed that on-going administration of medications to their child could be problematic, with the word '*battle*' used to describe the interaction between parent and child. Although this was not applicable to all drugs, with parents describing situations where it would be straightforward to get their child to take one medication but that a different one would prove challenging. It was also not pertinent for all parents and children as one parent described a child who had always taken the various medications he was prescribed without difficulty. Though, this parent did nonetheless describe her child as 'fed up' with the unremitting daily routine of taking medications. These descriptions provided by parents in this study revealed that the administration could be a stressful process. The spontaneous description that used the term '*battle*' implies that this has an impact on both the child and their parent. Even where a child takes the medications with little protest the, often daily, repetitive nature of the process has an effect. It appears that, for some, with time the child may become accustomed to taking medications and with an increased understanding of why they need to take them administration can become easier. Fiese and Everhart (2006) reviewed medical adherence and childhood chronic illness and discussed that parents typically establish behavioural norms and model health behaviours and coping skills for their children. This study

indicates that the child and their parents take time both to adjust to the medication regimens and also, at times, to adapt to changes in this regimen.

Parents in this study described how they engaged in negotiation with their child to ensure that their medication was taken. Only one parent acknowledged that there were occasions where their child had not taken their prescribed medication. The other parents described persisting and ensuring that their child took the medication or in some instances discussing their difficulties with medical staff and, where possible, changing the prescription. It is acknowledged that there may have been reluctance in interviews to admit occasions where their child did not have their treatment. Nonetheless there were considerable efforts being made by parents to ensure that their child was adherent to their medication regimen. Gardiner and Dvorkin (2006) used case studies to illustrate issues relating to medication adherence in children; they noted medication adherence to be a complex issue involving the child, family members and other care providers. These authors further noted the importance of the family's cultural beliefs, their perceptions of disease severity, and their understanding of the benefits of treatment. Where the support needed by parents in managing treatment for children with cystic fibrosis was investigated parents described the stress of having to urge reluctant children to take medication, dealing with refusal and encouraging them to take some responsibility for their medication (Slatter et al., 2004). It is evident that the ease with which the child complies with their medication regimen needs consideration; although the medication may be being taken the impact of achieving adherence may be affecting the child and also their parents/carers.

There may be a parental influence on the willingness of the child to take solid dosage forms. Parents in this study described hesitancy when contemplating changing to their child taking tablets or capsules. Though the reasons for this are not clear, it may be that they do not want to change the *status quo* with their child's treatment that has been established. It may be that not only are they concerned about their child's ability to take tablets, but that they may be influenced by their own personal unwillingness to take tablets. Parental, especially

maternal, influences on children's expectations of taking medicines and their compliance have been previously shown to be strong (Yeung and Wong, 2005; Hameen-Anttila, 2011). While the evidence is limited, studies do imply that children can effectively learn to take tablets if appropriately supported. Yeung and Wong (2005) completed a retrospective survey of medical records on the age at which children converted from liquid to solid formulations of antiretroviral drugs, finding a wide age range of 2.9-8.1 years. Parental diffidence to their child taking tablets has been described in a study that investigated pill-swallowing training for children taking anti-HIV medications (Garvie et al., 2007). They found that when offered pill-swallowing training for their child parents/guardians often expressed reticence, the reasons for their reservations were considered to be related to parental perceptions of the child's ability to swallow pills or their own or their child's previous difficulties with swallowing pills. The parents interviewed in this study described some of the anxieties associated with changes in the prescribed drugs for their child. Cohen (1995) considered the triggers of heightened parental uncertainty in chronic, life threatening childhood illness. This author found that a plan to implement a new therapy or a procedure of unknown or unpredictable effectiveness can be alarming for parents. Any change proposed when the child is doing well under the current management was considered to threaten the precarious emotional equilibrium that has been established Cohen (1995).

5.12.5 Palatability

The parents who contributed to this study strongly believed that the availability of palatable liquid formulations would make it significantly easier for children to take medicines. Though this may seem to parents like a reasonable request it can be more difficult to achieve in reality. The financial implications of the development of liquid formulations for drugs that are not frequently in use in paediatrics may be prohibitive. It can prove difficult to achieve good organoleptic characteristics with liquid formulations (Davies and Tuleu, 2008). These properties refer not only to taste but include other possible sensory experiences of the product, such as smell

or texture. If the drug has a bitter taste there is little possibility that within a liquid formulation the taste can be masked (Breitkreutz and Boos, 2007). Furthermore, solubility characteristics may not be suitable for the liquid dosage forms. Compounds with high solubility can be difficult to taste mask in liquid preparations as they often cannot be easily formulated as suspensions (Cram et al., 2009). Excipients may also be a restricting factor. As Choonara and Rieder (2002) noted it is important to remember that medicines contain not only the desired active compound but also numerous other chemicals which are added to make the drug more palatable, more soluble or more stable. Oral liquids often require substantially larger amounts of excipients to ensure stability and palatability. Furthermore neonates and infants may not be able to metabolise/eliminate an excipient due to immature renal and hepatic function (Pandit et al., 2010). Though it may seem that the dose flexibility of oral liquids is a clear advantage, there can be dose accuracy questions. Yin et al. (2010) found a considerable number of measurement errors made by parents using dosing cups, though the use of oral syringes helped with accuracy. Though the accuracy of measurement of the correct volume in oral syringes, while better than other measuring devices, has also been questioned (Sobhani et al., 2008). The lack of safety and stability data and inclusion of excipients with elevated toxicological risks might hinder the advantages of liquid formulations, and their use in paediatric age groups needs to be assessed first (Pandit et al., 2010). There may be other influences on the availability of liquid formulations; as where these are only available as 'specials' the increasing cost of these means that hospitals and primary care trusts need to carefully consider their use (Wright and Tomlin, 2011). Furthermore it needs to be remembered that how palatable a liquid formulation is perceived to be will vary between individuals. Breitkreutz and Boos (2007) considered that the main problem with using liquids is the palatability of the solution, especially when considering that taste sensation differs age-dependently and between individuals.

5.12.6 Drug manipulations

When drug manipulations were required, parents were generally guided by information they received from health care professionals on how to complete them. They did not seem to seek additional information from other sources. Referring to the summary of product characteristics (SPC) leaflet that is provided with drug product was not mentioned by parents as a source of information for manipulations. The reasons for this may be two-fold, firstly that the manipulation may not be sanctioned by the drug company and therefore will not be in the SPC. Secondly, it may be that the information is not clear. Breitkreutz and Boos (2007) noted that by simply reading the product labelling even experts cannot often elucidate whether the tablet may be split or not and that product information provided with the drugs is often unreadable for patients or caregivers. Furthermore parents did not mention consulting websites, such as the 'Medicines for Children' website⁸. Though this website provides useful information for parents about how to administer their child's medication, much of the advice relating to possible manipulations notes that parents should discuss these with healthcare professionals.

As the initial interview transcripts were reviewed and analysed with the experienced paediatrician the brevity of answers relating to drug manipulation provoked discussion. There was consideration during the initial analysis as to whether the addition of further questions or topics in this area would be appropriate in the forthcoming interviews. However apprehensions relating to the possibility of stimulating parental concern in this area, without prior discussion with the appropriate clinical team, were considered a risk of the addition of further questions. It was decided that during the interviews the process of exploring any issues raised by parents relating to manipulation would continue, without the addition of further planned questions, but with an awareness of the brevity of

⁸ This website has been established for parents by the Royal College of Paediatrics and Child Health (RCPCH), the Neonatal and Paediatric Pharmacists Group (NPPG) and the child health WellChild, (<http://www.medicinesforchildren.org.uk/>)

answers in previous interviews. Where parental needs and views about giving medicines to children are to be explored a delicate line of questioning may be the most appropriate (Sweis and Wong, 2004).

The parents interviewed here were, in the main, unconcerned about undertaking manipulations. They did highlight areas of unreliability with manipulations, such as tablets crumbling or measuring proportions of a dispersed tablet. Parents had received inconsistent information from health care professionals. Some had been supplied with equipment (tablet splitters) and given careful instructions. Others had been informed that proportions of the intact dose were needed and given little further information on how to achieve this. It appears that if they are advised by healthcare professionals to manipulate parents do not generally feel that they need to ask further questions about this. There may be reasons that contribute to this, such as that they have been advised to do this by healthcare staff that they have a relationship of trust with. It may though be symptomatic of a general unawareness about the use of medicines in children, and a trust that that the medicines that are prescribed for children will have been through the same drug testing and safety process as those for adults. It may therefore be being assumed that the manipulation is a safe, effective and validated action. Mukattash et al. (2008) explored the awareness of the unlicensed use of medicines in children, finding that most participants were oblivious to the use of unlicensed medicines in children. These findings were not unexpected as these authors and others (Sweis and Wong, 2004) have noted the preference by health care professionals not to explain that children are being prescribed off-label or unlicensed medicines. This may be indicative of a reluctance to discuss potential difficulties relating to their treatment with a child's parents. Arnott et al. (2012a) investigated parents' experiences of their child's suspected adverse drug reactions and found that from the parents' perspective clinicians' communication about adverse drug reactions was poor.

5.13 CONCLUSIONS

This study provides an exploratory analysis of the methods used by parents to administer medications required for long-term use and areas where they think changes would be helpful for both their children and themselves. In doing so it has highlighted that this can be challenging and may have a negative impact both on the child and their parents. Conversely some can find it wearisome but not problematic. Drug manipulation does not appear to unduly concern the parents undertaking it, though the reasons for this are not clear. There is a disconnect between professional concerns about manipulations and parental perspectives. This disconnect is likely to hamper efforts to address the case for research.

Primary school age children are dependent on their parents or carers for their medication requirements. While priority has to be given to whether (or not) the child will take the medication it is nonetheless important to ensure that they and their parents/carers are supported with appropriate, timely and consistent information.

Underpinning the approach used for this study was whether it could be judged on catalytic validity; the potential to influence or change practice or research. The outcomes from this study provide not solely description of parental views. They also highlight the importance to some parents of the support of healthcare professionals and question aspects of this, particularly of how healthcare professionals provide explanations relating to medications and drug manipulations to parents.

CHAPTER 6: DISCUSSION

6.1 BACKGROUND LEADING TO THIS RESEARCH

Infants and children were first described as therapeutic and pharmaceutical orphans over forty years ago (Shirkey, 1968). Nunn, in 2003, commented that little had changed (Nunn, 2003). This lack of progress in the availability of appropriate paediatric drug products may even be argued to be an evolving issue as the treatment and survival age for many chronic and/or life-threatening conditions of childhood have advanced. Changes implemented through the EMA and FDA and the development of the EuPFI have drawn attention to the need for medications that are designed to meet the dose requirements for administration to babies and children. It is recognised that children cannot be treated as small adults and their healthcare, treatment and services should be suitable for their needs. The prescription of off-label and unlicensed drugs in paediatric practice is known. This use is accepted as a current necessity; without it children would not be able to be prescribed drugs that may be the most applicable to their needs (Conroy and Peden, 2001; Hoppu, 2008). Previous studies have established that off-label or unlicensed use is endemic in practice (Conroy et al., 2000; Di Paolo et al., 2006). The availability of appropriate doses in products that are designed for paediatric use will impact on whether the drug is actually taken as the design of the drug product has intended it to be. If there is not sufficient dose flexibility, the dose required for paediatric use may require manipulation to attain the dose required. As with the need to prescribe off-label and unlicensed drugs drug manipulation is established in practice. However this has not previously been systematically explored.

6.2 THESIS FINDINGS – SUMMARY

The impetus leading to the work in this thesis was that while drug manipulation appeared to be an established feature of paediatric clinical practice, what drugs and dosage forms are being manipulated and how these manipulations are undertaken was not known.

This thesis has investigated and described drug manipulation across paediatric practice. It has included: what evidence is available relating to drug manipulation (Chapter 2), what drugs and dosage forms are manipulated and in which in-patient clinical settings, how manipulations are undertaken (Chapters 3 and 4), and how parents view undertaking manipulations at home (Chapter 5).

This thesis has elucidated that drug manipulation is an intrinsic part of administering drugs to babies and children. There is a dearth of evidence to support drug manipulation. Findings have indicated that, while they may be more prevalent within the more high dependency clinical areas, drug manipulations occur throughout specialist and generalist in-patient areas, across a range of diagnoses and throughout all ages of childhood. Furthermore parents are undertaking manipulations prior to administering medications to their children at home. Despite the lack of evidence parents do not appear to be concerned.

6.3 INTERNATIONAL PERSPECTIVES

This research has focused on practice within the UK. Internationally there are liable to be cultural, traditional, regulatory or financial reasons for variances in the use of drugs and/or dosage forms in different countries. The issues relating to children's medicines have an international basis. Consequently the outcomes of this investigation into drug manipulation in paediatric practice have implications that will be relevant beyond the UK. The description of the drug manipulations within this thesis has implications both for current practice and for future research.

6.4 DRUG MANIPULATIONS – TABLETS

It is apparent that the evidence base to support or refute drug manipulation is insubstantial (Chapter 2). What evidence is available relates principally to tablet manipulations. Throughout the observational study (Chapter 3) and questionnaire responses (Chapter 4) tablets were the largest dosage form group in which drug manipulations are carried out in paediatric practice. Tablets are split, crushed and

dispersed and a proportion of the intact tablet dose administered to patients. The conclusion that can be drawn from the evidence base in the systematic review relating to tablet manipulations is that this manipulation is unreliable. Though for some tablets manipulation to obtain a proportion of the original dose can achieve an accurate dose, for others this cannot be stated with any confidence. This is further complicated by the unfeasibility of inferring that a tablet of the same dose of the same drug will consistently give the same outcomes. There may be a variety of formulations of this drug that may give dissimilar outcomes when manipulated; that is, though the drug and dose may be the same, there may be several drug products that have been formulated differently by various manufacturers and thus the outcome of the manipulation may differ. Though the evidence is limited, it is clear that tablet manipulations can be unreliable and at worst potentially dangerous, such as where the dose achieved is outwith adapted pharmacopoeial limits.

Many tablet manipulations involve the segmenting of a tablet. The inadequacy and ambiguity of the scorelines on some tablets has been recognised. Work is underway with the FDA and USP to scientifically define the term 'functional score' for tablets. This functional score will designate only tablets that reliably split into equal portions, American Society of Health-System Pharmacists 2012, (<http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3789#>).

Developments like this will be beneficial to both healthcare professionals and patients who are splitting tablets. However specific consideration on the usage in children is needed, as knowing a scoreline is functional for splitting in half will not prove sufficient should a smaller dose, such as a quarter, of the tablet be required.

6.5 NON-TABLET MANIPULATIONS

The dearth of non-tablet studies identified during the systematic review (Chapter 2) led to questions relating to the manipulations of other dosage forms. Is it that this lack of evidence is because they were not being manipulated or because they were they being manipulated but this practice had not been investigated? It is apparent

that, though tablets represent the highest proportion of manipulations, other dosage forms are being manipulated. Manipulations were described as being undertaken using a range of dosage forms: sachets, capsules, transdermal patches, nebuliser solutions, suppositories and enemas. With the paucity of evidence, any impact of manipulations on those receiving manipulated drugs is undetermined. It cannot be inferred that these manipulations are harmful and should not be undertaken; correspondingly it cannot be assumed that manipulations are effective in achieving the dose required and are safe.

6.6 INTRAVENOUS MANIPULATIONS AND MEASUREMENT OF SMALL VOLUMES

Most intravenous manipulations are occurring within neonatal units or high dependency areas, areas where experience has shown the value of guidance for drug preparation and administration. Much of this guidance is generated locally, though this may raise questions relating to the validation of guidance and whether all units are following optimal practice. Consequently for intravenous manipulations within neonatal units there are more reference materials available. What was identified during a concurrent quantitative review (Nunn et al., 2013) is that it is not always evident where intravenous injections are required is whether a manipulation occurs or whether a small volume, such as <0.2mL, has been measured in the process of achieving the small dose required. If such small doses are being measured the accuracy of such measurements may not be reliable. Although any error in these measurements may appear to be very small, with doses of this size, even an apparently small error could nonetheless result in a substantial under or over dosage.

The additional dilution of intravenous manipulations risks errors with calculations and/or measurements. This leads to the question of whether it is more accurate and less prone to error if a small volume is measured or if additional dilution is used allowing the measurement of a larger volume?

6.7 RESOURCE IMPLICATIONS

The frequency of manipulations may have implications for clinical practice due to the time that may be involved in drug manipulation and the resulting pressures on busy wards. A study which considered the administration of oral medicines to children found that where tablets or capsules were crushed, cut or dispersed and either all or a proportion of the original dosage form administered, then the drug administration took a significantly longer time (median time 4 minutes compared with 2 minutes ($p < 0.001$)) (Skwierczynski and Conroy, 2008). With drug manipulation to obtain the required dose, this potential impact on clinical time may be increased by the need to calculate the proportion of the available strength. While these may appear to be small fractions of time, the practice in many paediatric areas is to require that all drugs are checked by two nurses, consequently manipulations may add considerably to the workload in already busy clinical areas.

There are potential resource implications relating to manipulations, due to the time taken for manipulations. In addition, where manipulations need to be repeated there will be wastage of drug products. As discrete, individual events these will not have an impact, nonetheless there may be a cumulative impact.

6.8 REFERENCE DOCUMENTATION AND PROFESSIONAL LIABILITY

Further consideration needs to be given to ensuring that what is considered to be best practice in drug manipulation is used. A variety of manipulation methods have been described and it appears that practice may be inconsistent and best practice is not known. The BNF/BNFC is by far the most frequently consulted reference document, though in many cases the BNF/BNFC will not provide information that will assist with the manipulation. Within neonatal areas there appears to be much more reliance on local supportive documentation. This may be because many of the manipulations in this area are of intravenous injections and there is widespread use of intravenous drug administration guides.

There is a need for more formal recognition that manipulations occur and the development of suitable supportive documentation, such as protocols or policies. However, for this to be facilitated there will need to be some agreement or recognition of where the responsibility lies. Within prescribing in paediatrics it is accepted that off label and unlicensed prescribing may be necessary when no suitable alternative is available (Hill, 2005). It does not appear that similar thought has been given to the process of actually achieving the prescribed dose, the means of administering it and any implications that these actions may have professionally for those undertaking them. There has been some discussion within nursing journals relating to the possible legal implications of crushing tablets and opening capsules. However, this has centred on adult and community care, and has involved cases where the whole dose is administered and thus the crushing or opening has been to assist with administration (Wright, 2002; Griffith and Davies, 2003; Griffith et al., 2003; James, 2004). These authors have cautioned that any liability associated with the administration of crushed medication might lie with the administering nurse (Wright, 2002) and that health professionals must be sure that their reasons for crushing tablets could be justified in a court of law (Griffith and Davies, 2003). The importance of relevant protocols has also been described (Wright, 2002). It does appear that drug manipulations are known and acknowledged in practice but that the possible legal and professional implications within paediatric practice have not been further considered. The Nursing and Midwifery Council (NMC) 'Standards for Medicines Management' notes that for the crushing of medicines pharmacy advice should be sought and that the patient's best interests need to be determined. In considering good practice in the administration of medicines to children, Crawford (2012) noted that there are powerful and unlicensed drugs that are administered without parental knowledge of the lack of a licence, often with assumed parental consent. Furthermore, with these there are ethical and professional implications for the nurse who administers these medications (Crawford, 2012). Drug manipulations may not be sanctioned by those manufacturing the drug product. This raises questions of individual and corporate responsibility. Consideration could be given to discussing drug manipulation with

experienced practitioners; there may be an acceptance of what they view as usual practice that should be challenged. Drug manipulation has been a conventional feature of paediatric practice and may be accepted by practitioners as such. This acceptance of conditioned practice may mean that the need to develop reference documentation relating to drug manipulation has not been considered. Or it may be that there has been reticence relating to the development of supportive reference documentation, as the individual accountability and/or hospital liability relating to drug manipulation is unclear.

6.9 GUIDELINES

The outcomes from the systematic review (Chapter 2), observational study (Chapter 3) and survey of paediatric nurses (Chapter 4) have been utilised by a group of clinical, research and pharmacy experts to develop guidelines relating to drug manipulation. However, though these guidelines have been produced, their generic nature and focus on the need to seek expertise prior to many manipulations is liable to make them unwieldy and impractical in clinical situations. Their value is more likely to be in decision-making with those who are making drug planning and purchasing decisions. In consultation with paediatric pharmacy experts, this planning could potentially avoid some manipulations. Additionally, these guidelines will provide a platform for the consideration of the priorities for future research. These guidelines epitomise the difficulties in making generic guidelines for a clinical practice like drug manipulation that spans dosage forms and encompasses many different drugs (each with potentially several available drug products and therefore formulations).

6.10 IMPLICATIONS FOR KNOWLEDGE AND TRAINING

The prescription of drugs within paediatrics can be complex and the appropriate doses and methods of administration may change frequently throughout childhood. Failure to make these adjustments may reduce the benefits of treatment (Menson

et al., 2006). The dose of many drugs is calculated on weight, age or surface area, alongside any clinical condition specific factors. When prescribers are calculating the dose required, the question arises as to whether they give any consideration to which dosage forms and/or drug products are available. Concern has been expressed about the amount of pharmacology and prescribing teaching within medical training. Heaton et al. (2008) found that few medical students and recent graduates in medicine felt confident about prescribing and calculating drug doses and that less than a third (2413 respondents) considered that they met the standard expected of them at the point of graduation. In acknowledgement of the complexities involved, concern about the knowledge of prescribers has been specifically broached within paediatrics (Conroy et al., 2008; Conroy and Carroll, 2009). For non-medical prescribers the NMC standards for prescribers note that only nurses with relevant knowledge, competence, skills and experience in nursing children should prescribe for children (www.nmc-uk.org/Documents/Standards). Increasing planning and teaching within postgraduate programmes, with possible further development of the role of trained paediatric clinical pharmacologists (Conroy and Carroll, 2009) and the development and use of electronic prescribing (Davis, 2011), have been suggested as means of increasing knowledge and awareness of paediatric prescribing and reducing prescribing errors.

Furthermore the knowledge of, or teaching of, nurses administering medicines has been questioned. Akram and Mullen (2012) completed interviews with a small number of paediatric nurses working in general or psychiatric areas and considered that there is a lack of formal training on drug stability/degradation issues and/or possible clinical impact.

If there was more pharmacological knowledge and increased awareness of what dosage forms and drug products are available, people who prescribe and/or administer medicines (or those who advise prescribers and/or those who administer) would be able to consider and offer alternatives that may not require manipulation. This could involve aspects of prescribing such as whether an alternative drug in the same class could be used. Or it could involve the

appropriate use of dose rounding or dose ranges, if those prescribing had the knowledge and the confidence to calculate the drug doses and to appropriately use such flexibility where it is available.

It appears that there may be a need for sustained and consistent implementation of pharmacology, prescribing and drug administration teaching for both students and health professionals working in paediatric practice.

6.10.1 Avoidable manipulations

It may be that to obtain the dose needed for some drugs and formulations manipulation is necessary. However, what has emerged from this work is that there may be manipulations that could potentially be avoided. Drugs were reported and observed being manipulated where several differing strengths and dosage forms exist. Analgesics were a particular example of this, such as paracetamol or ibuprofen. These drugs are available as tablets, capsules, soluble tablets and oral suspension of various strengths. With some drugs there may be dose ranges that can be used, or some flexibility with the number of occasions a dose can be divided into over 24 hours. This provokes the question as to whether there is a lack of awareness of the different strengths and dosage forms that the drugs are available in. Or it may be that methods such as dose rounding or dose ranges are not being utilised. Or is the practice of manipulating so ingrained and habitual that in a busy clinical area it is not contested? If there has been acceptance that drug manipulation is a part of practice it may be that it has become habitual and not questioned or methods that could avoid it not implemented. With anecdotal descriptions of students having commented on registered practitioners showing them how to crush tablets (Wright, 2002), it may be that ingrained practice could be challenged with increased focus on training needs. The likelihood that there are drug manipulations that could be avoided raises questions such as the role of habitual practice and the potential of methods of prescription that could provide an appropriate dose that avoids the need to manipulate. However, further work is

needed in this area to consider education or training needs and potentially to challenge ingrained or accepted practice.

6.10.1.1 Dosage form preferences

Providing patient choice or meeting patient preference may influence the use of a drug manipulation. The observational study (Chapter 3) and questionnaire study (Chapter 4) provided examples where the preference was for segments of a tablet rather than a liquid formulation. It may seem that liquid formulations provide the solution to many difficulties with children's medications. They provide greater dose flexibility and are generally considered easier to swallow than solid dosage forms. When parents who were interviewed (Chapter 5) advocated strongly for the availability of liquid medicines, they did so with the proviso that they would also be palatable. However, as Breitzkreutz and Boos (2011) noted there is limited evidence-based information on acceptability and preference of dosage forms in children, despite the fact that the therapeutic outcomes are closely linked to it. The development of suitable and palatable oral solutions is often problematic; many bitter tasting drugs cannot be effectively masked in a liquid formulation. Additionally, there have been safety concerns about the use of some excipients in children (Choonara and Rieder, 2002; Breitzkreutz and Boos, 2011). Moreover liquid formulations can provide challenges due to shorter expiry dates once opened or storage issues. There may also be cost issues related to the liquid formulation development.

Although parents may consider liquid formulations to be a solution, some children have shown preferences for taking halved tablets rather than liquids. It has been suggested that the large volumes needed to achieve some doses have been disliked by some children (Nunn, 2003). Tablet manipulations occur for reasons of patient choice in a way that other manipulations do not. There is inconsistency in the limited research about the age at which children can take solid dosage forms (Yeung and Wong, 2005). Expert consensus in the EMA is that children younger than six years have difficulty with solid oral dosage forms (Breitzkreutz and Boos,

2011). The influence of parental preference will be a factor in this process, perhaps especially if the parents themselves dislike taking tablets. It is evident that children cannot be treated as a homogenous group and it is not going to be viable to have drug products that cater to what may be a wide range of possible preferences. Nevertheless, further research relating to the palatability and dosage form preferences of children taking long-term medication would provide valuable data for those manufacturing drug products, as well as those prescribing and administering them.

6.11 MANIPULATIONS, DRUG ERRORS AND ADVERSE DRUG REACTIONS

Drug manipulations add supplementary steps to drug administration; this can include the calculation of the proportion of the available dose that is required and additional volume measurements. This need for calculations and extra steps (such as dilution and measurements) where manipulation is required in drug administration replicates processes that have been implicated in increasing the risk of drug errors. If strategies to reduce risk are to be effectively targeted, it is necessary to identify the stages where errors are most likely (McDowell et al., 2010). The potential for error with the additional steps used during drug manipulation may exacerbate risks that have been previously recognised with other known aspects of paediatric medication administration, such as the use of unlicensed/off label drugs. Reports of errors in a UK children's hospital were analysed and it was found that 60% (12/20) of the errors that were considered to have caused moderate harm involved unlicensed/off label drugs (Conroy, 2011). Beyond the accuracy of the dose and safety issues that are directly related to the manipulated product, there is a further unknown implication. That is that babies and children may already be at increased risk of adverse drug events. It has previously been noted that medicines that are extemporaneously prepared are commonly given to some of the most vulnerable patients in hospitals (such as neonates, children, elderly patients and patients with feeding tubes)(Lowey and Jackson, 2008). These groups include individuals who may not be able to alert

carers or staff to any adverse events they are experiencing (Lowey and Jackson, 2008). Therefore those administering drugs to them need to be aware of any potential adverse events. Several studies suggest that about one-third of adverse drug events are associated with medication errors and are thus preventable (Kaushal et al., 2001). Furthermore, use of unlicensed medicines carries a greater risk of adverse drug reactions than the use of licensed medicines (Sutcliffe, 1999; Lowey and Jackson, 2008). It is not known if receiving a manipulated drug also increases the risk of an adverse drug reaction, a manipulation effectively renders the drug product to be unlicensed. There are associations of adverse drug reactions with medicines that have been prepared extemporaneously, medication errors and unlicensed medicines; as these have links with manipulated drugs the possibility of an increased risk of adverse drug reactions should be considered.

6.12 IMPLICATIONS FOR PARENTS

It appears that parents are trusting of the prescribed medications that they are advised to administer to their children. A previous study has found that there is limited public knowledge of the unlicensed use of medicines in children (Mukattash et al., 2008). The interviews I completed with parents here found that generally parents were unconcerned about undertaking a drug manipulation prior to administering a medication. The information and support provided by healthcare professionals to parents about undertaking manipulations appears to be inconsistent. If there is further focus on the need for all involved in paediatric drug prescribing and administration to have sufficient knowledge and training, then communication about drug related issues with children and parents should also improve. As has been previously noted by (Breitkreutz and Boos, 2007) when there is dependence on the abilities of the caregivers, drugs that are patient-adapted should be designed appropriately for caregivers as well.

Ultimately provision of appropriate medicines depends on political will. Individual parents did not report concerns about manipulations. This was despite noticing problems such as unreliability in splitting tablets, variable measurements of 5mL

volumes and the oral liquid viscosity on the consistency of manipulations. In general parents did not further consider the potential consequences of their observations. As long as those concerns are not expressed by parents it will be difficult to develop public advocacy for improvements in the situation.

6.12.1 Implications of long-term medication administration

Parents described the conflict (spontaneously using the term '*battle*') that can arise during the administration of some medications. The need to take long-term medications can have a substantial impact on some children and their parents. When administering medications some parents use a variety of methods. A widely-used approach is to use foodstuffs and/or drinks to mask the taste, or in some cases to disguise from the child that a medication is being taken. This can help with ensuring that administration is achieved. As with drug manipulations a pragmatic decision-making process may be being used, where the importance of getting a child to take a medication takes priority over the methods used to achieve this. Again, this is reasonable and may not impact on the effectiveness or safety of the drug involved. However, for many drug products this is not known. Parents have reported that they were advised to use food or drinks by healthcare staff. This advice may help with the medication administration and be a helpful response to a parental query. However, those advising the use of food or drinks may need to consider how confident they are that this is the correct advice. The uncertainty of nurses about whether or not medication should be mixed into foodstuffs could be seen in a study by Akram and Mullen (2012) when they interviewed nurses about it. These authors found that they were unable to complete the number of interviews that they had intended as only a small number of nurses agreed to participate; it was considered that nurses were apprehensive about discussing a potentially 'pseudo-illegal' practice with another health colleague. If it was well-defined where a drug product can be effectively and safely administered with foodstuffs and/or drinks, this would allow this method to be confidently used. It would not be feasible to test drug products in a variety of food or drinks but perhaps the testing of those

to be administered to children in a small number of selected foods or drinks should be considered.

6.13 LIMITATIONS

The methods used to explore drug manipulation within this thesis were selected with the aim of ensuring that the outcomes would provide a comprehensive depiction of current practice. This depiction provides a basis from which to contribute to the discussion about the provision of appropriate drugs for administration to babies and children. In scoping this practice it is accepted that there are related limitations.

The systematic review completed in this thesis investigated a broad topic where potentially any drug and/or dosage form could be included. This proved a challenge with search strategy development and database searching. Though measures were included with the aim of ensuring the aptness of the search strategy, the generality of many of the terms that had to be used meant that to achieve a retrieval that was reasonable, some specificity of the search had to be forfeited. This review acknowledged and allowed for relevant research that was available from studies that were completed solely within laboratories and did not include administration of the drugs involved. The inclusion of these studies provided a challenge for the quality assessment and synthesis of the evidence found within the review. To accommodate these studies and the breadth of studies involved, a review-specific quality assessment tool had to be devised. The breadth of the studies involved in this review meant that definitive conclusions could not be drawn, though a comprehensive picture of the evidence relating to manipulations and the gaps within it were apparent.

The observation of drug manipulations provided the initial data on the nature of manipulations occurring and on which drugs and dosage forms. Observing drug manipulations was feasible in in-patient areas, though the needs of the ward area always had to take precedence and there are practical difficulties with observing in these areas. Tools to enable the data recording of manipulations had to be devised.

These went through a considerable drafting and review process, were piloted and are considered to be fit for purpose. These tools did allow the recording of data that was considered to be valid, nonetheless there were adaptations that had to be made during data collection; notably where intravenous injections were being observed.

The outcomes from both the observational study and the questionnaire depict drug manipulations are occurring throughout neonatal and paediatric practice, involving the administration of a range of drugs and dosage forms. However, though this provides rich data, the use of purposive sampling in these studies means that there can be no conclusions drawn about the incidence of drug manipulations.

It is accepted that there may have been some care taken by participants in their answers to interview questions to conform to how they think a parent should respond. As with all studies where there is no attempt to sample representatively, the generalisability of the outcomes is a question. This study aimed purely to explore and in doing so provide outcomes that can illuminate areas where parents have concerns or issues and areas where they do not. To approach this study using more quantitative methods without any underlying understanding of the issues would have been inappropriate.

6.14 FUTURE CONSIDERATIONS

Those working within paediatric drug development, prescription and administration need to consider how feasible it is to resolve issues relating to drug manipulation. Ideally all drugs and dosage forms would be in child sized doses and in a formulation that was acceptable to children. Even allowing for the improbability of achieving a formulation that all children would find acceptable, this is unlikely. The FDA and EMA are promoting the development and availability of medicinal products for paediatric use. The importance of a syndicate approach in drug development has been discussed. It has been considered to be of paramount importance to strengthen the health system so that the individual child's medical need is both scientifically and ethically addressed right from drug manufacturer to

its administration (Yewale and Dharmapalan, 2012). As there may be a wide range in the doses required or the drug may not be frequently prescribed for children, it may not be feasible for some drugs, practically or economically, to be provided in appropriate single unit doses.

The focus may need to be not on preventing all drug manipulation, but in validating those manipulations that may be considered unavoidable. That is, to ensure that where manipulations cannot be avoided, the formulation is suitable, so that the efficacy and safety of the product are not compromised by the manipulation. There also should be consistency in practice. As has been previously identified, it is extremely important, particularly when the dosage form may have to be manipulated, to restrict the influence administration could have on intra- and inter-individual variations (Pandit et al., 2010). With drug manipulations the inherent difficulty in assessing and producing collective guidance or advice is that the effectiveness of each manipulation will be specific to that formulation. To achieve consistency, there needs to be further consideration and agreement on the best practice for drug manipulations.

CHAPTER 7: FINAL CONCLUSIONS

It is true that drug development has historically neglected the provision of drug products that within the required dose range and are suitable for administration to infants and children. The current professional and regulatory focus on improving this situation aims to provide improved access to appropriate paediatric medications. Alongside these developments it is appropriate to question paediatric drug prescription, preparation and administration practices such as drug manipulation.

The crux of the issue that underlies this thesis and the need to consider drug manipulation is the effectiveness and safety of the drug treatment. The overarching conclusion that can be drawn from exploring drug manipulation is that it is relevant to current practice and impacts throughout general and specialist areas. In establishing that manipulation is intrinsic to practice the outcomes of this thesis have raised more questions about issues that need to be reflected on.

To appropriately address drug manipulation there are a multiplicity of issues to be considered. Perhaps it is fitting to begin by considering situations where drug manipulation could be avoided. Prescribing within neonatal and paediatric practice is complex. It often requires child specific calculations relating to factors like age, weight or surface area, as well as any condition-specific considerations. Appropriate use of dose ranges or dose rounding following this calculation, and a awareness of the drug products available, may either avoid a manipulation or at least ensure that it is for a more easily calculable and measurable proportion. The onus for ensuring this cannot be solely that of the prescriber but requires a combination of the prescriber and the nurse administering the drug, with support and advice provided by pharmacists. For this to be effective there needs to be sufficient pharmacology related training of all healthcare professionals working within neonatal and paediatric areas.

Where drug manipulation is unavoidable then it is important that the practice is consistent and appropriate. Drug manipulation has been a longstanding necessity within paediatric practice; as such it may have become habitual. There are

questions relating to the liability of practitioners both in completing manipulations themselves and advising patient or carers to do so. There needs to be recognition that manipulation may not be avoidable in some cases and that there needs to be consideration given to what is best practice. It is acknowledged that there are substantial gaps in the evidence-base to support drug manipulation. Nonetheless it is imperative that there are reference sources available relating to drug manipulation. Care had to be taken within this research to ensure that it was clear what drug manipulation was defined as. To develop appropriate source materials there needs to be a suitable nomenclature that ensures that where a manipulation is discussed it is consistently clear what it refers to. Furthermore there needs to be discussion and recognition of the personal and corporate liability aspects of drug manipulations, so that those undertaking them can feel supported and justified in their practice.

This thesis has demonstrated the difficulties of investigating drug manipulation that is that the data about the manipulation of a particular dosage form provides reliable data only for that individual formulation. Testing and validation of all potential formulations is not possible. Therefore further consideration of this issue requires some prioritisation. Overall incidence of manipulations cannot be assumed from the outcomes in this thesis. Nevertheless expert review of the drugs manipulated would provide recommendations as to priorities of future work. This review should include health care professionals, children, parents/carers and research expertise alongside consultation with regulatory and industry representatives. While priority areas need to be discussed and decided by these relevant groups, they may include, for example, drugs that are frequently prescribed for children where the dose required will often render manipulation unavoidable or those which are less frequently used but there are specific effectiveness or safety concerns raised by the manipulation.

With intravenous injection manipulations where dilutions are used to access doses that maybe a very small fraction of the dose in the vial there are further questions to be considered. With all drug manipulations there is a risk of miscalculation when

the dose needed is being calculated from the dose available. This may be particularly pertinent with intravenous drug manipulations as these may involve more complex fractions of the original dose. Moreover from review of the prescribed and available doses it is not always evident whether a manipulation is occurring or it may be that to avoid manipulating there may be attempts made to measure very small volumes. The accuracy of these possible small volume measurements may not be assured. There needs to be further consideration as to whether undertaking manipulations or measuring small volumes are acceptable and provide sufficient accuracy in the final dose that is administered to the patient.

It is accepted that the provision of choices of paediatric formulations to encompass differing preferences and tastes will be impracticable. There are a variety of food and drink vectors used to assist with the administration of medications to children. Testing for the effectiveness of drug products across a variety of these is also likely to not be realistic. Nonetheless it may be feasible to consider whether the testing of effectiveness with a very small range of foodstuffs could be approached with paediatric drug development. This would assist with the appropriateness and confidence with which related advice could be provided to parents. It may also be worth reflecting on the development and validation of programmes which can applicably teach children how to take tablets or capsules.

In exploring drug manipulation this thesis has added to the knowledge and discussion around the need for appropriate medication for paediatric use. The ultimate aim is to provide drugs that are effective, safe and tolerated and therefore can optimise patient treatment and outcomes. The thesis has identified specific gaps in the literature, scoped out the nature and practicalities of manipulations conducted by nurses and parents and indicated key areas for future work.

REFERENCES

Abdul S, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. *J Control Release* 2004;97(3):393-405

Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. *Int J Pharm Pract* 2012;20(3):191-198

Allegaert K, Anderson BJ, Vrancken M, Debeer A, Desmet K, Cosaert K, Tibboel D, Devlieger H. Impact of a paediatric vial on the magnitude of systematic medication errors in neonates. *Paediatric and Perinatal Drug Therapy* 2006;7(2):59-63

Altmann J. Observational study of behaviour: sampling methods. *Behaviour* 1974;49(3):227-267

Arnet I, Hersberger KE. Misleading score-lines on tablets: facilitated intake or fractional dosing? *Swiss Med Wkly* 2010;140(7-8):105-110

Arnott J, Hesselgreaves H, Nunn AJ, Peak M, Pirmohamed M, Smyth RL, Turner MA, Young B. Enhancing communication about paediatric medicines: lessons from a qualitative study of parents' experiences of their child's suspected adverse drug reaction. *PLoS One* 2012a;7(10):e46022

Arnott J, Hesselgreaves H, Nunn AJ, Peak M, Pirmohamed M, Smyth RL, Turner MA, Young B. What can we learn from parents about enhancing participation in pharmacovigilance? *Br J Clin Pharmacol* 2012b;75(4):1109-17

Baker LM. Observation: a complex research method. *Library Trends* 2006;55(1):171-189

Barber ND, Alldred DP, Raynor DK, Dickinson R, Garfield S, Jesson B, Lim R, Savage I, Standage C, Buckle P, Carpenter J, Franklin B, Woloshynowych M, Zermansky AG. Care homes' use of medication study: prevalence, causes and potential harm of medication errors in care homes for older people. *Qual Saf Health Care* 2009;18(5):341-346

Barker KN. Data collection techniques: observation. *Am J Hosp Pharm* 1980;37(9):1235-1243

Barker KN, Flynn EA, Pepper GA, Bates DW, Mikeal RL. Observation method of detecting medication errors. *Am J Health Syst Pharm* 2002a;59(23):2314-2316

Barker KN, McConnell WE. How to detect medication errors. *Mod Hosp* 1962;99:95-106

Barner-Barry C. An introduction to nonparticipant observational research techniques. *Politics and Life Sciences* 1986;5(1):139-147

Berg C, Ekedahl A. Dosages involving splitting tablets: common but unnecessary? *Journal of Pharmaceutical Health Services Research* 2010;1(3):137-141

Berman W, Whitman V, Marks KH, Friedman Z, Maisels MJ, Musselman J. Inadvertent overadministration of digoxin to low-birth-weight infants. *J Pediatr* 1978;92(6):1024-1025

Best BM, Capparelli EV. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Defic Syndr* 2011;58(4):385-391

Bhambhani V, Beri RS, Puliyl J. Inadvertent overdosing of neonates as a result of the dead space of the syringe hub and needle. *Arch Dis Child Fetal Neonatal Ed* 2005;90(5):F444-445

BNFC. BNF for Children London BMJ Group, Pharmaceutical Press, and RCPCH Publications. 2009

Boggie DT, DeLattre ML, Schaefer MG, Morreale AP, Plowman BK. Accuracy of splitting unscored valdecoxib tablets. *Am J Health Syst Pharm* 2004;61(4):1482-1483

Bourlon S, Baronnet A, Provost S, Meunier P. Evaluation des erreurs medicamenteuses dans une unite de sions pediatriques. *Journal de Pharmacie Clinique* 2006;25(1):23-29

Bowen GA. Naturalistic inquiry and the saturation concept: a research note. *Qualitative Research* 2008;8:137-152

Boynton J, Glanville J, McDaid D, Lefebvre C. Identifying systematic reviews in Medline developing an objective approach to strategy design. *Journal of Information Science* 1998;24(3):137-154

Boynton PM, Greenhalgh T. Selecting, designing and developing your questionnaire. *BMJ* 2004;328(7451):1312-1315

Breitkreutz J, Boos J. Drug Delivery and Formulation. Pediatric Clinical Pharmacology, Handbook of Experimental Pharmacology. Berlin Heidelberg, Springer-Verlag 2011;205

Breitkreutz J, Wessel T, Boos J. Dosage forms for peroral drug administration to children. Paediatric and Perinatal Drug Therapy 1999;3:25-33

Brion F, Nunn AJ, Rieutord A. Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. Acta Paediatr 2003;92(4):486-490

Broadhurst EC, Ford JL, Nunn AJ, Rowe PH, Roberts M. Dose uniformity of samples prepared from dispersible aspirin for paediatric use. EJHP Science 2008;14(2):27-31

Bush A. Evidence-based medicines for children: important implications for new therapies at all ages. Eur Respir J 2006;28(6):1069-1072

Caldwell SM, Raitt JR. Oral medication administration: implications caused by capsule splitting. J Am Pharm Assoc 2010;50(4):532-533

Carr-Lopez SM, Mallett MS, Morse T. The tablet splitter: barrier to compliance or cost-saving instrument? Am J Health Syst Pharm 1995;52(23):2707-2708

Carthey J. The role of structured observational research in health care. Qual Saf Health Care 2003;12:13-16

Chappell K, Newman C. Potential tenfold drug overdoses on a neonatal unit. Arch Dis Child Fetal Neonatal Ed 2004;89(6):F483-484

Choe HM, Stevenson JG, Streetman DS, Heisler M, Standiford CJ, Piette JD. Impact of patient financial incentives on participation and outcomes in a statin pill-splitting program. Am J Manag Care 2007;13(6 Part1):298-304

Choi HM, Halpern SH, Malik N, Jadad AR, Tramler MR, Walder B. Examining the evidence in anaesthesia literature; a critical appraisal of systematic reviews. Anesth Analg 2001;92(3):700-709

Choonara I. Children's medicines – a global problem. Arch Dis Child 2009;94(6):467

Choonara I, Rieder MJ. Drug toxicity and adverse drug reactions in children – a brief historical review. Paediatric and Perinatal Drug Therapy 2002;5(1):12-18

- Chua SS, Chua HM, Omar A. Drug administration errors in paediatric wards: a direct observation approach. *Eur J Pediatr* 2010;169(5):603-611
- Cleary JD, Evans PC, Hikal AH, Chapman SW. Administration of crushed extended-release pentoxifylline tablets: bioavailability and adverse effects. *Am J Health Syst Pharm* 1999;56(15):1529-1536
- Clyne W, White S, McLachlan S. Developing consensus-based policy solutions for medicines adherence for Europe: a Delphi study. *BMC Health Serv Res* 2012;12(1):425
- Cohen MH. The triggers of heightened parental uncertainty in chronic, life-threatening childhood illness. *Qual Health Res* 1995;5(1):63-77
- Conroy S. Association between licence status and medication error. *Arch Dis Child* 2011;96(3):305-306
- Conroy S, Carroll WD. Prescribing in paediatrics. *Arch Dis Child* 2009;94(2):55-59
- Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, van den Anker J. Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 2000;320(7227):79-82
- Conroy S, McIntyre J, Choonara I, Hull PS. Unlicensed and off label use in neonates. *Arch Dis Child* 1999;80(2):F142-144
- Conroy S, Newman C, Gudka S. Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. *Annals of Oncology* 2003;14(1):42-47
- Conroy S, North C, Fox T, Haines L, Planner C, Wong ICK, Sammons H. Educational interventions to reduce prescribing errors. *Arch Dis Child* 2008;93(4):313-315
- Conroy S, Peden V. Unlicensed and off label analgesic use in paediatric pain management. *Paediatr Anaesth* 2001;11(4):431-436

Conroy S, Sweis D, Planner C, Yeung V, Collier J, Haines L, Wong IC. Interventions to reduce dosing errors in children – a systematic review of the literature. *Drug Safety* 2007;30(12):1111-1125

Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med* 1997;126(5):376-380

Cook TJ, Edwards S, Gyemah C, Shah M, Shah I, Fox T. Variability in tablet fragment weights when splitting unscored cyclobenzaprine 10mg tablets. *Journal of American Pharmacists Association* 2003;44:583-586

Corbett AH, Hosseinipour MC, Nyirenda J, Kanyama C, Rezk NL, Mkupani P, Sichali D, Tien H, Kashuba ADM, Mwansamba C, Weigel R, Kazembe P. Pharmacokinetics of generic and trade formulations of lamivudine, stavudine and nevirapine in HIV-infected Malawian children. *Antivir Ther* 2010;15(1):83-90

Costa P, Amaral H, Sousa Lobo JM. Dissolution characteristics of divisible tablets. *S.T.P. Pharma Sciences* 2000;10(5):373-377

Costello I, Wong IC, Nunn AJ. A literature review to identify interventions to improve the use of medicines in children. *Child Care Health Dev* 2004;30(6):647-665

Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med* 1997;127(5):380-387

Cousins DH, Sabatier B, Begue D, Schmitt C, Hoppe-Tichy T. Medication errors in intravenous drug preparation and administration: a multicentre audit in the UK, Germany and France. *Qual Saf Health Care* 2005;14:190-195

Coyne I, Cowley S. Using grounded theory to research parent participation. *Journal of Research in Nursing* 2006;11:501-515

Cram A, Breitzkreutz J, Desset-Brethes S, Nunn T, Tuleu C. Challenges of developing palatable oral paediatric formulations. *Int J Pharm* 2009;365(1-2):1-3

Crawford D. Maintaining good practice in the administration of medicines to children. *Nurs Child Young People* 2012;24(4):29-35,36

CRD. Systematic Reviews; CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination. 2009

Davies EH, Tuleu C. Medicines for children: a matter of taste. *J Pediatr* 2008;153(5):599-604

Davis T. Paediatric prescribing errors. *Arch Dis Child* 2011;96(5):489-491

Dean AJ, Walters J, Hall A. A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness. *Arch Dis Child* 2010;95(9):717-723

Dean B, Barber N. Validity and reliability of observational methods for studying medication administration errors. *Am J Health Syst Pharm* 2001;58:54-59

DiMatteo MR. The role of effective communication with children and their families in fostering adherence to pediatric regimens. *Patient Educ Couns* 2004;55(3):339-344

DiPaolo ER, Stoetter H, Cotting J, Frey P, Gebri M, Beck-Popovic M, Tolsa J-F, Fanconi S, Pannatier A. Unlicensed and off-label drug use in a Swiss paediatric university hospital. *Swiss Med Wkly* 2006;136(13-14):218-222

Dixon-Woods M, Agarwal S, Jones D, Young B, Sutton A. Synthesising qualitative and quantitative evidence: a review of possible methods. *J Health Serv Res Policy* 2005;10(1):45-53

Donaldson SI, Grant-Vallone EJ. Understanding self-report bias in organizational behaviour research. *Journal of Business and Psychology* 2002;17(2):245-262

Durand C, Alhammad A, Willett KC. Practical considerations for optimal transdermal drug delivery. *Am J Health Syst Pharm* 2012;69(2):116-124

Dybwik K, Tollali T, Nielsen EW, Brinchmann BS. Fighting the system: families caring for ventilator-dependent children and adults with complex health care needs at home. *BMC Health Serv Res* 2011;11:156

Edwards P. Questionnaires in clinical trials: guidelines for optimal design and administration. *Trials* 2010;11:2

Ekins-Daukes S, Helms PJ, Taylor MW, McLay JS. Off-label prescribing to children: attitudes and experience of general practitioners. *Br J Clin Pharmacol* 2005;60(2):145-149

EMA. Reflection paper: Formulations of choice for the paediatric population 2006

Ernest TB, Craig J, Nunn A, Salunke S, Tuleu C, Breitzkreutz J, Alex R, Hempenstall J. Preparation of medicines for children – a hierarchy of classification. *Int J Pharm* 2012;435(2):124-130

Erramouspe J, Jarvi EJ. Effect on dissolution from halving methylphenidate extended-release tablets. *Ann Pharmacother* 1997;31(10):1123-1126

Erstad AJ, Erstad BL, Nix DE. Accuracy and reproducibility of small-volume injections from various-sized syringes. *Am J Health Syst Pharm* 2006;63(8):748-750

Fagerstrom PO. Pharmacokinetics of whole and half Theo-Dur tablets. *Eur J Respir Dis Suppl* 1980;109:62-66

Fawell NG, Cookson TL, Scranton SS. Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. *Am J Health Syst Pharm* 1999;56:2542-2545

Ferron GM, Ku S, Abell M, Unruh M, Getsy J, Mayer PR, Paul J. Oral bioavailability of pantoprazole suspended in sodium bicarbonate solution. *Am J Health Syst Pharm* 2003;60(13):1324-1329

Fiese BH, Everhart RS. Medical adherence and childhood chronic illness: family daily management skills and emotional climate as emerging contributors. *Curr Opin Pediatr* 2006;18(5):551-557

Finney E. Children's medicines: a situational analysis. 2011

Fisher HR. The needs of parents with chronically sick children: a literature review. *J Adv Nurs* 2001;36(4):600-607

Flynn EA, Barker KN, Pepper GA, Bates DW, Mikeal RL. Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities. *Am J Health Syst Pharm* 2002;59(5):436-446

Flynn K. VA Technology Assessment Program Short Report – tablet splitting. VA Technology Assessment Program (VATAP) Reports 1-8. 2000

Footitt AR. Dose accuracy in paediatric medicine. *British Journal of Pharmaceutical Practice* 1983;Sept:16-17, 20-22, 26-27

Foster C, Eiser C, Oades P, Sheldon C, Tripp J, Goldman P, Rice S, Trott J. Treatment demands and differential treatment of patients with cystic fibrosis and their siblings: patient, parent and sibling accounts. *Child Care Health Dev* 2001;27(4):349-364

Gardiner P, Dvorkin L. Promoting medication adherence in children. *Am Fam Physician* 2006;74(5):793-798

Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. *Clin J Am Soc Nephrol* 2008;3(1):253-260

Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics* 2007;119(4):e893-899

Gee M, Hasson NK, Hahn T, Ryono R. Effects of a tablet-splitting program in patients taking HMG-CoA reductase inhibitors: analysis of clinical effects, patient satisfaction, compliance and cost avoidance. *J Manag Care Pharm* 2002;8(6):453-458

Gendall P. A framework for questionnaire design: Labaw revisited. *Marketing Bulletin* 1998;9:28-39

Gerber A, Kohaupt I, Lauterbach KW, Buescher G, Stock S, Lungen M. Quantification and classification of errors associated with hand-repacking of medications in long-term care facilities in Germany. *Am J Geriatr Pharmacother* 2008;6(4):212-219

Ghaleb MA, Barber N, Franklin BD, Yeung VWS. Systematic review of medication errors in pediatric patients. *Ann Pharmacother* 2006;40(10):1766-1776

Gill D, Spain M, Edlund BJ. Crushing or splitting medications: unrecognised hazards. *J Gerontol Nurs* 2012;38(1):8-12

Golder S, Loke Y, McIntosh HM. Poor reporting and inadequate searches were apparent in systematic reviews of adverse events. *J Clin Epidemiol* 2008;61(5):440-448

Goldsmith MR, Bankhead CR, Austoker J. Synthesising quantitative and qualitative research in evidence-based patient information. *J Epidemiol Community Health* 2007;61(3):262-270

Goss C, Lowenstein S, Roberts I, DiGuseppi C. Identifying controlled studies of alcohol-impaired driving prevention: designing an effective search strategy. *Journal of Information Science* 2007;33(2):151-162

Green G, Berg C, Polli JE, Barends DM. Pharmacopeial standards for the subdivision characteristics of scored tablets. *Pharm Times* 2010;42(9):15-23

Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews: audit of primary sources. *BMJ* 2005;331(7524):1064-1065

Griffith R, Davies R. Tablet crushing and the law: the implications for nursing. *Prof Nurse* 2003;19(1):41-42

Griffith R, Griffiths H, Jordan S. Administration of medicines. Part 1: the law and nursing. *Nurs Stand* 2003;18(2):47-53

Groves RM, Presser S, Dipko S. The role of topic interest in survey participation decisions. *Public Opinion Quarterly* 2004;68(1):2-31

Gulmezoglu AM, Say L, Betran AP, Villar J, Piaggio G. WHO systematic review of maternal mortality and morbidity: methodological issues and challenges. *BMC Med Res Method* 2004;4:16

Hameen-Antilla K, Halonen P, Siponen S, Holappa M, Ahonen R. Parental attitudes toward medicine use in children in Finland. *Int J Clin Pharm* 2011;33(5):849-858

Harden A, Thomas J. Methodological issues in combining diverse study types in systematic reviews. *International Journal of Social Research Methodology* 2005;8(3):257-271

- Haw C, Stubbs J, Dickens G. An observational study of medication administration errors in old-age psychiatric inpatients. *International Journal for Quality in Health Care* 2007;19(4):210-216
- Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. *Qual Health Res* 2002;12(9):1284-1299
- Heaton A, Webb DJ, Maxwell SRJ. Undergraduate preparation for prescribing: the views of 2143 UK medical students and recent graduates. *Br J Clin Pharmacol* 2008;66(1):128-134
- Herzer M, Godiwala N, Hommel KA, Driscoll K, Mitchell M, Crosby LE, Piazza-Waggoner C, Zeller MH, Modi AC. Family functioning in the context of pediatric chronic conditions. *J Dev Behav Pediatr* 2010;31(1):26-34
- Higgins JPT, Green S. (eds) *Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.2)*. The Cochrane Collaboration 2009
- Hill P. Off licence and off label prescribing in children: litigation fears for physicians. *Arch Dis Child* 2005;90 Suppl 1:i17-18
- Hill SW, Varker AS, Karlage K, Myrdal PB. Analysis of drug content and weight uniformity for half-tablets of 6 commonly split medications. *J Manag Care Pharm* 2009;15(3):253-261
- Hodgkinson R, Lester H. Stresses and coping strategies of mothers living with a child with cystic fibrosis: implications for nursing professionals. *J Adv Nurs* 2002;39(4):377-383
- Hoppu K. Paediatric clinical pharmacology: at the beginning of a new era. *Eur J Clin Pharmacol* 2008;64(2):201-205
- Horn LW, Kuhn RJ, Kanga JF. Evaluation of the reproducibility of tablet splitting to provide accurate doses for the paediatric population. *The Journal of Pediatric Pharmacy Practice* 1999;4(1):38-42
- Horsburgh D. Evaluation of qualitative research. *J Clin Nurs* 2003;12(2):307-312

Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res* 2005;15(9):1277-1288

Hsien L, Breddemann A, Froebel AK, Heusch A, Schmidt KG, Laer S. Off-label drug use among hospitalised children: identifying areas with the highest need for research. *Pharm World Sci* 2008;30(5):497-502

Isaac RE, Duncan H, Marriott JF, Ng A. The effect of different manipulation techniques on the accuracy and reproducibility of small dose volumes intravenous measurements. *Arch Dis Child* 2010;95(6):e1

James A. The legal and clinical implications of crushing tablet medication. *Nurs Times* 2004;100(50):28-29

Katrak P, Bialocerkowski AE, Massy-Westropp N, Saravana Kumar VS, Grimmer KA. A systematic review of the content of critical appraisal tools. *BMC Med Res Methodol* 2004;4:22

Kaushal R, Bates DW, Langrigan C, McKenna KJ, Clapp MD, Federico F, Goldmann DA. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285(16):2114-2120

Kaye JL. Review of paediatric gastrointestinal physiology data relevant to oral drug delivery. *Int J Clin Pharm* 2011;33(1):20-24

Kayitare E, Vervaet C, Ntawukulilyayo JD, Seminega B, Van Bortel , Remon JP. Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications. *Int J Pharm* 2009;370(1-2):41-46

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology – drug disposition, action and therapy in infants and children. *N Engl J Med* 2003;349(12):1157-1167

Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care* 2003;15(3):261-266

Kim TW, Rognerud CL, Ching-Nan O. Accuracy in the alteration of acetaminophen suppositories. *Anesth Analg* 2005;100(5):1303-1305

Kohen DE, Brehaut JC, Garner RE, Miller AR, Lach LM, Klassen AF, Rosenbaum PL. Conceptualizing childhood health problems using survey data: a comparison of key indicators. *BMC Pediatr* 2007;7:40

Koren G, Haslam RH. Pediatric medication errors: predicting and preventing tenfold disasters. *J Clin Pharmacol* 1994;34(11):1043-4045

Long T, Johnson M. Rigour, reliability and validity in qualitative research. *Clinical Effectiveness in Nursing* 2000;4:30-37

Lowey A, Jackson M. How to ensure the quality and safety of unlicensed oral medicines. *Pharmaceutical Journal* 2008;281:240

Lucas-Bouwman ME, Roorda RJ. Crushed prednisolone tablets or oral solution for acute asthma? *Arch Dis Child* 2001;84(4):347-348

Lucas PJ, Roberts HM, Baird J, Kleijnen J, Law CM. The importance of size and growth in infancy: integrated findings from systematic reviews of scientific evidence and lay perspectives. *Child Care Health Dev* 2007;33(5):635-640

MacKintosh DA, Baird-Lambert J, Buchanan N. Theo-Dur: no loss of sustained-release effects with chewing or crushing. *Aust NZ J Med* 1985;15(3):351-352

Mandal TK. Effect of tablet integrity on the dissolution rate of sustained-release preparations. *J Clin Pharm Ther* 1996;21(3):155-157

Matsui D. Assessing the palatability of medications in children. *Paediatric and Perinatal Drug Therapy* 2007;8(2):55-60

Matsui DM. Drug compliance in paediatrics. Clinical and research issues. *Pediatr Clin North Am* 1997;44(1):1-14

McCall GJ. Systematic field observation. *Ann Rev Sociol* 1984;10:263-282

McCull E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, Thomas R, Harvey E, Garratt A, Bond J. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients. *Health Technol Assess* 2001;5(31):1-256

McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. *Pharmacotherapy* 1998;18(1):193-197

McDowell SE, Mt-Isa S, Ashby D, Ferner RE. Where errors occur in the preparation and administration of intravenous medicines: a systematic review and Bayesian analysis. *Qual Saf Health Care* 2010;19(4):341-345

McEwen J, Durnin C, McMurdo MET, Moreland TA. Sustained-release verapamil: multiple-dose pharmacokinetic comparison of 120-mg and 240-mg and the effect of halving a 240-mg tablet. *J Cardiovasc Pharmacol* 1989;13 Suppl 4:S57-59

McIntyre J, Choonara I. Drug toxicity in the neonate. *Biol Neonate* 2004;68(4):218-221

Meier CM, Simonetti GD, Ghiglia S, Fossali E, Salice P, Limoni C, Bianchetti MG. Palatability of angiotensin II antagonists among nephropathic children. *Br J Clin Pharmacol* 2007;63(5):628-631

Menson EN, Walker AS, Sharland M, Wells C, Tudor-Williams G, Riordan FAI, Lyall EGH, Gibb DM. Underdosing of antiretroviral in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ* 2006;332(7551):1183-1187

Meyer-Masseti C, Cheng CM, Schwappach DLB, Paulsen L, Ide B, Meier CR, Guglielmo BJ. Systematic review of medication safety assessment methods. *Am J Health Syst Pharm* 2011;68:227-240

Milani G, Ragazzi M, Simonetti GD, Ramelli GP, Rizzi M, Bianchetti MG, Fossali EF. Superior palatability of crushed lercanidipine compared with amlodipine among children. *Br J Clin Pharmacol* 2010;69(2):204-206

Miller MR, Robinson KA, Lubomski LH, Rinke ML, Pronovost PJ. Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. *Qual Saf Health Care* 2007;16(2):116-126

Moher D, Schulze KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7(2):e1000217

Moreland TA, McMurdo ME, McEwen J. Multiple dose comparison of a whole 240-mg verapamil sustained-release tablet with two tablets. Biopharm Drug Dispos 1989;10(3):311-319

Mukattash TL, Millership JS, Collier PS, McElnay JC. Public awareness and views on unlicensed use of medicines in children. Br J Clin Pharmacol 2008;66(6):838-845

Mulla H, Tofeig M, Bu'Lock F, Samani N, Pandya HC. Variations in captopril formulations used to treat children with heart failure: a survey in the United Kingdom. Arch Dis Child 2007;92(5):409-411

Nahata MC. Lack of pediatric drug formulations. Pediatrics 1999;104(3 Pt 2):607-609

Nakash RA, Hutton JL, Jorstad-Stein EC, Gates S, Lamb SE. Maximising response to postal questionnaires – a systematic review of randomised trials in health research. BMC Med Res Methodol 2006;6:5

National Prescribing Centre. Prescribing specials; five guiding principles for prescribers. 2011 Retrieved 18th January 2012, http://www.npc.nhs.uk/improving_safety/prescribing_specials/resources/5_guiding_principles.pdf

Nilsen P, Roback K, Brostrom A, Ellstrom P-E. Creatures of habit: accounting for the role of habit in implementation research on clinical behaviour change. Implement Sci 2012;7:53

Nissen LM, Haywood A, Steadman KJ. Solid medication dosage form modification at the bedside and in the pharmacy of Queensland hospitals. Journal of Pharmacy Practice and Research 2009;39(2):129-134

Nolan M, Grant G, Nolan J. Busy doing nothing: activity and interaction levels amongst differing populations of elderly patients. J Adv Nurs 1995;22(3):528-538

Nunn AJ. Making medicines that children can take. *Arch Dis Child* 2003;88(5):369-371

Nunn AJ, Richey RH, Shah UU, Barker CE, Craig JV, Peak M, Ford JL, Turner MA. Estimating the requirement for manipulation of medicines to provide accurate doses for children. *European Journal of Hospital Pharmacy* 2013;20:3-7

O’Cathain A, Thomas KJ. Any other comments? Open comments on questionnaires – a bane or a bonus to research? *BMC Med Res Methodol* 2004;4:25

Olski TM, Lampus SF, Gherarducci G, Raymond AS. Three years of paediatric regulation in the European Union. *Eur J Clin Pharmacol* 2011;67(3):245-252

Pandit S, Shah U, Kirby DJ, Nunn T, Tuleu C. Inappropriate oral formulations and information in pediatric trials. *Arch Dis Child* 2010;95(9):754-756

Paolucci P, Jones KP, Cano Garcinuro MC, Catapano M, Iolascon A, Ceci A. Challenges in prescribing drugs for children with cancer. *Lancet Oncol* 2008;9(2):176-183 in Rocchi et al. 2010

Paradise LM, Roughhead EE, Gilbert AL, Cosh D, Nation RL, Barnes L, Cheek J, Ballantyne A. Crushing or altering medications: what’s happening in residential aged-care facilities. *Australian Journal on Aging* 2002;21(3):123-127

Parra D, Beckey NP, Raval HS, Schnacky KR, Calabrese V, Coakley RW, Goodhope RC. Effect of splitting simvastatin tablets for control of low-density lipoprotein cholesterol. *Am J Cardiol* 2005;95(12):1481-1483

Parshuram CS, To T, Seto W, Trope A, Koren H, Laupacis A. Systematic evaluation of errors occurring during the preparation of intravenous medication. *CMAJ* 2008;178(1):42-48

Polit DF, Beck CT. *Nursing research: generating and assessing evidence for nursing*. Philadelphia, Wolters Kluwer Health. 2008

Polli JE, Kim S, Martin BR. Weight uniformity of split tablets required by a Veterans Affairs policy. *J Manag Care Pharm* 2003;9(5):401-407

Porta A, Hsia Y, Doerholt K, Spyridis N, Bielicki J, Menson E, Tsolia M, Esposito S, Wong ICK, Sharland M. Comparing neonatal and paediatric antibiotic prescribing between hospitals: a new algorithm to help international benchmarking. *J Antimicrob Chemother* 2012;67(5):1278-1286

Powers JE, Cascella PJ. Comparison of methods used to prepare tablets for nasogastric tube administration. *Journal of Pharmacy Technology* 1990;6:60-62

Primrose WR, Clee MD, Moody JP, Hockings N. Alteration of pharmacokinetics after halving a slow-release theophylline tablet. *Pharmatherapeutica* 1983;3(6):429-432

Prot S, Fontan JE, Alberti C, Bourdon O, Farnoux C, Macher MA, Foureau A, Faye A, Beaufile F, Gotto S, Brion F. Drug administration errors and their determinants in pediatric-in-patients. *Int J Qual Health Care* 2005;17(5):381-389

Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, Haefeli WE. The frequency of inappropriate tablet splitting in primary care. *Eur J Clin Pharmacy* 2006;62(12):1065-1073

Ragupathy R, Tordoff J, Norris P, Reith D. Access to children's medicines in the United Kingdom, Australia and New Zealand in 1998, 2002 and 2007. *Pharm World Sci* 2010;32(3):386-393

Rashed SM, Nolly RJ, Robinson L, Thoma L. Weight variability of scored and unscored split psychotropic drug tablets. *Hospital Pharmacy* 2003;38(10):930-934

Rattray J, Jones MC. Essential elements of questionnaire design and development. *J Clin Nurs* 2007;16(2):234-243

Ray LD. Parenting and childhood chronicity: making visible and the invisible work. *J Pediatr Nurs* 2002;17(6):424-438

Redline C, Oliver J, Fecso R. The effect of cover letter appeals and visual design on response rates in a government mail survey. *American Association for Public Opinion Research*. 2004. Retrieved 26th April 2012
www.amstat.org/sections/srms/proceedings/y2004/files/JSM2004-000330.pdf

Rianthavorn P, Ettenger RB. Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. *Pediatr Transplant* 2005;9(3):398-407

Richey RH, Craig JV, Shah UU, Ford JL, Barker CE, Peak M, Nunn AJ, Turner MA. The manipulation of drugs to obtain the required dose: systematic review. *J Adv Nurs* 2012;68(9):2103-2112

Richey RH, Shah UU, Peak M, Craig JV, Ford CE, Nunn AJ, Turner MA. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. *BMC Pediatr* 2013;13(1):81

Rindone JP. Evaluation of tablet-splitting in patients taking lisinopril for hypertension. *JCOM* 2000;7(4):22-24

Roberts KA, Dixon-Woods M. Factors affecting uptake of childhood immunisation: a Bayesian synthesis of qualitative and quantitative evidence. *Lancet* 2002;360(9345):1596-1599

Rocchi F, Paolucci P, Ceci A, Rossi P. The European paediatric legislation; benefits and perspectives. *Ital J Pediatr* 2010;36:56

Rocchi F, Tomasi P. The development of medicines for children. Part of a series on pediatric pharmacy. *Pharmacol Res* 2011;64(3):169-175

Rosenberg JM, Nathan JP, Plakogiannis F. Weight variability of pharmacist-dispensed split tablets. *J Am Pharm Assoc* 2002;42(2):200-205

Ross LM, Wallace J, Paton JY. Medication errors in a paediatric teaching hospital in the UK: five years operational experience. *Arch Dis Child* 2000;83(6):492-497

Salmon P, Peters S, Rogers A, Gask L, Clifford R, Iredale W, Dowrick C, Morriss R. Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Fam Pract* 2007;24(3):269-275

Sampson M, McGowan J. Errors in search strategies were identified by type and frequency. *J Clin Epidemiol* 2006;59(10):1057-1063

Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol* 2009;62(9):944-952

Sayeed VA, Gupta A, Khan MA. Stability of split tablets in Pharmaceutical Stability Testing to Support Global Markets. K. Huynh-Ba, Springer. 2010

Schultz A, Sly PD, Zhang G, Venter A, Devadason SG, le Souef PN. Usefulness of parental response to questions about adherence to prescribed inhaled corticosteroids in young children. *Arch Dis Child* 2012;97(12):1092-1096

Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ, Khan MA. Tablet splitting of a narrow therapeutic index drug: a case with levothyroxine sodium. *AAPS PharmSciTech* 2010;11(3):1359-1367

Shah T, Tse A, Gill H, Wong ICK, Sutcliffe A, Gringras P, Appleton R, Tuleu C. Administration of melatonin mixed with soft food and liquids for children with neurodevelopmental difficulties. *Dev Med Child Neurol* 2008;50(11):845-849

Shah VP, Yamamoto LA, Schuirman D, Elkins J, Skelly JP. Analysis of in vitro dissolution of whole vs. half controlled-release theophylline tablets. *Pharm Res* 1987;4(5):416-419

Shaw A, Thompson EA, Sharp D. Complementary therapy use by patients and parents of children with asthma and the implications for NHS care: a qualitative study. *BMC Health Serv Res* 2006;6:76

Shilling V, Williamson PR, Hickey H, Sowden E, Smyth RL, Young B. Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study. *Health Technol Assess* 2011a;15(15):11-16

Shilling V, Williamson PR, Hickey H, Sowden E, Beresford MW, Smyth RL, Young B. Communication about children's clinical trials as observed and experienced: qualitative study of parents and practitioners. *PLoS One* 2011b;6(7):e21604

Shirkey H. Therapeutic orphans. *J Pediatr* 1968;72(1):119-120

Silagy CA, Middleton P, Hopewell S. Publishing protocols of systematic reviews: comparing what was done to what was planned. *JAMA* 2002;287(21):2831-2834

Simons KJ, Frith EM, Simons ER. Dissolution and bioavailability studies of whole and halved sustained-release theophylline tablets. *J Pharm Sci* 1982;71(5):505-511

Simunovic N, Sprague S, Bhandari M. Methodological issues in systematic reviews and meta-analyses of observational studies in orthopaedic research. *J Bone Joint Surg Am* 91 Suppl 2009;3:87-94

Sinha I, Jones L, Smyth RL, Williamson PR. A systematic review of studies that aim to determine which outcome to measure in clinical trials to children. *PLoS Med* 2008;5(4):e96

Sinha Y, Cranswick NE. How to use medicines in children: principles of paediatric clinical pharmacology. *J Paediatr Child Health* 2007a;43(3):107-111

Sinha Y, Cranswick NE. Prescribing safely for children. *J Paediatr Child Health* 2007b;43(3):112-116

Skwierczynski C, Conroy S. How long does it take to administer oral medicines to children? *Paediatric and Perinatal Drug Therapy* 2008;8(4):145-149

Slatter A, Francis SA, Smith F, Bush A. Supporting parents in managing drugs for children with cystic fibrosis. *Br J Nurs* 2004;13(19):1135-1139

Sobhani P, Christopherson J, Ambrose PJ, Corelli RL. Accuracy of oral liquid measuring devices: comparison of dosing cup and oral dosing syringe. *Ann Pharmacother* 2008;42(1):46-52

Standing JF, Tuleu C. Paediatric formulations – getting to the heart of the problem. *Int J Pharm* 2005;300(1-2):56-66

Stern MJ, Smyth JD, Mendez J. The effects of item saliency and question design on measurement error in a self-administered survey. *Field Methods* 24. 2012;13:2013

Stimpel M, Vetter H, Kuffer B, Groth H, Greminger P, Vetter W. The scored tablet – a source of error in drug dosing? *J Hypertens* 1985;3 Suppl (1):S97-99

Stockis A, DeBruyn S, Deroubaix X, Jeanbaptiste B, Lebacq E, Nollevaux F, Poli G, Acerbi D. Pharmacokinetic profile of a new controlled-release isosorbide-5-monomitrate 60mg scored tablet (Monoket Multitab). *Eur J Pharm Biopharm* 2002;53(1):49-56

Stone DH. Design a questionnaire. *BMJ* 1993;307(6914):1264-1266

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. 2000;*JAMA* 283(15):2008-2012

Sutcliffe AG. Prescribing medicines for children. *BMJ* 1999;319 (7202):70-71

Sweiss D, Wong IC. Giving medicines to children: understanding the parents' views. *Paediatr Drugs* 2004;6(1):67-69

Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. *BMJ* 2003a;326(7391):684

Taxis K, Barber N. Causes of intravenous medication errors: an ethnographic study. *Qual Saf Health Care* 2003b;12(5):343-347

Teng JC, Song CK, Williams RL, Polli JE. Lack of medication dose uniformity in commonly split tablets. *J Am Pharm Assoc* 2002;42(2):195-199

Thomas J, Song CK, Williams RL, Polli JE. Lack of medication dose uniformity in commonly split tablets. *J Am Health Syst Pharm* 2002;42(2):195-199

Thorne S. Data analysis in qualitative research. *Evid Based Nurs* 2000;3:68-70

Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. *Arthritis Care Res* 2012;64(9):1392-1404

Tong A, Lowe A, Sainsbury P, Craig JC. Experiences of parents who have children with chronic kidney disease: a systematic review of qualitative studies. *Pediatrics* 2008;121(2):349-360

Tourangeau R. Cognitive sciences and survey methods. *Cognitive Aspects of Survey Methodology: Building a Bridge Between Disciplines*. Washington DC, National Academy Press 73-100. 1984

Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: a systematic review. *Ther Drug Monit* 2005;27(1):10-17

Tuleu C, Grange J, Seurin S. The need for pediatric formulation: oral administration of nifedipine in children, a proof of concept. *J Drug Del Sci Tech* 2005;15(4):319-324

Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric ward: prospective study. 1998;BMJ 316:343-345 in Rocchi et al., 2010

Turnock C, Gibson V. Validity in action research: a discussion on theoretical and practice issues encountered whilst using observation to collect data. *J Adv Nurs* 2001;36(3):471-477

Uppal N, Yasseen B, Seto W, Parshuaram CS. Drug formulations that require less than 0.1mL of stock solution to prepare doses for infants and children. *CMAJ* 2011;183(4):E246-248

Upton D, Upton P. Development of an evidence-based practice questionnaire for nurses. *J Adv Nurs* 2006;53(4):454-458

van de Mortel TF. Faking it: social desirability response in self-report research. *Australian Journal of Advanced Nursing* 2008;25(4):40-48

van del Bruel A, Thompson MJ, Haj-Hassan T, Stevens R, Moll H, Lakanpaul M, Mant D. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. 2011;BMJ 342:3082

van Santen E, Barends DM, Frijlink HW. Breaking of scored tablets: a review. *Eur J Pharm Biopharm* 2002;53(2):139-145

van Vooren L, De Spiegeleer B, Thonissen T, Jove P, van Durme J, Slegers G. Statistical analysis of tablet breakability methods. *J Pharm Sci* 2002;5(2):190-198

Verrue C, Mehuys E, Boussey K, Remon J-P, Petrovic M. Tablet-splitting: a common yet not so innocent practice. *J Adv Nurs* 2011;67(1):26-32

Viergever RF, Rademaker CMA, Gherzi D. Pharmacokinetic research in children: an analysis of registered records of clinical trials. *BMJ Open* 2011;1(1):e000221

von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP. The strengthening in the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61(4):344-349

Walker J, Abdulsalam A, Theobald AE, Subrahmanyam R, Verma SK. Multiple-scored tablets. Weight and content uniformity of subdivisions and distribution of active constituent within and between tablets. *J Pharm Pharmacol* 1978;30(7):401-406

Waller DG. Off-label and unlicensed prescribing for children: have we made any progress? *Br J Clin Pharmacol* 2007;64(1):1-2

Walsh KE, Mazor KM, Stille C, Torres I, Wagner JL, Moretti J, Chysna K, Stine CD, Usmani GN, Gurwitz JH. Medication errors in the homes of children with chronic conditions. *Arch Dis Child* 2011;96(6):581-586

Weissman EM, Dellenbaugh C. Impact of splitting risperidone tablets on medication adherence and on clinical outcomes for patients with schizophrenia. *Psychiatr Serv* 2007;58(2):201-206

WHO. WHO Model Formulary for Children. 2010 Retrieved 30th November 2011, from http://www.who.int/selection_medicines/list/WMFc_2010.pdf

Williams A. How to.....write and analyse a questionnaire. *J Orthod* 2003;30(3):245-252

Williams MC, Tsibris JC, Davis G, Baiano J, O'Brien WF. Dose variation that is associated with approximated one-quarter tablet doses of misoprostol. *Am J Obstet Gynecol* 2002;187(3):615-619

Williams NT. Medication administration through enteral feeding tubes. *Am J Health Syst Pharm* 2008;65(24):2347-2357

Wilmot-Lee B. Improving medicine taking in epilepsy. *Pediatr Nurs* 2008;20(9):37-42

Wong IC, Wong LY, Cranswick NE. Minimising medication errors in children. *Arch Dis Child* 2009;94(2):161-164

Wong SS-L, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *J Med Lib Assoc* 2006;94(1):41-47

Wright D. Medication administration in nursing homes. *Nurs Stand* 2002;16(42):33-38

Wright D, Tomlin S. How to help if a patient can't swallow. *The Pharmaceutical Journal* 2011;286:271-274

Wright EB, Holcombe C, Salmon P. Doctors' communication of trust, care, and respect in breast cancer: qualitative study. *BMJ* 2004;328:864

Yeung VW, Wong IC. When do children convert from liquid antiretroviral to solid formulations? *Pharm World Sci* 2005;27(5):399-402

Yewale VN, Dharmapalan D. Promoting appropriate use of drugs in children. *Int J Pediatr* 2012:906570

Yin HS, Mendelson AL, Wolf MS, Parker RM, Fierman A, van Schaick L, Bazan IS, Kline MD, Dreyer BP. Parents' medication administration errors: role of dosing instruments and health literacy. *Arch Pediatr Adolesc Med* 2010;164(2):181-186

Young B, Ward J, Salmon P, Gravenhorst K, Hill J, Eden T. Parents' experiences of their children's presence in discussions with physicians about leukemia. *Pediatrics* 2011;127(5):e1230-1238

Zaid AN, Ghosh AA. Compliance of scored tablet halves produced by Palestinian pharmaceutical companies with the new European Pharmacopoeia requirements. *Arch Pharm Res* 2011;34(7):1183-1189

Zeitz K. Nursing observations during the first 24 hours after a surgical procedure: what to we do? *J Clin Nurs* 2005;14(3):334-343

Ziaian T, Sawyer MG, Reynolds KE, Carbone JA, Clark JJ, Baghurst PA, Couper JJ, Kennedy D, Martin AJ, Staugas RE, French DJ. Treatment burden and health-related

quality of life of children with diabetes, cystic fibrosis and asthma. J Pediatr Child Health 2006;42(10):596-600

Zindani GN, Streetman DD, Streetman DD, Nasr SZ. Adherence to treatment in children and adolescent patients with cystic fibrosis. J Adolesc Health 2006;38(1):13-17

Appendix 1

PubMed search strategy

Example search strategy to find drug manipulation studies (any type of drug) –
PUBMED:

("Pharmaceutical Preparations/administration and dosage"[Mesh]) OR
("Pharmaceutical Preparations/adverse effects"[Mesh]) OR ("Pharmaceutical
Preparations/analysis"[Mesh]) OR ("Pharmaceutical
Preparations/chemistry"[Mesh]) OR ("Pharmaceutical
Preparations/economics"[Mesh]) OR ("Pharmaceutical
Preparations/standards"[Mesh]) OR ("Dosage forms"[Mesh])

AND

(cut OR cutting OR split OR splitting OR crush OR crushed OR crushing OR grind OR
grinding OR halve OR halving OR halved OR halves OR quarter OR quartered OR
quarters OR quartering OR suspend OR suspension OR suspending OR suspends OR
manipulate OR manipulates OR manipulated OR manipulating OR segment OR
segmented OR segmenting OR segments OR portion OR portions OR dissolve OR
dissolves OR dissolved OR dissolving OR divides OR disperse OR disperses OR
dispersing OR dispersed OR diluted OR dilution OR dilute OR dilutes)

AND

((accuracy OR accurate OR accurately OR concentration OR repeatable OR
repeatability OR reliable OR reliability OR reproducible OR reproducibility OR
variable OR variability OR equal OR unequal OR equivalent OR inaccurate OR
inaccuracies OR inaccuracy) AND (dose OR dosage OR volume)) OR (absorption OR
bioavailability OR "drug stability" OR dissolution OR solubility OR soluble OR
"particle size" OR quality OR interaction OR interacts OR "drug toxicity" OR "adverse
effects" OR safety OR safe OR "adverse event" OR "adverse reaction" OR "adverse
drug reaction" OR "adverse effects" OR harms OR error OR errors OR overdose OR
over-dose OR underdose OR under-dose OR "dose delivery" OR "dose dumping" OR
"dose uniformity" OR sub-therapeutic OR compliance OR comply OR adherence OR
adhere OR taste OR palatable OR palatability OR tolerable OR tolerability OR cost
OR waste OR contamination))

Appendix 2

Individual drug search strategy

Example drug specific search strategy example (for warfarin) – EMBASE:

((Aldocumar or Anasmol or Befarin or Circuvit or Coumadin or Coumadine or Cumar or Fargem or Jantoven or Lawarin or Marevan or Marfarin or Maforan or Orfarin or Panwarfin or Romesa or Simarc-2 or Sofarin or Tedicumar or Tufam or Uniwarfin or Varfine or Warf or Warfant or Warfarex or Warfilone or Warfin or Waran or warfarin or Zyfarin or adoisine or athrombin k or athrombine k or athrombinek or carfin or coumafene or coumaphene or kumatox or panwarfarin or prothromadin or sodium warfarinum or tintorane or wafarin or warfarine or warnerin or alpha acetonilbenzyl)

adj15

(cut or cutting or split or splitting or crush or crushed or crushing or grind or grinding or halve or halved or halving or halves or quarter or quartered or quarters or quartering or fourths or thirds or eighths or suspend or suspension or suspending or suspends or manipulate or manipulates or manipulated or manipulating or manipulation or segment or segmented or segmenting or segments or portion or portions or dissolve or dissolves or dissolved or dissolving or dissolution or divide or divides or divided or dividing or division or disperse or disperses or dispersing or dispersed or dispersion or diluted or dilution or dilute or dilutes or disintegrate or disintegrates or disintegrating or disintegration or disintegrated)).ti,ab

Appendix 3

Author Year Paper title

	N/A ⁹	N/R ₁₀	Yes	Further details (if req.)	Descriptor
Internal validity:					
Title summarises the study?					
Abstract: structured?					
Abstract: provides clear summary of the study?					
Are funding sources identified?					
Are any potential conflicts of interest identified and adequately explained?					
Introduction/background:					Rationale for the study to be identified
- Population identified?					Patient groups to whom this manipulation may apply
- Incidence?					Of the situation for the manipulation
- Driver for study identified?					Reasons/explanation why this particular study is being undertaken
Were eligibility criteria for participants clear?					Include in further details any possible concerns about bias
Clear rationale for the selection of all the medications involved given?					To include both the medications under investigation and any controls (where used)
Were concomitant medications/foods specified?					
Were adverse events considered?					

⁹ Not applicable

¹⁰ Not reported

	N/A ⁹	N/R ₁₀	Yes	Further details (if req.)	Descriptor
Were adverse events clearly reported?					
Methods:					
Medication details given? <ul style="list-style-type: none"> - Generic name - Brand name - Form - Strength - Shape - Scoring - Manufacturer - Lot number 					
Primary aim/purpose of the study clearly stated?					
Any secondary aims clearly stated?					
Hypothesis clearly stated?					
Sample size determination completed?					Should include type 1 error, power, event rate in control group, treatment effect of interest
RCTs/CCTs:					
- Sequence generation					Was there sequence generation and was it adequately described
- Allocation concealment					Was there allocation concealment and was it adequately described
- Blinding of participants, personnel and outcome assessors					

	N/A ⁹	N/R ₁₀	Yes	Further details (if req.)	Descriptor
Crossover studies:					
- Has the order of receiving treatments been randomised?					Randomisation needed to avoid the risk of changes in outcome over time
- Was it clear how many treatments or periods were being used?					
- Was a suitable wash-out period used?					Need to avoid the bias of a possible carry-over effect from the drug from one period to the next
- Were drop-outs reported and considered acceptable?					Possible risk of bias where participants received one treatment but not the second
- Paired analysis completed?					Needed to account for within person differences
Surveys:					
- Is the sample considered to be representative of the population to be studied?					
- Is there evidence of matching of the questions to the concepts being measured and the population studies?					
- Was the questionnaire appropriately piloted?					
- Were interviewers trained on interviewing techniques and the subject matter of the survey?					
- Were measures taken to assess inter-interviewer agreement?					
- Were there appropriate attempts to maximise response rate?					
- Was there appropriate analysis and reporting techniques?					
Manipulation:					
- Is the manipulation clearly described? (could it be					

	N/A ⁹	N/R ₁₀	Yes	Further details (if req.)	Descriptor
reproduced)					
- Was there a justification for any equipment used for the manipulation?					Such as reason for the choice of tablet splitter used
- Was a description of the equipment given?					Note if manufacturer specified
- Was there any effort made to ensure that all the drug was administered?					Additional effort relating to the manipulation
- Were there adequate descriptions of any physical changes during the manipulation?					Qualitative descriptions e.g. powdering or crumbling or fragmentation or difficulties with dissolution?
- Was the person undertaking the manipulation specified?					To include – health care professional; parent; student; training etc.
- Were there measures to ensure consistency/reproducibility of the manipulations by the person undertaking the manipulation?					Such as, training of those doing the manipulations, all manipulations completed by the same person
- Were there measures to ensure consistency/reproducibility of the technique used?					Such as orientation of the tablet, or methods of ensuring all of the tablet crushed?
- Were any adverse events related to taking a manipulated drug reported?					
Measurement methodology:					
- Has the measurement methodology been reported as validated?					Stated that a valid method has been used
- Could it be repeated?					Is there sufficient explanation of the method to allow for replication
- Are sources of variability quantified; intra assay variability, inter assay variability?					
- Was the active ingredient measured to assess the accuracy of the manipulation or was a marker such as weight used?					

	N/A ⁹	N/R ₁₀	Yes	Further details (if req.)	Descriptor
- Where weight was measured were there sufficient description of the measures used?					Details of the balance used including sensitivity and quality checks
- Were regulatory criteria used for assessing tablet dose accuracy?					Such as adapted USP criteria for half tablets
- Was there incomplete data reporting?					Yes if high drop-out rates, outcomes reported for some groups of participants, pre-specified outcomes not reported
External validity:					
Are the results/conclusions relevant to the aims/objectives of the study?					
Are results critically appraised in relation to previous work?					
Are claims made for other situations?					Other clinical situations or other patient groups
Is a target group of those liable to be using this manipulation identified?					
How are links made between the study and any application in other contexts? – literature, analogy/experience					Lines of argument from the literature Unsubstantiated lines of argument, relating to what is assumed to be expected practice
Are pharmaceutical factors that impact on generalisability identified and discussed					e.g. excipients, manufacturing process and how they might affect the results
Are the implications of therapeutic index of the drug and possible implications for manipulations identified and discussed?					
Is there consideration of whether the manipulation would require quality assurance in clinical practice?					Methods of ensuring consistency in manipulation in clinical situations
Are manipulation risks to those manipulating the drug discussed? Are manipulation risks to those taking the manipulated drug discussed?					

	N/A ⁹	N/R ₁₀	Yes	Further details (if req.)	Descriptor
Are the conclusions of the study supported by the results and the discussion?					

Appendix 4

Observational study reference guide

MODRIC – data observation forms: definitions of data to be collected

Overall: where data is missing/unavailable at the time of the observation note in additional comments box if boxes on the form are left blank it will be assumed that this data has been accidentally not recorded and will be treated as missing data

Section A: Background data

Box on form	Data to be collected
Date/Time	Date and time drug prescribed to be given at
Time given	Time administered
Patient ID	AH no. to be taken from drug kardex (if not on the drug kardex and taken from elsewhere or if the patient only has an NHS no. then record this and note in additional comments)
Gestation age at birth	
HCP	The HCP checking and giving the drug
Weight	To be taken from the drug kardex (if not on kardex, take from notes and note in additional comments)
Route of administration	Oral, rectal, IV etc. (where oral being given via PEG/NG tube note this additionally)
Product name/manufacturer	To be taken from the packaging used
Pharmacist comments	Note any pharmacy annotations to the drug kardex (if there are none note this or put a line through the box)
Diagnosis	To be asked of the HCP giving the drug

Section B: Tablets or Capsules

Tablet cut or broken	
Box on form	Data to be collected
Score line	Y/N also note number of score lines
Tablet shape	Oval, round, square etc. (where the observer thinks that perceptions may differ e.g. between oval/round note in additional comments and an assessment can be made retrospectively)
Number of segments	Where there is an odd number note the reason (e.g. 3 segments as the tablet has been split into 2 halves and 1 half split into quarters)
Segments appeared equal in size	Refers to the segment of which $\frac{1}{2}$ is being given
Powder generated	Y/N (unintentionally generated fragments/particles as a result of the manipulation (regardless of size) i.e. fragments not intended to be administered)
Approximate fraction of tablet given	$\frac{1}{2}$, $\frac{1}{4}$ etc.
Location of manipulation	Where manipulation took place e.g. medicine trolley, treatment room, bedside (in ICU this includes preparation on the trolley in the bedside)
Equipment used	Specify e.g. syringe, medicine cup etc.
Remaining segments	Discarded/retained (if retained where stored)

Tablet crushed	
Box on form	Data to be collected
Enteric coated	Y/N (to be taken from product packaging, where Y check with HCP if this is routine/expected practice)
Fraction of tablet given	½, ¼ etc.
Location of manipulation	Where manipulation took place e.g. medicine trolley, treatment room, bedside
Equipment used	Specify e.g. syringe, medicine cup etc.
Tablet dispersed	
Box on form	Data to be collected
Dispersible tablet	Y/N (to be taken from product packaging)
Dispersed in(liquid & volume)	Specify (e.g. water and 5mL, if volume unclear note in additional comments)
Tablet split first? Powder?	Y/N for both (powder refers to powder generated i.e. unintentionally generated fragments/particles as a result of the manipulation)
Powder included in dispersal?	Y/N (Y where any powder that has been generated by the splitting of the tablet has been dispersed, N where this residue has not been added to the liquid being used to disperse the tablet)
Tablet appeared fully dispersed	Y/N (if N add details)
Mixed (specify)	Y/N (note how mixed e.g. stirred with syringe, spoon etc.)
Time: dispersal to administration	Approximate time e.g. 1min, 10mins etc.
Location of manipulation	Where the manipulation took place e.g. medicine trolley, treatment room, bedside
Equipment used	Specify e.g. syringe, medicine cup etc.
Drawn from approx. what depth	Note whether the portion to be administered was taken from the top, middle or bottom of the container
Capsule dispersed	
Box on form	Data to be collected
Dispersed in(liquid & volume)	Specify (e.g. water and 5mL, if volume unclear note in additional comments)
Contents appeared fully dispersed	Y/N (if N add details)
Mixed (specify)	Y/N (note how mixed e.g. stirred with syringe, spoon etc.)
Time: dispersal to administration	Approximate time e.g. 1min, 10mins etc.
Location of manipulation	Where the manipulation took place e.g. medicine trolley, treatment room, bedside
Equipment used	Specify e.g. syringe, medicine cup etc.
Drawn from approx. what depth	Note whether the portion to be administered was taken from the top, middle or bottom of the container

Section C: Liquids, Suppositories, Enemas, Nebulisers or Transdermal Patches

Liquid diluted	
Box on form	Data to be collected
Dispersed in(liquid & volume)	Specify (e.g. water and 5mL, if volume unclear note in additional

	comments)
Mixed (specify)	Y/N (note how mixed e.g. stirred with syringe, spoon etc.)
Dilution appeared to change the appearance of the liquid	Give details such as changes in colour or consistency
Location of manipulation	Where the manipulation took place e.g. medicine trolley, treatment room, bedside
Equipment used	Specify e.g. syringe, medicine cup etc.
Drawn from approx. what depth	Note whether the portion to be administered was taken from the top, middle or bottom of the container
Suppository	
Box on form	Data to be collected
Cut direction	Vertically (cut along the length of the suppository), horizontally (cut across the width of the suppository)
Number of segments	Total number of pieces the suppository cut into
Segments appeared equal in size	Y/N, specify if N, or if cut horizontally give further details
Approx. % of suppository given	e.g. 25%, 50%, 66%, if other approx. % give details
Direction suppository given	End of the suppository inserted first; blunt or pointed
Location of manipulation	Where the manipulation took place e.g. medicine trolley etc.
Cut with a knife	Y/N
Other equipment	Specify
Enemas	
Box on form	Data to be collected
Enema manipulation prior to or after administration	Prior/after e.g. ½ an enema given by discarding ½ first or by giving ½ to the patient and discarding the remainder
Proportion enema contents removed (specify)?	Approx. volume of enema contents removed e.g. 25mL, or if less accurately done ½, ¼ etc. specify how removed e.g. using syringe to measure, volume approximated by HCP
Approx. % of enema given	e.g. 25%, 50%, 66%, if other approx. % give details
Location of manipulation	Where the manipulation took place e.g. medicine trolley etc.
Equipment used	Specify
	Where there is any other type of manipulation of an enema e.g. a dilution, record the details as free text in additional comments
Transdermal patches	
Box on form	Data to be collected
Patch cut or covered	Cut/covered (specify if there are markings on the patch to guide cutting/covering)
If cut, no. of segments	Where this is an odd number note the reason (e.g. 3 segments as the patch has been split into 2 halves and 1 half has been split into quarters)
If covered approx. % of patch covered	e.g. 25%, 50%, 66%
Approx. % of patch applied	e.g. 25%, 50%, 66%
Remainder of patch	Discarded/stored (if stored specify where)
Location of manipulations	Where the manipulation took place e.g. medicine trolley etc.
Equipment used	Specify
Extra adhesion needed for patch	If used specify what used and if it covered whole or part of the patch

Nebuliser	
Box on form	Data to be collected
Dispersed in(liquid & volume)	Specify (e.g. water and 5mL, if volume unclear note in additional comments)
Location of manipulation	Where the manipulation took place e.g. medicine trolley etc.
Equipment used	Specify

Section D: IVs

IV bolus	
Box on form	Data to be collected
Original drug	Powder for reconstitution/ready prepared solution/other (specify)
Reconstitution details	e.g. mixed with 2mL water
Volume and dose of reconstituted drug or ready prepared solution taken	e.g. 1.2mL being 0.5mg of drug taken from the vial
Diluted in(liquid & volume)	e.g. saline, 100mL
Volume given and dose	Volume removed from diluted solution and the dose that this is presumed to contain (e.g. 2mL, 0.05mg of drug)
Location of manipulation	Where the manipulation took place e.g. medicine trolley etc.
Equipment used	Specify
Syringe labelled	Y/N, note when e.g. as soon as drawn up, at bedside

IV infusions (≥2 dilutions)	
Box on form	Data to be collected
Original drug	Powder for reconstitution/ready prepared solution/other (specify)
Reconstitution details	e.g. mixed with 2mL water
Volume and dose of reconstituted drug or ready prepared solution taken	e.g. 1.2mL being 0.5mg of drug taken from the vial
First dilution, diluted in(liquid & volume)	e.g. saline, 100mL
Volume removed and dose	Volume removed from diluted solution and the dose that this is presumed to contain (e.g. 2mL, 0.05mg of drug)
Second dilution, diluted in(liquid & volume)	Volume and liquid used for the infusions e.g. saline 50mL
Location of manipulation	Where the manipulation took place e.g. medicine trolley etc.
Equipment used	Specify
Syringe labelled	Y/N, note when e.g. as soon as drawn up, at bedside

Sections B, C and D

Box on form	Data to be collected
Manipulation checked by 2 HCPs	Y/N (if N note if there was a reason for this)
Manipulation expected practice by HCP	Y/N, ask HCP giving the drug, if N ask for further details
Manipulation repeated for any reason	Note reason
Any source of reference used	Note source if used

Appendix 5

Parent/Carer interview prompt guide

Background: Child's age; Diagnosis; Current prescribed medication

- a) Were they taking medicines from a very young age/since babyhood
 - b) Is the child taking a fairly regular set of medicines that they are almost always on, or do their prescriptions change regularly?
 - c) What are the medicines for?
-
- 1) What do you feel about administering medicines to your child at home?

 - 2) What are the challenges you face when administering medicines to your child at home?

 - 3) What happens when your child is reluctant to/refuses to or is unable to take their medicines?
 - a) Could you describe these situations and any methods that you use when they occur?
 - b) Any reasons for refusal to take the meds? Can you describe what happened?
 - c) Could you describe a typical drug administration where this happens and the methods that you may use to ensure that the medicine is taken?
 - d) Does your child ever have difficulties with swallowing medicines (if so – are there any particular medicines that this applies to and what methods do you use to ensure that the medicine is taken in this situation)?

 - 4) Some parents have told us that giving a child the prescribed dose is difficult. What is your experience about this?
 - a) Have you had to give your child any medicines where getting this prescribed dose was difficult – such as where half a tablet/portion of a sachet/half of a nebuliser dose was needed?

- b) Can you describe examples of this and methods that were used to get the dose prescribed?
 - c) Do you have any concerns about this?
 - d) Was there any advice on this that you received that was helpful, or would have been helpful, from healthcare professionals?
- 5) Do you have any further thoughts/concerns about administering medicines to your child or children generally that may be helpful for those designing medicines for children?