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Drug-related Problems (DRPs) in Children with Kidney Disease

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Thesis presented for the degree of

Doctor of Philosophy

PLAGIARISM STATEMENT

I certify that this thesis is my original work and that any collaboration and materials from work of others are clearly acknowledged and cited.

17th SEPTEMBER 2014

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Signature Date

DEDICATION

My husband

Mama & Abah

Mama Aida & Abah Md Noor

and

Fellow pharmacists who share the passion of bringing the wind of positive changes to practice and professionalism

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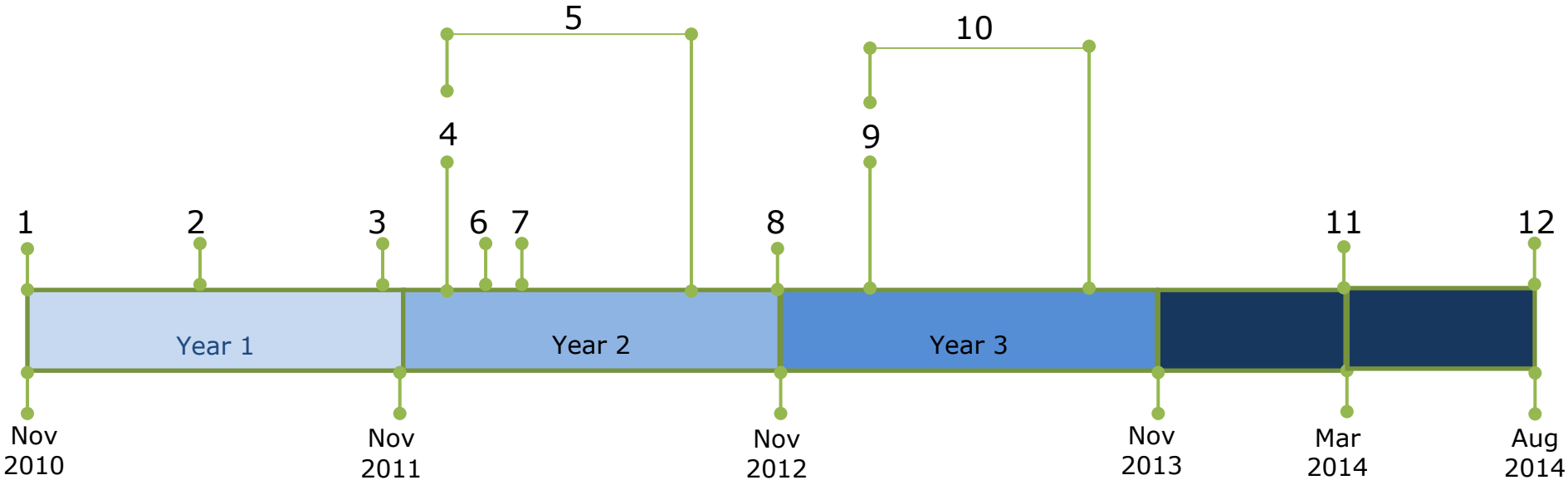

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ABSTRACT

Introduction

Medicines are used with the intention of benefitting from their effect. The effects of medicines can also be undesirable and potentially lead to harm. A drug-related problem (DRP) is a term used to describe problem(s) that exist in the use of medicines. There remains a distinct paucity of data on the epidemiology of DRPs in children with kidney disease.

Aim

To investigate the epidemiology of DRPs in children with kidney disease in clinical practice at tertiary Paediatric Nephrology units.

Methods

Study 1: Prospective observational study on the characteristics of DRPs in hospitalised children with kidney disease.

Study 2: Randomised control trial on clinical pharmacist (CP) interventions in resolving DRPs on the renal outpatient clinic.

Results

Study 1: A total of 127 patients were recruited and a total of 203 DRPs were identified. The incidence of DRP was 51.2% (95% CI 43.2-60.6%) of patients reviewed by the CPs. The number of medicines prescribed per child was the only significant risk factor for the occurrence of DRPs (OR 1.06, 95% CI 1.02-1.10, p=0.002). The majority of DRPs were minor in clinical significance (68%, n=138/203). The predominant DRPs were sub-optimal drug effect. These DRPs were associated with drug selections and dosage errors.

Study 2: A total of 100 patients were recruited (Control n=53, Intervention n=47). The trial showed no effect of intervention in the resolution of active DRPs (p=0.96) between the Control and Intervention arms.

Conclusion

DRPs are common in children with kidney disease and necessitate a comprehensive approach to their identification and resolution. Their characteristics in both settings are different even though the majority of them shared a similar level of clinical significance. Further research is required to evaluate the effectiveness of pharmacists' intervention in resolving DRPs at the outpatient clinics.

OVERVIEW OF THE THESIS CHAPTERS

CHAPTER 1 Introduction

This thesis starts with an introduction to chronic kidney disease (CKD) in childhood, followed by the concept of pharmaceutical care (PC) and drug-related problems (DRPs).

CHAPTER 2 Systematic literature review: Drug-related problems in children with chronic kidney disease

Chapter 2 presents a review of current literature on DRPs in children with CKD and the justification for research on this topic. The research aim, research questions and strategies are presented at the end of this chapter.

CHAPTER 3 Methodological approach

Based on the predetermined research questions, this chapter discusses the selections of study designs and the research tools used in the two main studies which are reported in Chapter 5 and 6.

CHAPTER 4 Feasibility studies

Two feasibility studies that were conducted prior to each of the main studies are presented in this chapter. Feasibility Study (I) works on developing an operational definition for Pharmaceutical Care Network (PCNE) classification system for DRPs and to test the feasibility of an observational study at the

selected hospitals. Feasibility Study (II) is to test the conduct of a randomised control trial at the renal outpatient clinic. The challenges in the proposed method for the studies in this research are also described.

CHAPTER 5 Prospective observational study on the characteristic of DRPs in hospitalised children with kidney disease

Chapter 5 presents the work of the first study (Study 1) of this research. Children hospitalised with kidney disease are hypothesised to have higher incidence of DRPs than those without kidney impairment who are hospitalised at the general medical wards; and the characteristics of DRPs in this population are also assumed to be similar to those in their adult counterparts. To the best of our knowledge, there has been no study carried out to identify the epidemiology of DRPs in this group of patients. Findings reported in this study therefore add new knowledge.

CHAPTER 6 The effect of clinical pharmacist-led interventions in resolving DRPs at the renal outpatient clinic: A randomised control trial

Chapter 6 reports a randomised control trial (RCT) of clinical pharmacists-led interventions to identify and resolve DRPs in children attending the renal outpatient clinic (Study 2). Findings reported in this trial give new insight in understanding the characteristics and the management of DRPs in this population of interest at the outpatient setting.

CHAPTER 7 Overall discussions

Finally, Chapter 7 summarises and discusses the epidemiology of DRPs in children with kidney disease and provides practice implications of the research findings. The strengths as well as the limitations of the overall research are also discussed and future research topics are identified.

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ABBREVIATIONS

ADE(s)	Adverse drug event(s)
ADR(s)	Adverse drug reaction(s)
ATC	Anatomical Therapeutic Chemical
BSA	Body surface area
CI	Confidence Interval
CKD	Chronic kidney disease
CP(s)	Clinical pharmacist(s)
CPG	Clinical practice guideline
CSN	Clinical specialist nurse
DRP-Rf	Drug-related Problem Registration Form
DRP(s)	Drug-related problem(s)
DTP(s)	Drug-therapy problem(s)
ELCH	Evelina London Children's Hospital
eMR(s)	Electronic Medical Record(s)
ePS	Electronic Prescribing System
ESCAs	Effective Shared Cage Agreements
ESKF	End-stage kidney failure
GFR	Glomerular filtration rate
GOSH	Great Ormond Street Hospital for Children
GSTT	Guy's and St. Thomas'
HD	Haemodialysis
ME(s)	Medication error(s)
MeSH	Medical subject headings
MR	Medication review

NHS	National Health Service
NKF/ DOQI	National Kidney Foundation/ Dialysis Outcome Quality Indicator
NMS	New Medicine Service
OR	Odds ratio
PC	Pharmaceutical care
PCNE	Pharmaceutical Care Network Europe
PD	Peritoneal dialysis
PE(s)	Prescribing error(s)
PN	Pharmacist Note
RCT	Randomised control trial
R&D	Research & Development
REC	Research Ethics Committee
RRT	Renal replacement therapy
UK	United Kingdom
UKRR	UK Renal Registry
USRDS	United States renal data system
WHO	World Health Organisation

CHAPTER 1

Introduction

1.1 Introduction

Chronic kidney disease (CKD) is one of the most common chronic illnesses in childhood, and the patient requires lifelong healthcare as well as potential future solid organ transplantation (Kim et al., 2013; Warady and Chadha, 2007). Pharmacotherapy management of patients with kidney disease is specialised and complex, thus putting this group of children at risk of developing problems associated with drug therapy, or so-called drug-related problem (DRP). Pharmaceutical Care (PC) has been advocated as a strategy to manage DRPs. This chapter begins with an introduction to CKD in childhood, followed by the concept of PC and DRP.

1.2 Chronic kidney disease in childhood

The current definition and classification of CKD in children is based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) clinical practice guidelines (CPG) which is also adopted by the United Kingdom (UK) National Institute of Health and Clinical Excellence (NICE) CPG (Hogg et al., 2003). The criteria for the definition of CKD according to the NKF/KDOQI are described in Table 1.1.

Table 1.1 Criteria for the definition of CKD according to the NKF/KDOQI guideline (Hogg et al., 2003)

A patient has CKD if either of the following criteria are present:

1) Kidney damage for ≥ 3months, as defined by structural or functional abnormalities of the kidney with or without decreased GFR, manifested by one or more of the following features:

- Abnormalities in the composition of the blood or urine
- Abnormalities in imaging tests
- Abnormalities on kidney biopsy

2) GFR < than 60 ml/min/1.73m^2 for ≥ 3months with or without the other signs of kidney damage as described above.

There are five stages of CKD that correspond to the glomerular filtration rate (GFR). Among patients with CKD, the stage of disease should be assigned based on the level of GFR, as shown in Table 1.2.

CKD Stage 5 or end-stage kidney failure (ESKF) is defined as either GFR less than 15 ml/min/1.73m^2 or need for initiation of renal replacement therapy (RRT). The two types of RRT are dialysis (which includes haemodialysis (HD) and peritoneal dialysis (PD)) and kidney transplantation.

Table 1.2 The staging of CKD according to the NKF/KDOQI guideline

CKD Staging	GFR (ml/min/1.73m^2)	Description	Action Plan
1	>90	Kidney damage with normal or increased GFR	Treat primary and comorbid conditions. Slow CKD progression, cardiovascular disease risk reduction
2	60-89	Kidney damage with mild reduction of GFR	Estimate rate of CKD progression
3A 3B	59-45 44-30	Moderate reduction of GFR	Evaluate and treat complications
4	15-29	Severe reduction of GFR	Prepare for kidney replacement therapy
5	<15	Kidney failure	Renal replacement therapy

1.2.1 Prevalence and incidence

The sources of the epidemiology data on CKD during childhood concentrate on the severe and late stages of renal impairment (Warady and Chadha, 2009). The exact number of children with moderate to severe pre-dialysis CKD (Stages 1 to 4) is unknown (Harambat et al., 2011). In the UK, the number of children being treated in specialist paediatric nephrology units is probably 7 to 10 times more than the prevalent dialysis population (Kim et al., 2013).

In 2012, a total of 861 children and adolescents under the age of 18 with ESKF were receiving treatment at paediatric centres in the UK, of which 78.9% (n=679) were receiving RRT (Pruthi et al., 2012b). In children aged less than 16 years, the incidence and prevalence of ESKF were 9.0 and 56.7 per million age-related population (pmarp) and these figures have risen steadily over the last 15 years (Pruthi et al., 2012b). Similar trends were also reported from population-based studies in other European countries with prevalence of 29 to 74 and incidence of 7 to 12 cases pmarp in children less than 18 years of age (Ardissino et al., 2003; Deleau et al., 1994; Esbjorner et al., 1997).

1.2.2 Causes of kidney disease in childhood

Causes of CKD in children are different from those in adults. In the adult population, CKD is secondary to uncontrolled hypertension and diabetes mellitus (Levey et al., 2003). In the paediatric population, almost half of all CKD cases are due to congenital kidney disorders such as obstructive uropathy and aplasia, hypoplasia and dysplasia (Warady and Chadha,

2007). An analysis of demographic characteristics of children with CKD Stage 3 to Stage 5 in South East England over a five-year period showed that the most common cause of ESKF in children were renal dysplasia (44%), followed by glomerular disease (17%) and obstructive uropathy (15%) (Kim et al., 2013). A fairly similar distribution of primary kidney disease has been reported over the years in the UK Renal Registry (UKRR) annual reports (Lewis et al., 2009; Lewis et al. 2010; Sinha et al., 2011b; Pruthi et al., 2012b).

Drug nephrotoxicity accounts for only a small fraction of the cause of ESKF in the UK cohort, which is 0.5% and 1.6% in the 2009 and 2010 annual reports respectively (Lewis et al. 2010; Pruthi et al., 2012a). This is probably the result of safe prescribing in paediatrics (Sinha and Cranswick, 2007) and that only serious drug events are usually reported (Brown et al., 2008b). Therefore, the actual occurrence of drug problems during treatment of paediatric nephrology patients is yet to be evaluated.

1.2.3 Mortality and morbidity

The mortality rates in paediatric patients requiring RRT is lower than in their adult counterparts (Warady and Chadha, 2009). However, compared to the general paediatric population, the mortality rate for children receiving dialysis therapy is between 30 and 150 times higher (McDonald and Craig, 2004). As an example, the expected remaining lifetime for a child 0 to 14 years of age and on dialysis is only 20 years (USRDS, 2004 cited in Warady and Chandha, 2007 page 2000). Kidney transplantation offers better survival compared to dialysis (Pruthi et al., 2012b; Harambat et al., 2011).

The average life expectancy in young adults who started RRT during childhood was reported as 63 years for those with successful kidney transplantation compared with 38 years for those who remain on dialysis (Kramer et al., 2009). The main causes of mortality in children on RRT are cardiovascular disease and infection (Harambat et al., 2011; Warady and Chadha, 2009, Pruthi et al., 2012b).

The nature of CKD progression and its complications requires the use of multiple drug therapy. Furthermore, most medicines used in children are used unlicensed and off-label with limited data on safe and effective doses; and this can lead to an increase in risk of adverse drug events (Impicciatore et al., 2001) and other problems in the use of medicines. In pharmacy practice, the management and resolution of DRP is the core activity of PC (Hepler and Strand, 1990). The following section introduces the concept of PC and DRP.

1.2.4 Factors associated with the occurrence of DRPs

The risk factors for the occurrence of DRPs in children with kidney disease are unknown. A study on DRPs in the general paediatric population concluded that children with an average of five or more prescriptions and children who were transferred from another hospital or ward were more likely to experience DRPs (Rashed et al., 2012b).

In patients with kidney disease, it is generally accepted that those who are on dialysis or post kidney transplant are at higher risk of DRP because more drugs are required to control disease progression and complications

(Cardone et al., 2010; Kaplan et al., 1994b). Furthermore, dialysis removes medicines from blood circulation and complicates drug therapy in these patients (Verbeeck and Musuamba, 2009).

DRPs were expected to be higher in young children including those with kidney disease. Age as a predictor for DRPs has shown conflicting results in previous research. Some studies have reported that adverse drug events are more prominent in young children (Kaushal et al., 2001; Zakharov et al., 2012) while others have shown the opposite (Rashed et al., 2012a; Avery et al., 2013). In the UK, the age group of 0-4 years was reported to be most vulnerable for medication incidents. Administration of incorrect dose was reported as the highest medication incident in neonates and children (NPSA, 2009). In the adult renal population, DRPs were found to increase with age. A possible explanation for this is the effect of aging on kidney function (Rowe et al., 1976) and increasing age in the adult population coincides with more comorbidities (Nascimento et al., 2009). Declining kidney function reduces the excretion of drugs and toxic metabolites. In contrast, paediatric kidneys have dynamic changes in physiology and improve with age (Atiyeh et al. 1996; Coulthard 1985; Heilbron et al. 1991).

The effect of gender in the occurrence of DRPs was also inconclusive. In the adult population, female gender was reported as a factor related to DRPs in dialysis treatment, specifically non-adherence to medications (Kammerer et al., 2007). Some studies in adults suggest that females are more prone to develop ADR but this is not consistent in all studies (Bates et al., 1999; Blix et al., 2004; Fattinger et al., 2000).

1.3 Pharmaceutical Care and Drug-related problems

Pharmaceutical care (PC) is a philosophy that shifted pharmacy practice from its traditional role of being product-focused to being patient-outcome-focused. In 1990, Helper and Strand published a landmark article on pharmacy practice and defined PC as:

> "The responsible provision of drug therapy for the purpose of achieving definite outcomes intended to improve a patient's quality of life"

Drug therapy is administered for the purpose of achieving definite outcomes that improve a patient's quality of life. However, whenever drugs are given, the potential for outcomes that diminish the patient's quality of life is always present and may lead to drug-related morbidity and mortality (Hepler and Strand, 1990). An example of this is when an antibiotic with a narrow therapeutic index is prescribed for the treatment of septicaemia. Considering other medical conditions are taken care of, inappropriate drug level monitoring may either result in sub-optimal dose or drug toxicity. Sub-optimal dose is an example of treatment failure to cure septicaemia and nephrotoxicity is an adverse drug event as a consequence of drug toxicity. Sub-optimal treatment and drug toxicity are examples of DRPs.

1.3.1 Drug-related problem: Definitions

The landmark article by Helper and Strand (1990) defined DRP as:

"An event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care"

Within this definition, the word 'problem' denotes a definite drug-related event that is open to detection, treatment or prevention. An event qualifies as a DRP when two conditions exist: (1) a patient must be experiencing or must be likely to experience symptoms and (2) these symptoms must have an identifiable or suspected relationship with drug therapy (Strand et al., 1990).

Other than DRP, terms that have been used to describe problems related to the use or outcome of medicines are drug therapy problem, medicine- or medication-related problem, pharmacotherapy failure, drug treatment failure, negative clinical outcome related to medicine and treatment-related failure (AbuRuz et al., 2006; Granada Consensus Committee, 2007; van Mil et al., 2004). These terms evaluate drug problems according to the Donabedian theory and hence contributed to many terms and classification systems for DRPs (Fernandez et al., 2004). Donabedian theory is a conceptual model that provides a framework for examining health services and evaluating quality of care (McDonald et al., 2007). According to the model, information about quality of care can be drawn from three categories: structure, process and outcomes. 'Structure' describes the context in which care is delivered, including hospital buildings, staff, financing, and equipment. 'Process' denotes the transactions between patients and providers throughout the delivery of healthcare. Finally,

'outcomes' refers to the effects of healthcare on the health status of patients and populations.

An example of how drug problems fit into the Donabedian theory as either the process or outcome of a treatment can be explained in the case of a patient who is taking a correct dose of ACEi and experiences a dry cough, the problem and cause of the dry cough are debatable depending on the perspective of the discussion. From the pharmacotherapy process point of view, the selection of ACEi is inappropriate for the patient and has created a problem, i.e. ACEi-induced dry cough. On the other hand, ACEi-induced dry cough is the outcome from inappropriate selection of medicine.

1.3.2 Drug-related problem: Classification systems

In order to give evidence on the benefits of managing DRPs, not only the types of problems have to be identified but their contributory factors and resolution should be documented. This situation lead to the development of classification systems for DRPs. The classification systems were developed based on the definition of DRP adapted by the individual researcher (AbuRuz et al., 2006; van Mil et al., 2004). From 1990 to 2003, 14 classification systems were introduced but only eight stated the definitions for DRPs (van Mil et al., 2004). Two classification systems were introduced after year 2003 (AbruRuz et al., 2006; Gordon et al., 2005). Some of the existing classifications were revised to newer versions (Granada Consensus, 2007; PCNE, 2010). Appendix 1 presents an overview of the definitions and classification systems for DRP classifications published from 1990 to 2010. The examples of DRP classification systems that have been used in research

are briefly explained in the following sub-sections. The classifications are represented by the name of the relevant researchers or organisation and arranged by year of publication.

1.3.2.1 Strand classification (1990)

Strand et al. in 1990 published a landmark article on the first classifications of DRP (Strand et al., 1990). The Strand classification is a simple scheme containing eight types of DRPs and has been the foundation of PC and the newer DRP classifications (Table 1.3).

1.3.2.2 Cipolle classification (1998)

The Cipolle classification refers to DRPs as 'drug-therapy problems (DTP)' (cited in van Mil, 2004 pg 861). This classification introduced a selection of causes for the identified problems. It is more comprehensive than the Strand classification but its use is limited to only problems that have happened or manifested (Table 1.4).

Table 1.3 Classifications of drug-related problems (Strand et al., 1990)

Drug-related problem*	Details
DRP1: Untreated indication	The patient is not receiving drug therapy for medical condition(s) that requires treatment.
DRP 2: Improper drug selection	The patient has a medical condition for which the wrong drug is being taken.
DRP 3: Sub-therapeutic dosage	The patient has a medical condition for which too little of the correct drug is being taken.
DRP 4: Over dosage	The patient has a medical condition for which too much of the correct drug is being used.
DRP 5: Adverse drug reaction	The patient has a medical condition resulting from an adverse drug reaction.
DRP 6: Drug interactions	The patient has a medical condition resulting from Drug-Drug, Drug-Food or Drug-Laboratory interactions.
DRP 7: Failure to receive medication	The patient has a medical condition that is the result of not receiving the prescribed drug.
DRP 8: Medication used without indication	The patient has a medical condition that is the result of taking a drug for which there is no valid medical indication.

Definition of DRP: an undesirable patient experience that involves drug therapy and that actually or potentially interferes with the desired patient outcome.

Table 1.4 Classifications of drug-therapy problem (Cipolle et al., 1998)

Drug therapy problem (DTP)	Causes
Indication	
1: The patient has a medical condition that requires the initiation of new or additional drug therapy	• The patient has a new medical condition requiring initiation of new drug therapy. • The patient has a chronic disorder requiring continuation of drug therapy. • The patient has a medical condition that requires combination pharmacotherapy to attain synergism/potentiation of effects. • The patient runs the risk of developing a new medical condition preventable by the use of prophylactic drug therapy and/or premedication.
2: The patient is taking drug therapy that is unnecessary given his or her present condition	• The patient is taking a medication for which there is no valid indication at this time. • The patient accidently or intentionally ingested a toxic amount of a drug or chemical resulting in the present illness or condition. • The patient's medical problem(s) are associated with drug abuse, alcohol use, or smoking. • The patient's medical condition is better treated with non-drug therapy. • The patient is taking multiple drugs for a condition

Drug therapy problem (DTP)	Causes
	for which only single-drug therapy is indicated. • The patient is taking drug therapy to treat an avoidable adverse reaction associated with another medication.
Effectiveness	
3: The patient has a medical condition for which the wrong drug is being taken.	• The patient has a medical problem for which this drug is not effective. • The patient is allergic to this medication. • The patient is receiving a drug that is not the most cost-effective for the indication being treated. • The patient has risk factors that contraindicate the use of this drug. • The patient is receiving a drug that is effective but not least costly. • The patient is receiving a drug that is effective but not the safest. • The patient has an infection involving organisms that are resistant to this drug. • The patient has become refractory to the present drug therapy. • The patient is receiving an unnecessary combination product when a single drug would be appropriate.

Drug therapy problem (DTP)	Causes
4: The patient has a medical condition for which too little of the correct drug is being taken	• The dosage used is too low to produce the desired response for this patient. • The patient serum drug concentration is too far below the desired therapeutic range. • Timing of prophylaxis (pre-surgical antibiotic given too early) was inadequate for this patient. • Drug, dose, route or formulation conversions were inadequate for this patient. • Dose and interval flexibility (insulin sliding scales, "as needed" analgesics) were inadequate for this patient. • Drug therapy was altered prior to adequate therapeutic trial for this patient.
Safety	
5: The patient has a medical condition resulting from an adverse drug reaction	• The drug was administered too rapidly for this patient. • The patient is having an allergic reaction to this medication. • The patient has identified risk factors that make this drug too dangerous to be used. • The patient has experienced an idiosyncratic reaction to this drug. • The bioavailability of the drug is altered due to an interaction with another drug or food the patient is

Drug therapy problem (DTP)	Causes
	taking. • The effect of the drug has been altered due to enzyme inhibition/induction from another drug the patient is taking. • The effect of the drug has been altered due to displacement from binding sites by another drug the patient is taking. • The patient's laboratory test result has been altered due to interference from a drug the patient is taking.
6: The patient has a medical condition for which too much of the correct dose is being taken	• Dosage too high for this patient. • The patient's serum drug concentration is above the desired therapeutic range. • The patient's drug dose was escalated too rapidly. • The patient has accumulated drug from chronic administration. • Drug, dose, route, formulation conversion were inappropriate for this patient. • Dose and interval flexibility (insulin sliding scales, "as needed" analgesics) were inadequate for this patient.

Drug therapy problem (DTP)	Causes
Compliance	
DRP 7: The patient has a medical condition resulting from not taking the drug appropriately	• The patient did not receive the appropriate drug regimen because a medication error prescribing, dispensing, administration or monitoring was made. • The patient did not comply (adhere) with the recommended directions for use of the medications. • The patient did not take the drug as directed owing to the high cost of the product. • The patient did not take the drug(s) as directed because of a lack of understanding of the directions. • The patient did not take the drug(s) as directed because it would not be consistent with the patient's health beliefs.
Definition of DTP: Any undesirable event experienced by the patient that involves or is suspected to involve drug-therapy and that actually or potentially interferes with a desired patient outcome	

1.3.2.3 Granada classification (1998, 2002, 2007)

The Granada classification was developed by a group of Spanish experts in 1998 and was further revised in 2002 and 2007 (Granada Consensus, 2007). In the First Granada Consensus, the term DRPs was changed to 'drug therapy problems' that affect health outcomes. In 2002, the second consensus clarified the misinterpretations about the context of health outcome from the previous consensus (Granada Consensus, 2002). The third Granada Consensus is similar to the second but established drug therapy problems as negative health outcome (Table 1.5). In this consensus, negative health outcome is defined as pharmacotherapy that for different reasons either do not achieves therapy objectives, or produce undesirable effects. The Granada Consensus did not solve the difficulty in distinguishing the cause of the problem from the actual problem (Amariles, 2006).

Table 1.5 Categories of drug-therapy problems of the third Granada Consensus

Domains	Sub-domains
Necessity	DTP 1: The patient suffers from a health problem as a consequence of not receiving the medication he needs.
	DTP 2: The patient suffers from a health problem as a consequence of receiving a medicine that he does not need.
Effectiveness	DTP 3: The patient suffers from a health problem as a consequence of a non-quantitative effectiveness of the medication.
	DTP 4: The patient suffers from a health problem as a consequence of a non-quantitative ineffectiveness of the medication.
Safety	DTP 5: The patient suffers from a health problem as a consequence of a non-quantitative safety problem of a medicine.
	DTP 6: The patient suffers from a health problem as a consequence of a quantitative safety problem of a medicine.
Definition of DTP: Negative health outcomes resulting from pharmacotherapy that for different reasons either do not achieve therapy objectives, or produce undesirable effects.	

1.3.2.4 Gordon classification (2005)

A group of researchers in the UK published a paper on the development and validation of a screening tool to identify patients' experience in taking medications at community pharmacies and surgeries (Gordon et al., 2005). As this study originated from the UK, the term 'medication-related problem (MRP)' was used instead of 'drug'. This work looked at drug problems from the patient's point of view rather than that of the healthcare providers. In this classification, MRP was defined as 'any problem experienced by a patient that may impact on their ability to manage or take their medicines effectively'. Problems that were not solved at the community level could be a trigger factor for poor treatment outcome in the long run. This classification is a potential tool that can be adapted for the DRP study in the outpatient clinic settings.

1.3.2.5 AbuRuz classification (2006)

AbuRuz and colleagues in 2006 proposed the term and classification for 'treatment-related problem' as an alternative to the term DRP. Treatment-related problem was defined as an event or circumstance involving patient treatment that actually or potentially interferes with an optimum outcome for a specific patient (AbuRuz et al., 2006). AbuRuz pointed out that the term DRP limits the scope of pharmaceutical care. Two examples were given: (1) untreated disease and (2) a diabetic or a hypertensive patient without prescription or proper education about the illness or treatment – both were suggested as an indication of a problem in the treatment rather than with the drug. This opinion is debatable depending on the perspective

of the discussion. For instance, in the aforementioned examples, one could argue that not providing a drug that has a definite indication to treat a disease indicates a problem in the use of the drugs (process of drug use). A diabetic or hypertensive patient without prescription or who has a lack of knowledge about the illness and treatment would result in the drug not being used as intended and thus result in poorly controlled blood pressure and blood glucose levels (outcome of drug use). This tool also has the drawback of only identifying manifested problems. However, it has the advantage of being validated for the identification of DRP at the inpatient settings (AbuRuz et al., 2011).

1.3.2.6 Pharmaceutical Care Network Europe (PCNE) classification (1999-2010)

The PCNE classification system defines DRP as an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes (PCNE, 2010). The first version of the PCNE classification for DRP was developed in 1999. The most recent version is version 6.2, introduced in 2010. At present, this is the only classification that has options to record the types of problems, the causes, the interventions to solve the problems and the outcome of the intervention.

1.3.2.7 DRP classification systems in the present research

The evolutionary development of DRP classifications demonstrates the need for practical application of theoretical concepts. Being pragmatic about the

selection of existing DRP classifications that best suit individual practice or research objectives could be an alternative to the introduction of more new concepts. The work in this thesis adapted two DRP classification systems – the PCNE and the Gordon classifications.

The present research adapted the PCNE classification system for DRP because it was the most appropriate option available at the time of the study's initiation. The PCNE classification system has been successfully adapted in a similar international multicentre study investigating DRPs in general paediatric patients involving the paediatric population in the UK (Rashed et al., 2012b). It also has an open hierarchical structure for each category, which consists of: type of problems, causes of the problems, recommendations taken to solve the problems, and resolutions. The open hierarchical structure enables addition of new elements to this classification system, which is an advantage for this study. The hierarchical structure also applies a coding system to facilitate data recording.

The Gordon classification system was developed using information from patient interviews at the pharmacies and surgeries as well as during home visits. Even though it has not been used in studying DRPs in paediatrics, the Gordon classification could be adapted for the second study of this research (Study 2), which was conducted at the outpatient setting.

1.3.3 'Drug-related problem' as a term in medication safety

There is no consensus in current literature on whether DRP should be regarded as similar to adverse drug event (ADE), adverse drug reaction

(ADR) or medication error (ME) which are synonymous with harm. The scientific community agrees that there is a lack of homogeneity in the terminologies not only in the context of DRP but also in the context of medication safety in general (Pintor-Marmol et al., 2012; Yu et al., 2005).

Even though DRP was introduced as an element that could contribute to drug-related morbidity and mortality (Hepler and Strand, 1990) it has never been endorsed as an official term in medication safety. For instance, medication safety-related terms identified from an electronic search of websites of organisations associated with medication safety did include ADE, ADR and ME (Yu et al., 2005) but not DRP or its equivalent. In another review on classification of terminology in drug safety the main focus of discussion was only on ADRs (Aronson and Ferner, 2005).

The European Council Expert Group on Safe Medication Practices suggested avoiding the use of 'medication-' or 'drug-related problems' in describing medication safety (Airaksinen et al., 2006). According to this expert group, the working definition of DRP is designed for pharmaceutical care and not seen as applicable to medication safety. Based on the discussion above, it is reasonable to refer to DRP as a broader term to describe potential or manifested problems arising from the use of drugs in a patient's treatment whereby ADR and ME are incorporated as potential causative factors in the treatment process. The concept of DRP promotes medication safety and the rational use of medicines.

1.3.4 Linking DRP to ADR, ADE and ME

In the scope of this thesis, DRP is perceived to be connected to medication safety in several perspectives. In the examples of DRP classifications previously described, the elements of medication safety can either be a type or the contributory factors of DRPs. As an example, ADR was listed as a type of DRP in the Strand classifications (refer to DRP 5 in Table 1.3). In the Cipolle classification, 'allergy reaction' was listed as the cause of DRP (refer to Table 1.4). In the PCNE classification, prescribing error (PE) was listed as a cause for DRP (refer to Chapter 3, Figure 3.5). Thus, it is important to distinguish between the ADEs, ADRs, MEs and DRPs before embarking in the present research.

An ADE is an unintended noxious event occurring during drug therapy. It is an injury or harm suspected to be drug-related (Leape et al., 1991; MHRA, 2006).

An ADR is an unwanted or harmful reaction which occurs after administration of a drug or drugs and is suspected or known to be due to the drug(s). The reaction may be a known side effect of the drug or it may be new and previously unrecognised (MHRA, 2006).

Medication error is a failure in any step of the treatment process that leads to, or has the potential to lead to, harm to the patient (Morimoto et al. 2004). Medication errors include errors in the process of prescribing, transcribing, dispensing and administration. Prescribing error (PE) is an important aspect of ME and it a common cause of ADE in paediatrics (Ghaleb et al., 2006; Kaushal et al., 2001).

The link between DRP to ADR and ME can be explained in these two cases: (Case 1) If a patient on a correct dose of angiotensin-converting enzyme inhibitor (ACEi) experiences a dry cough, this case qualifies as a DRP because the patient experiences a dry cough, a symptom which is directly related to drug therapy, which in this case is an ACEi. If the ACEi is prescribed for a patient who has a known history of ACEi-induced dry cough, then the cause is 'medication error'; whereas, if it was prescribed for a patient who does not have a known history of ACEi-induced dry cough, then it is a non-allergic 'adverse drug reaction' (ADR).

Another example (Case 2) is a patient on a phosphate binding agent who experiences itchiness due to hyperphosphataemia. This case also qualifies as a DRP because the patient experiences symptoms of hyperphosphataemia, which may be related to sub-optimal treatment due to a number of reasons, such as sub-therapeutic dose requiring additional phosphate binders or, alternatively, patient's non-adherence. Table 1.6 summarises the differences between ADE, ADR, ME and DRP.

Table 1.6 The differences between drug-related problem (DRP), adverse drug reaction (ADR), adverse drug event (ADE), and medication error (ME) (Ibrahim et al., 2013)

	Drug-related Problem (DRP)	**Adverse Drug Reaction (ADR)**	**Adverse Drug Event (ADE)**	**Medication Error (ME)**
Definition	An event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care	An unwanted or harmful reaction which occurs after administration of a drug or drugs and is suspected or known to be due to the drug(s)	An unintended noxious event suspected to be drug-related	A failure in the treatment process that leads to, or has the potential to lead to, harm to the patient
*Dose of the drug during the incident	↔ ↑ ↓	↔	↔ ↑ ↓	↔ ↑ ↓
Potential cause of the harm	Inappropriate drug or dosage regimen, drug form, dose, treatment duration, administration, supply and procurement and	Type A (predictable): Exaggerated reaction towards the desired pharmacology effect of the drug. The reaction is dose dependent and	Suspected to be related to the effect of the drug	Mishaps or accidents during any stage of drug handling - prescribing, transcribing, dispensing and administering

	Drug-related Problem (DRP)	**Adverse Drug Reaction (ADR)**	**Adverse Drug Event (ADE)**	**Medication Error (ME)**
	patients' behaviour towards drug therapy	reversible with dosage adjustment. Type B (idiosyncratic): Unknown cause and could possibly be related to immunology response towards the drug (e.g. allergic reaction)		
Improvement measures	Pharmaceutical care practice	ADR detection and reporting system	Medication safety awareness and prevention	Medication safety awareness and prevention
Example Case 1 Patient A experienced a dry cough that is suspected to be due to an angiotensin converting enzyme inhibitor (ACEi). The	YES, because the patient is experiencing a symptom which is related to the drug	YES, because the symptom could be an idiosyncratic response to ACEi	YES, because the symptom is suspected to be induced by ACEi	YES, if ACEi is prescribed for a patient who has a known history of ACEi-induced dry cough. NO, if ACEi was prescribed for a patient who has no history of

	Drug-related Problem (DRP)	**Adverse Drug Reaction (ADR)**	**Adverse Drug Event (ADE)**	**Medication Error (ME)**
drug was stopped and changed to an alternative therapy.				ACEi-induced dry cough.
Example Case 2 Patient B experienced itchiness, identified as a symptom of hyperphosphataemia despite being on a phosphate binding agent	YES, because the symptom is related to suboptimal treatment with phosphate binding agent	NO, because the symptom is not a pharmacological effect of phosphate binding agent	NO, because the symptom is not suspected to be caused by phosphate binding agent	YES If there is a prescribing error contributing to suboptimal treatment dose. NO If there are no incidents of mishaps or accidents (e.g. patient's non-adhering to treatment)
* ↔ Normal dose; ↑ Overdose/Toxic ; ↓ Under dose				

1.4 Summary

Previous studies in the adult populations have shown that DRPs are common in patients with kidney disease and their management has been shown to improve disease-oriented and patient-oriented outcomes (Kaplan et al., 1994a; Pai et al., 2009; Cardone et al., 2010). The next chapter addresses the gap in the knowledge regarding DRPs in children with CKD.

CHAPTER 2

Systematic Review: Drug-Related Problems In Children With Chronic Kidney Disease

2.1 Introduction

The focus of this chapter is the review of published studies on DRPs in children with CKD.

2.2 Methods

2.2.1 Search terms and strategy

Search terms were derived from three main keywords: 'drug-related problem', 'paediatric' and 'chronic kidney disease'. A list of search terms associated with each keyword was generated from the MeSH database in PubMed and Alm Tree mapping in Embase. Relevant terms were also handpicked from literature (van Mil et al., 2004; AbuRuz et al., 2006). Keywords not listed as Medical subject headings (MeSH) term were searched for as phrases using the free text search mode. The following electronic databases were searched for all periods until 31st May 2011: BIOSIS Preview (Web of Knowledge), Embase (Ovid), International Pharmaceutical Abstract (Ovid) and Medline (Ovid). The list of search terms and the search strategy are shown in Appendix 2.

2.2.2 Eligibility criteria of selected articles

The criteria for relevant studies were: (1) involving participants aged 18 years and below who were diagnosed with CKD at all stages; (2) studies reported in the English language; and (3) studies reporting on the types of DRP, possible causes of the problem and outcomes of interventions (or

actions taken) to solve the identified problem in children with kidney disease. The above inclusion criteria were based on literature in the adult CKD population. Articles related to medications that referred to specific therapeutic medications or routes of administration were excluded.

2.2.3 Data extraction

All articles were merged into the EndNote X3® program (Thomas Reuters, New York, US). Three reviewers (NI, YG and SP) were involved. In the initial screening, duplicates were removed and all identified abstracts were manually read for their applicability of the predetermined criteria. To standardise the assessment for relevant articles in the screening phase, all reviewers followed a standard assessment protocol (Figure 2.1). The full-text manuscripts of the potentially relevant articles were obtained by electronic or paper copy for assessment. Otherwise, the corresponding authors were contacted.

Information extracted from the full-text manuscripts was recorded in a proforma and this included the following data: year and country of study, subject characteristics (age, clinical characteristic, sample size), study design, epidemiology data of DRP (type, possible causes and classification scheme) and outcomes of intervention or suggestions for the DRP. Throughout this process, any disagreement was solved by consensus among the research team.

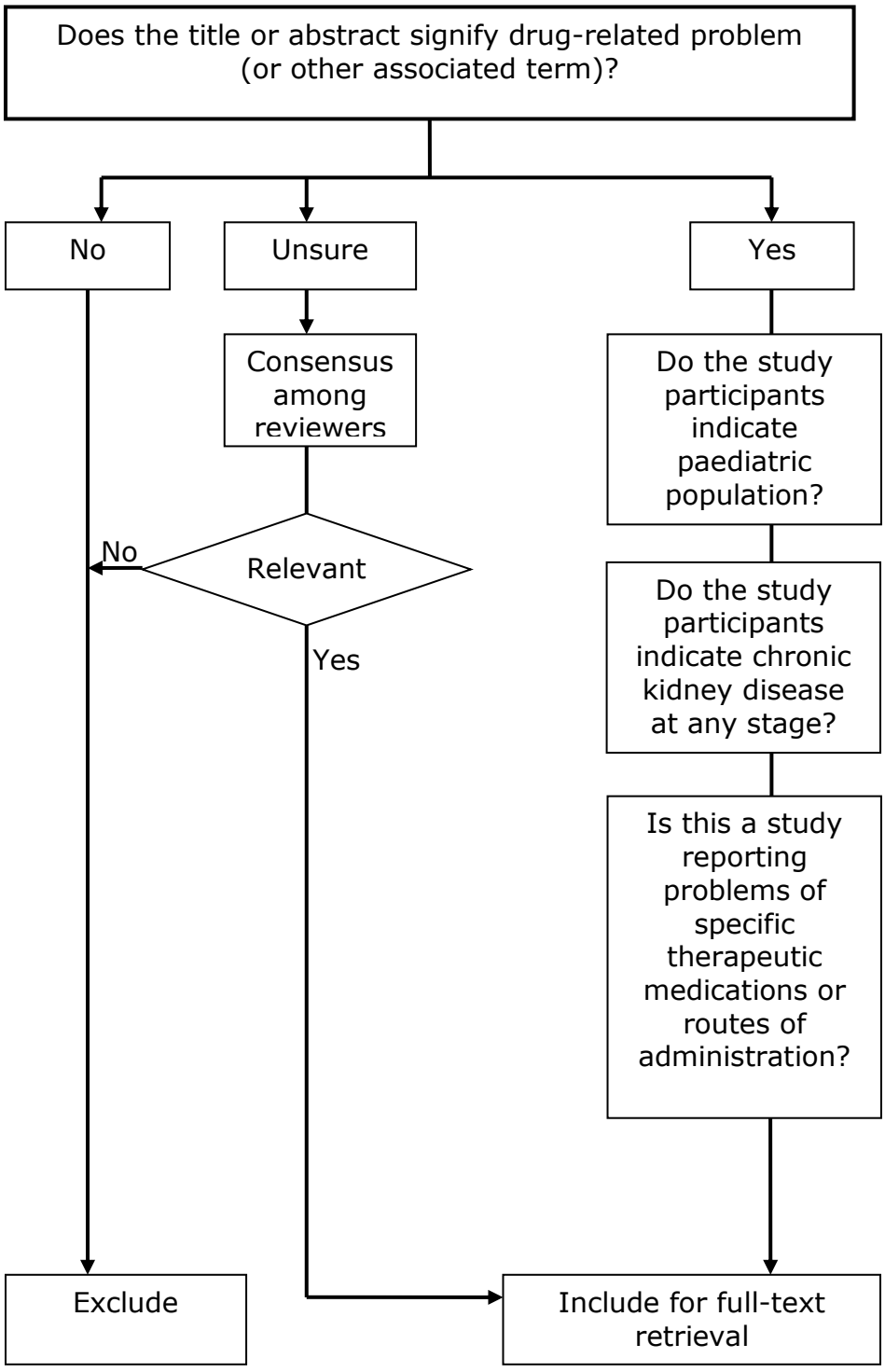


Figure 2.1 Flowchart of data extraction

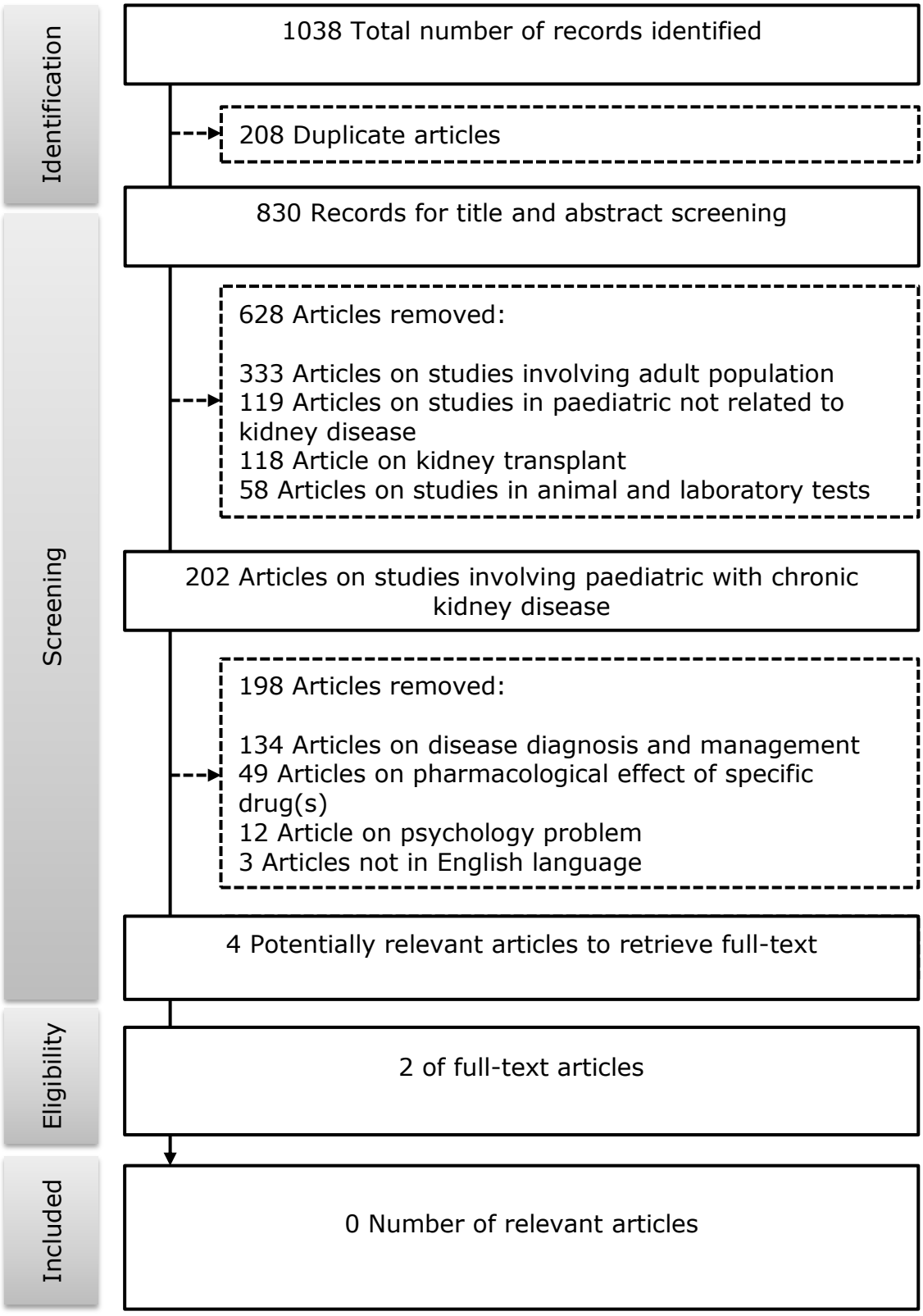


Figure 2.2 Flowchart of result analysis

2.2.4 Excluded literature

Of the aforementioned four potentially relevant articles (Table 2.1), one was a descriptive study aimed at identifying the potential roles of clinical pharmacists in a paediatric nephrology and hypertension clinic through the provision of cognitive pharmacy services (So et al., 2010). Another study reported on the impact of electronic prescribing system (ePS) on the rate of prescribing errors (PE) at a paediatric nephrology clinic (Jani et al., 2008). The remaining two articles were abstracts of unpublished studies (Lincenberg et al. 1986; Perrier-Cornet et al., 2010). For the two abstracts, efforts to retrieve the full-text by contacting the corresponding author and checking for availability in the British Library Integrated Catalogue were unsuccessful. Further information from the BLIC showed that the two studies had not been published in full. The details of the excluded data are described in the following paragraphs and summarised in Table 2.1.

So et al., 2011

This is a descriptive study aimed at identifying the potential roles of the CPs as a provider in a paediatric nephrology and hypertension clinic. The study was conducted at a referral clinic for children and adolescents with CKD and hypertension from Central and Eastern North Carolina in the US. The study was conducted for eight months and involved a total of 283 patients with the mean age (SD) of 10.3 (5.6). The patients' clinical characteristic was described as having CKD Stage 1 to 5 or high blood pressure.

The CP's potential role was determined by providing a cognitive pharmacy service which was referred to as services provided by pharmacists related to the management of the effectiveness and appropriateness of patients' therapeutic regimens. Within this service, for each patient, the pharmacist would discuss treatment recommendations and pharmaceutical care issues with the physicians before medical consultation. After medical consultation, patients would be referred back to the pharmacist if there was a change in drug regimen or if there was a need for further management of pharmaceutical care issues.

The pharmacy-based interventions that were performed during clinic visits include: (1) counselling and/or verification of understanding on current drug therapy; (2) adherence assessment; (3) conveying patients' concerns/issues regarding their drug therapy to physicians; (4) provision of information to patients/parents about drugs that were not prescribed by their nephrologists; (5) drug dosing/monitoring recommendation; (6) provision of drug information; (7) identification of drug discrepancies; (8) medication education for kidney transplant candidates; (9) counselling on new drugs; (10) updating drug allergies; (11) customised letters warning against pregnancy for females of child-bearing age on ACEi or angiotensin receptor blockers and (12) calling the patient's pharmacy to obtain refill rate if the patient did not bring drugs to clinic or in situations where there was a suspicion of non-adherence.

The study result showed the mean number of pharmacist's intervention per patient was 2.3 (SD: 1.0) and the mean number of medication prescribed per patient was 5.7 (SD: 4.8). Counselling on medication regimens to

patients and family members was the most frequent pharmacy service provided at the clinic (85%). The most challenging part of the counselling was to provide an understanding of medication indication and side effects. Factors that contributed to this challenge were: the lack of understanding of medications; difficulty in interpreting medication labels; below-average literacy level of study population; lack of parental supervision for adherence; and lack of appropriate drug formulations. This study also reported a trend that showed patients on haemodialysis or after kidney transplant were on more medications compared to those in the pre-dialysis stage ($p<0.05$); this is expected because disease complications increase with severity. The overall rate of non-adherence was 15%. Indeed, it would be interesting to have more information on the different rate of non-adherence between patients at different stages of CKD.

This study is useful to determine the types of pharmacy services at a paediatric nephrology clinic, but there was a lack of information on DRPs as well as the clinical and non-clinical outcomes of the services towards patients' treatment. Such information would be beneficial to evaluate the impact of clinical pharmacy practice (Fernandez-Llimos et al., 2004). It would also provide guidance in initiating medicine improvement programmes at facilities with restricted numbers of renal pharmacists (or nurses) and financial resources.

Perrier-Cornet et al., 2010

This study fulfils most of the criteria of interest; however, the results were not published. Thus, information presented here is limited to what was reported in the abstract. This study aimed to describe pharmaceutical care issues in a nephrology paediatric care unit in France. The study was conducted over seven months and involved a total of 28 patients aged in the range of two months to 20 years. The acceptance of pharmacists' interventions by prescribers and clinical significance for each intervention were also evaluated.

Drug dose adjustment was the most frequently encountered DRP, representing 30% of the reported problem. Antihypertensive and drugs affecting haematopoiesis were the two groups of drugs most frequently associated with DRP. Out of 44 pharmacists' interventions to solve the identified DRPs, 66% were accepted by prescribers. Clinical significance of the interventions was rated as moderate in 22 cases, of mild importance in 15 cases and major in seven cases. Further information on the causes of the identified DRPs, outcomes of the intervention and the description of severity were not mentioned in the abstract.

Jani et al., 2008

Jani and colleagues conducted a pre- and post- intervention study aimed at determining the impact of ePS on the rate of prescribing error (PE) at a paediatric nephrology clinic of a tertiary paediatric hospital in the UK. The outcome measures were prescribing error rate, number of illegible items and number of patients' visits that were error-free.

In the pre-intervention phase, prescribers handwrote prescriptions on a designated form. This form was given to patients or parents who then took it to the pharmacy for dispensing. Four months after the introduction of the ePS at the clinic setting, prescriptions were prospectively collected. A total of 1140 prescriptions containing 2242 items were retrospectively reviewed for errors by two researchers. The inter-rater reliability for error identification was 0.65 (95% CI 0.46-0.85).

This study concluded that the introduction of ePS reduced the rate of prescribing error by approximately 94% from 77.4 to 4.8% in the pre- and post-intervention phases respectively (95% CI 75.3-79.4%), reduced the number of items with missing essential information from 73.3% (95% CI 71.1-75.4%) to 1.4% (95% CI 0.7-2.6%) and increased error-free visits by 69% (95% CI 64-73.4%).

This study is useful to justify the need for an ePS but it was limited to the occurrence of PE rates at the renal outpatient settings.

Lincenberg et al., 1986

This abstract reported on the influence of group-based reinforcement to improve dietary and medication compliance in five adolescents undergoing continuous ambulatory peritoneal dialysis; patients were aged between 14 and 18 years. Further information regarding the country where the study took place, the method and results was not reported.

Table 2.1 Characteristics of the excluded articles

Author/ Year of publication/ Country of study	Study design/ Study duration	Settings	Sample size	Age of study participants (year)	Clinical characteristic of study participants	Characteristics of DRP	Description of the causes of DRP	Type of intervention to manage the DRP	Outcome of intervention	Reasons for exclusion
So et al., 2011 USA	Observational 8 months	Paediatric nephrology and hypertension clinic	283 patients	10.3 (SD:5.6)	Patients with primary diagnosis of kidney disease or hypertension	Not reported	Not reported	Pharmacy cognitive service at the nephrology clinic	Not reported	No information on characteristics of DRP and outcome of interventio n
Perrier-Cornet et al., 2010 France	Descriptive 6 months	Nephrology care unit of a teaching hospital	28 patients	Between 0.2 to 20	All patients	Inappropria te drug doses (other characteristics not mentioned)	Not reported	Pharmaceut ical intervention through provision of pharmaceut ical care by pharmacist	Not reported	Full-text not available Full characteristics of DRP, causes and outcome of interventio n not reported in

Author/ Year of publication/ Country of study	Study design/ Study duration	Settings	Sample size	Age of study participants (year)	Clinical characteristic of study participants	Characteristics of DRP	Description of the causes of DRP	Type of intervention to manage the DRP	Outcome of intervention	Reasons for exclusion
										abstract
Jani et al., 2008 UK	Pre- and Post- 12 months	Paediatric nephrology clinic of an acute tertiary care paediatric hospital	520 patients	8.8 (SD:5.6)	All patients	Prescribing error	Conventional hand written prescriptions	Electronic prescribing system	94% reduction in prescribing errors after electronic prescribing was introduced	Only one specific type of DRP
Lincenberg et al., 1986	Pre- and Post-	Not reported	5 patients	Between 14 to 18	On CAPD	Non-adherence to medication and dietary restrictions	Not reported	Group-based reinforcement on adherence	Not reported	Full-text not available Only one specific type of DRP

CAPD (continuous ambulatory peritoneal dialysis), DRP (drug-related problem), SD (standard deviation), USA (United States of America), UK (United Kingdom)

2.3 Discussion

2.3.1 Generating search terms

The development of the search terms and strategy was based on a trial-and-error approach whereby the candidate search terms identified were entered into the bibliographic database with the corresponding syntax and tested regarding whether references from the development set could be detected. The major problem in retrieving relevant articles contributed to the non-standardised terms used to describe problems related to the use of drugs. It became even more complicated because the phrase 'drug-related problems' is not listed as a MeSH term. The word 'drug' without appropriate syntax attracted an enormous amount of articles related to the use of abusive substance.

As previously explained in Chapter 1, DRP is not a unique term to describe problems related to the use of medicines. Revision of secondary sources by Fernandez-Llimos et al. (2004) on published papers using the concept of DRP between 1990 to 1999 reported that, from a total 457 articles, 77.6% were retrieved for the term 'drug-related problem', 11.6% for 'drug-therapy problem', 10.7% for 'medication-related problem' and less than 1% for 'medicine-related problem'. One of the reasons that contribute to the varieties of terminologies are the use of the term 'medicine' or 'medication' and 'drug' by publications in British and America respectively (Fernandez-Llimos et al., 2004; Granada Consensus, 2007; van Mil et al., 2004).

In this systematic review, the researcher generated a list of candidate search terms by referring to two references. One was a review on DRP

classification systems from 1999 until 2003 (van Mil et al., 2004) and the second article was a study aimed at developing and validating a tool to assess treatment-related problems (AbuRuz et al. 2006). These two articles also reported difficulties in identifying previous literature on DRP from electronic journal databases; each article suggested a list of search terms for 'drug-related problems'.

The terms 'medication error' and 'prescribing error' were initially categorised under 'questionable search term'. The aforementioned terms were questionable because they refer to accidents that can potentially cause harm to patients during any stage of drug use. In contrast, DRP refers to inappropriate use of drug, which can interfere with the desired treatment outcome, both actual and potential. However, these terms were then included to increase specificity based on the fact that errors can contribute to the occurrence of DRPs.

2.3.2 Justification for research

The limitations of the excluded articles demonstrate the gap in knowledge in this area. The reasons for the need of epidemiological data on DRP in children with kidney disease are outlined below.

Firstly, paediatric doses for most drugs are calculated by estimated GFR, BSA or body weight (Atiyeh et al., 1996; Brandt et al., 2006); determining the appropriate dosage regimen for an optimum therapeutic effect poses challenges in daily practice. The availability of data on DRPs is beneficial to construct proactive strategies to promote drug safety in treating children

with kidney diseases. Furthermore, kidney disease and dialysis alter the pharmacokinetic properties of drugs, which makes dosing more difficult (Hassan et al., 2009).

Secondly, children with kidney impairment may be at greater risk of developing DRPs due to the nature of disease progression and complications that demand complex drug therapy. The NKF/KDOQI clinical practice guideline for CKD in children and adolescents recommends that a medication review should be performed at all visits for dosage adjustment, detection of potentially adverse drug effects on kidney function or complications of CKD, detection of drug interactions and therapeutic drug monitoring (Hogg et al., 2003). Even though the term 'DRP' was not imposed, they are examples of problems related to the use of medicines. A better understanding of the nature and characteristics of DRPs in the paediatric-CKD population provides information on the risk factors for the occurrence of DRPs.

Currently, risk factors for the occurrence of DRPs in children with CKD are assumed to be similar to those of adults with CKD or general paediatric populations. However, this assumption may not be valid. Studies of DRPs in the general paediatric population indicate that the risk factors for this patient group are the use of off-labelled drugs, younger age and polypharmacy (Impicciatore et al., 2001; Kimland et al., 2007). Whereas risk factors identified from adult DRP studies are: higher stages of disease based on NKF/KDOQI clinical practice guideline; having more than three concurrent disease states; drug regimen changed more than four times in the past twelve months; more than five medications in present drug

regimen; on more than twelve medication doses per day; history of non-adherence; and presence of drugs that require therapeutic drug monitoring (Churchwell and Mueller, 2007; Grabe et al., 2007; Kaplan et al., 1994a; Manley et al., 2003).

Finally, most drug management studies in paediatric nephrology were conducted in the post kidney transplant group. For example, one area that has received much interest in post kidney transplantation is medication non-adherence. This may be related to the immediate malignant outcomes associated to both organ and patient outcomes as a direct result of non-adherence. In comparison, effects of non-adherence in children with CKD may not be evident relatively immediately (Chisholm-Burns et al., 2009; El Nahas, 2005). The consequences of underestimating non-adherence and other DRPs among children (and parents) in the pre-transplant stage may lead to unforeseen treatment failure. It is important to note that patients with dialysis-dependent CKD are also likely to experience DRPs.

2.4 Summary

There is currently no epidemiological data on DRPs in children with kidney disease. Children with kidney disease are at risk of experiencing DRPs and DRPs may potentially lead to harm. It is not known whether the characteristics of DRPs in this group of interest resemble their adult counterpart and/or the general paediatric population. The occurrence of DRPs in clinical practice is also difficult to recognise without a structured approach. Therefore, further research using a standardised method and

operational definition is required to identify the characteristics of the DRPs in this specific group.

2.5 Research Aims and Strategy

Arguments in the section above strongly justify the need for further research in this area of knowledge. The aims of this thesis were to investigate the epidemiology of DRPs using standardised definitions and methods, and the effect of CPs' intervention in the management of DRPs in paediatric nephrology patients. The research questions are:

1) What are the nature and characteristics of DRPs in paediatric nephrology patients?
2) What are the potential risk factors associated with the occurrence of DRPs in paediatric nephrology patients?
3) How significant are the DRPs in the clinical settings?
4) Is a pharmacy-based intervention effective in resolving DRPs in the renal outpatient clinic?

In order to answer the research questions, two studies were conducted. The first study (Study 1) was a prospective observational study at the paediatric renal wards and the second (Study 2) was a randomised control trial that took place at the paediatric nephrology clinics. Table 2.2 summarises the objectives and strategies for the whole research.

Table 2.2 Research objectives and strategies

Research Objectives	Strategy
To determine the gap in current knowledge on DRPs in children with chronic kidney disease.	Literature review on DRPs in children with chronic kidney disease (Chapter 2)
To identify the characteristics, predictors and severity rate of DRPs in hospitalised children at the inpatient setting	*Study 1: Prospective observational study on the characteristic of DRPs in hospitalised children with kidney disease (Chapter 5)
To identify the characteristics, predictors and severity rate of DRPs at the renal outpatient clinics To evaluate the effectiveness of pharmacist intervention in resolving DRP at renal outpatient clinics	*Study 2: The effect of CP interventions in resolving DRPs at the renal outpatient clinic: A randomised control trial (Chapter 6)
*Feasibility studies were conducted prior to the initiation of Study 1 and Study 2 and are reported in Chapter 4.	

The next chapter discusses the methodological approach that has guided the conduct of this research.

CHAPTER 3

Methodological Approach

3.1 Introduction

This chapter gives an overview of the study sites, study designs and tools adapted in this research. The first three sub-sections in this chapter give an overview on the setting of the study sites, the justification of the selected study designs and the evaluation of outcomes in patient safety research. The next three sub-sections describe the methods and tools that have been adapted to detect, classify and assess the severity of DRPs in the current research. The final section gives an overview of ethical considerations. Throughout this chapter, Study 1 refers to the prospective observation study that was conducted at the inpatient setting and Study 2 refers to the RCT on the effectiveness of CP interventions at the renal outpatient clinic setting.

3.2 Setting of the study sites

This research was conducted at two National Health Service (NHS) children's hospitals in London:

a) The Evelina London Children's Hospital (ELCH), Guy's and St. Thomas' Hospital NHS Foundation Trust, King's Health Partners
b) The Great Ormond Street Hospital for Children (GOSH), NHS Trust

The selection of both hospitals as the study sites is justified in the sense that they are among the largest renal units in the UK. The ELCH is the main referral centre for paediatric nephrology cases in London and the South East of England. The GOSH serves a bigger population which includes London, Eastern, South East, South West and West Midland regions. The total

number of children with CKD is difficult to determine and is suspected to be at least triple than the reported number for the established kidney failure population (Kim et al., 2013; Harambat et al., 2011).

Both sites are teaching hospitals that provide tertiary care to children aged less than 18 years. The renal units in both hospitals provide comprehensive inpatient and outpatient-based diagnostic and treatment services for children with renal disorders and are led by teams of paediatric renal consultants and specialists, supported by a dedicated team of medical, nursing and healthcare professionals including doctors, nurses, CPs and nutritionists.

3.2.1 Inpatient setting and ward pharmacy services

Study 1 was conducted in the renal wards at ELCH and GOSH. Both hospitals used paper-based multidisciplinary medical notes and electronic results for all laboratory tests. Paper-based drug charts were used in ELCH; however, an ePS was used in GOSH.

The clinical teams in both hospitals conducted full patient review and daily clinical rounds. A clinical round is a multidisciplinary discussion on the progress and treatment plan for individual patients. The types of patients that are seen in both hospitals include kidney transplant patients, patients with CKD, peritoneal and haemodialysis patients, and patients with any type of disorder that affects the kidneys and urinary tract system. The inpatient settings of the study sites are presented in Table 3.1.

Table 3.1 The inpatient settings of both study sites

	Study Sites*	
	ELCH	GOSH
Setting of the renal ward		
Number of ward beds	18	16
Availability of dialysis machines on the wards	Yes	Yes
Medical notes	Paper-based multidisciplinary notes with electronic laboratory results	Paper-based multidisciplinary notes with electronic laboratory results
Prescribing system	Paper-based prescriptions	Electronic prescribing system (ePS) with Electronic medicine administration (eMA) system
Operation time	Monday to Friday: 1000 to 1730 Saturday: 0900 to 1700 Other times and on Sunday: On-call pharmacist provides cover	Monday to Friday: 0830 to 1800 Saturday: 0900 to 1200 Other times and on Sunday: On-call pharmacist provides cover

*ELCH – Evelina London Children's Hospital; GOSH – Great Ormond Street Hospital for Children, London

3.2.1.1 The electronic prescribing system (ePS) at GOSH

The ePS is combined with the electronic medication administration (eMA) system. In order to prescribe using the ePS, the child's allergy status, weight and height are mandatory information to be entered before ordering the medicines. The prescribers have the option to use the 'Calculate Dose' option on the prescription screen to obtain a crude calculation based on the patient's weight, which will need to be rounded to a measurable dose. Prescriptions could be ordered as new items, renewed from previous admission or selected to continue at discharge from the patient's inpatient medication list (Jani, 2008). The current system does not offer dose checking. Checking of the appropriate does is carried out by the CPs during routine prescription chart review.

3.2.1.2 Ward pharmacy services

The wards received a typical UK pharmacy ward service with a daily visit from a designated CP on weekdays and a short visit on Saturdays (Franklin et al., 2009; Taxis et al., 1999). At the time of each visit, the CPs initiated the supply of any non-stock drugs required and also checked that all prescriptions were clinically appropriate. Non-stock drugs are medicines that are not normally stored on the wards. In order to supply the medicine, the CP has to order it from the main pharmacy. The CP also gathered information on patients' drug history, provided medication counselling to patients and family members especially at hospital discharge; and reviewed medication charts for the appropriate use of medicines. At GOSH, the availability of the ePS enables the CP to review patients' medication lists

from the pharmacy office to identify DRPs before attending the clinical rounds. On the wards at both hospitals, the CPs also discussed patients' drug-related issues with the clinical team on a regular basis. All these activities enable the CPs to identify and solve DRPs. The problems that could be solved at the pharmacy level with notification to the clinical team are for instance shortage of drug supply and compatibility of different pharmaceutical products. The CP also provided feedback on drug-related inquiries by the medical team. DRPs that required changes to the treatment regimen were discussed with the doctors, and followed up to assess their resolution. A DRP was defined as 'resolved' when actions were taken before causing any harm to patients or actions were taken to solve an ongoing DRP.

The pharmacy departments are open during office hours on Monday to Friday and have limited hours on Saturday. Outside the opening hours and on Sundays, an on-call pharmacist would be on duty (Table 3.1). The lead CPs at both study sites were in band 8, based on the UK NHS grading, with more than ten years of experience in paediatric renal pharmacy practice and similar academic qualifications. Figure 3.1 shows the flow of ward pharmacy activities in the standard care at the inpatient settings.

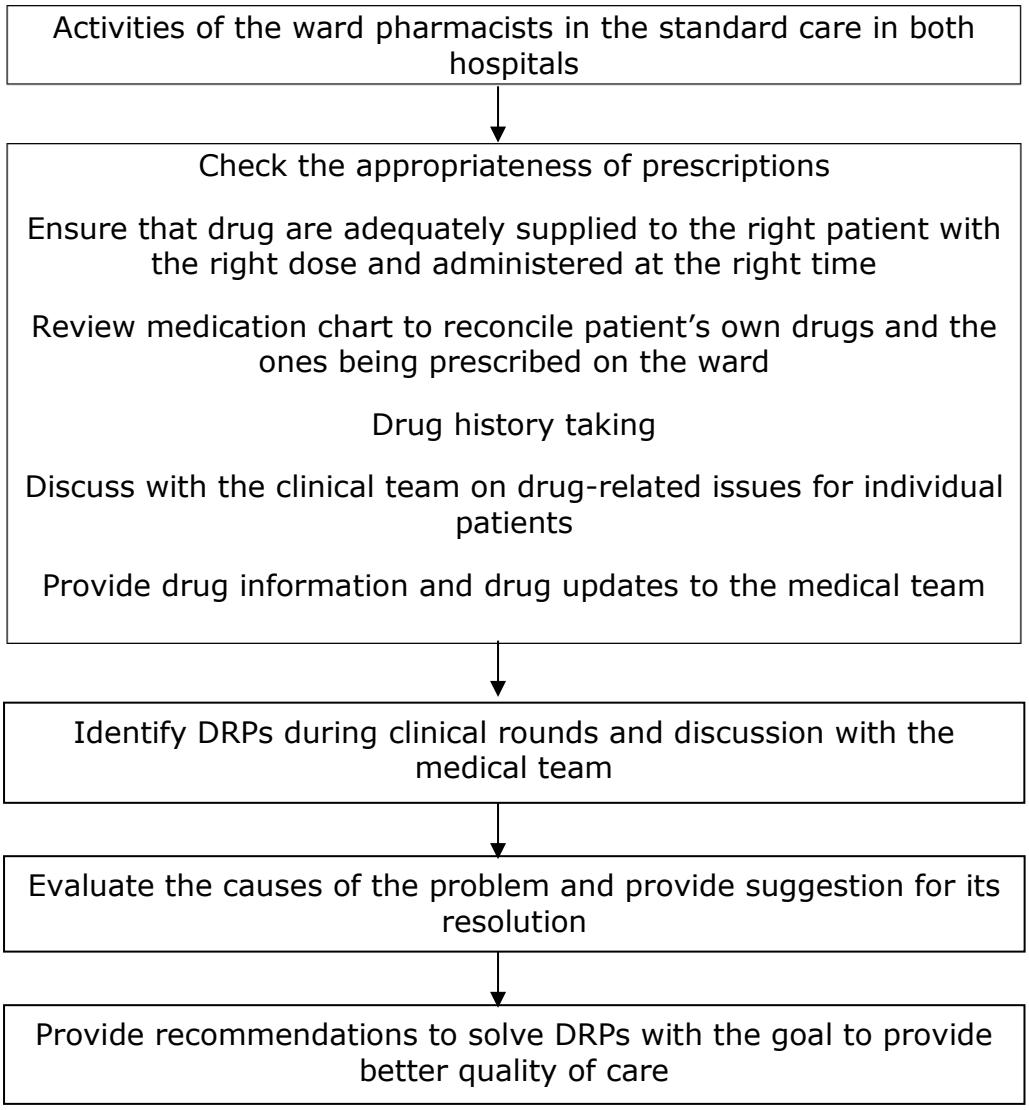


Figure 3.1 Ward pharmacy activities in the standard care at the inpatient settings

3.2.2 Outpatient setting

Study 2 was conducted at the ELCH. The initial plan was to include ELCH and GOSH; however, due to logistical reasons and staff constraints at GOSH, this was not possible. Thus, this is an overview of the setting of the renal outpatient clinic in ELCH.

The ELCH renal outpatient clinics used multidisciplinary electronic medical records (eMR), electronic records for all laboratory tests and paper-based prescriptions. These clinics comprise CKD clinics (for children living with reduced kidney function), renal transplant clinics (for children who are candidates for or who have had kidney transplantation) and general nephrology clinics (for children with previously diagnosed kidney disease or high blood pressure). The dialysis clinics for children who are undergoing peritoneal or haemodialysis treatment are based at the dialysis units in the wards. The renal clinics operate from Monday to Friday, and involve the paediatric renal consultants, registrars and specialist renal nurses.

The typical procedure of clinic visits starts with the patients receiving clinic letters that contain information about their medical progress and the tentative date for the next clinic appointment. When the patient attended the appointment, their vital signs were measured and phlebotomies were taken prior to the doctor's consultation. After the doctors' consultation session, patients collected the newly prescribed medications from the hospital pharmacy if needed. Other medications were to be continued (and supplied) at the community level by the general practitioners and the community pharmacies. Unlike the inpatient setting, pharmacy services have not been embedded in the standard care of the outpatient setting.

Figure 3.2 presents the workflow of the standard care in the outpatient clinics.

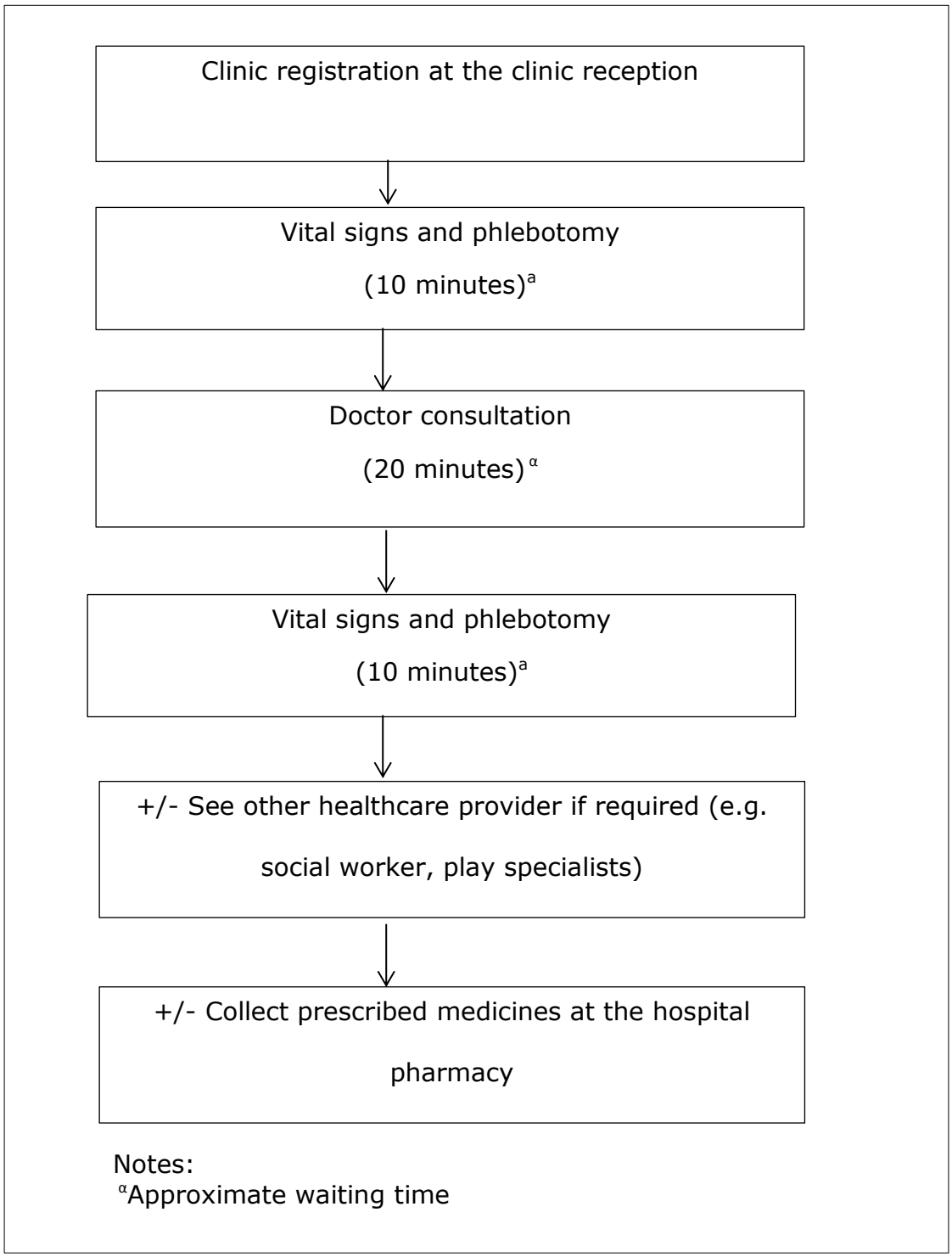


Figure 3.2 The workflow of the standard care in the outpatient clinics

3.3 Selection of study design

Observational study design was used in Study 1 and Study 2 was conducted as an RCT. The justification for selecting these two study designs is discussed in the following sub-sections.

3.3.1 Observational study design

The aim of Study 1 was to determine the characteristics of DRPs identified by the CPs during their routine ward pharmacy practice. Ward pharmacy service is a standard inpatient care on the paediatric renal wards at both study sites. The CPs' involvement in managing patients' treatment on the wards is already an intervention in the standard care; thus, it would be unethical to have a control group who would not receive the existing interventions. In observational studies the subjects receive no additional intervention beyond the standard care. Subjects are therefore observed in their natural state (Peacock and Peacock, 2013). Examples of observational study designs are cohort-study, case-control, cross-sectional and case study. The prospective cohort-study design was used in the current research.

3.3.1.1 Prospective cohort study design

Observational studies can be conducted prospectively and retrospectively. The prospective approach allows the estimation of the time course of event and the population at risk (Kumar, 2011). Cohort-study design is suitable to be used when there is a lack of information on the risk factors for an event

of interest in a particular population disease (Peacock and Peacock, 2013; Hennekens and Buring, 1987), which was the case with regard to risk factors for the occurrence of DRPs in children with kidney. This study design demonstrates an appropriate temporal sequence between exposure (i.e. potential risk factors) and outcome (i.e. DRPs). The above criterion is an advantage because identifying DRPs in the clinical setting involves complex decision making and the temporal sequence can be difficult to be determined.

In this study design, all potential subjects must be free from the event of interest at the initiation. The number of sample size and the length of follow-up should be sufficient to determine the occurrence of the event and potential risk factors (Peacock and Peacock, 2013). Cohort study-design is prone to several types of bias such as information bias and selection bias (Byona and Olsen, 2004; Hennekens and Buring, 1987; Kumar, 2011).

Information bias is the misinterpretation in the estimate of association between risk factor and outcome that is due to misclassification of subjects on one or more variables, either risk factor or disease status. In the current study, information bias could be related to the method of classifying the characteristics of DRPs. This can be minimised by adapting validated tools to determine the characteristics and severity of DRPs. Further descriptions of study tools are presented in sections 3.6 and 3.7.

The prospective approach of cohort study offers the benefit of minimising selection bias (Peacock and Peacock, 2013). Selection bias is the misinterpretation in the estimate of association between risk factor and outcome that results from how the subjects are selected for the study. It

can be minimised by selecting subjects that are representative of the target population. In the current study, subjects were selected from the renal wards to represent children with kidney diseases.

3.3.2 Interventional study design

The aim of Study 2 was to determine the effectiveness of CPs' intervention in resolving DRPs at the renal outpatient setting. Unlike the inpatient setting, clinical pharmacy services were not a standard care at the outpatient setting in both study sites. This situation offered the opportunity to introduce and test the effectiveness of interventions by CPs at the renal clinics. Randomised control trial could demonstrate the beneficial effects of interventions and was used in the current study.

3.3.2.1 Randomised control trial

The strength of RCT is the avoidance of bias when allocating interventions to trial subjects (Schulz et al., 2010). In RCT, subjects are placed into one of two groups at random: receive the intervention (Intervention group) or do not receive the intervention (Control group). In the current study, subjects in the Intervention group receive CP's interventions and the controls receive standard care. When an intervention is a programme of care, it is common practice for the control group to receive the standard care (Wong, 2004). Random allocation into either of the groups ensures that the individuals in the study are truly representative of the population from which they are drawn.

In order to gain the benefit of randomisation, all randomised participants should be retained in the group to which they were allocated and all participants should be included in the analysis whether or not they received the intervention or completed the trial. These are the conditions in the principle of intention-to-treat (ITT) analysis (Schulz et al., 2010). Non-adherence to the trial protocol is a condition that limits the application of ITT analysis. It refers to situations when participants deviate from the trial protocol, such as participants did not receive the intervention or loss of follow-ups. The Per Protocol analysis refers to a method of analysis that excludes participants who deviated from protocol.

Figure 3.3 shows the outline design for an RCT. The comparison of the intervention takes place in parallel and the observation for the intended outcome at baseline before and after intervention is compared between the control and intervention groups.

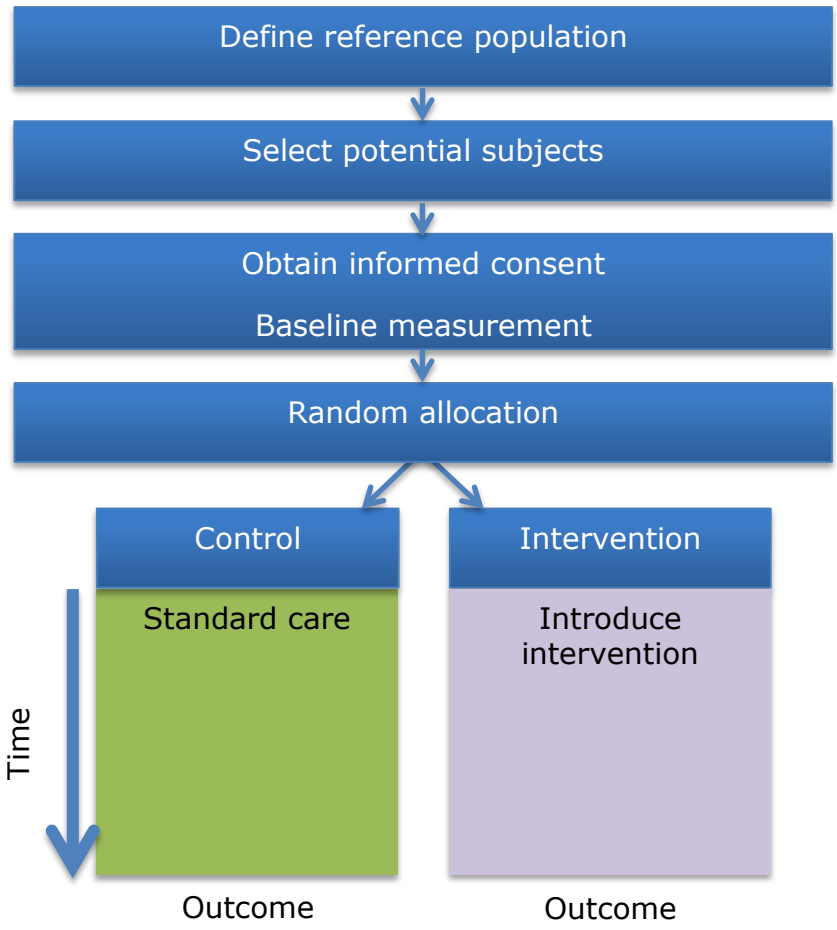


Figure 3.3 Basic outline for the design of randomised control trial

3.4 Evaluating outcomes in patient safety research

In the third article from a set of four series on the epistemology of patient safety research, the authors explained the use of multiple endpoint measurements in patients' safety research (Brown et al., 2008c). The authors of this paper introduced a model for causal link of intervention and outcome chain. This model demonstrates how interventions might work and also provides a conceptual map of the end points that may be measured in an evaluation of any patient safety intervention (Brown et al., 2008a). The model could be applied in developing the types of interventions to resolve DRPs at the renal outpatient clinic setting for the RCT. The following sub-section explains the aforementioned causal chain linking interventions to outcomes and the types of endpoint that could be considered in the current research.

3.4.1 Causal chain linking interventions to outcome

The types of endpoints in patient safety research originate from the causal link between intervention and outcomes. This link is derived from the Donabedian theory. Donabedian theory evaluates the elements of 'structure', 'process' and 'outcome' in appraising quality (McDonald et al., 2007).

Figure 3.4 illustrates the previously mentioned model for causal link of intervention and outcome chain. In the context of the causal chain of interventions to outcome, 'structure' refers to the external factors that are beyond the control of the managers within a particular health organisation. These may include national directives, licensing products and budget

constraints. 'Process' refers to the endogenous processes that are under local control. There are two types of processes: management (or organisational) processes and clinical processes.

The management processes are related to the process in managing the organisation e.g. training of staff and human resources. Errors in the management processes are latent and lie dormant within the system for many years before they combine with active errors to create an accident opportunity (Reason, 2000). Generic interventions are aimed at strengthening an organisation by reducing latent errors that affect patients' safety outcomes.

The clinical processes are the matters involved in providing treatment to patients e.g. adoption of medication safety and evidence based practices. Errors in the clinical processes are active and warrant specific interventions that affects clinical practice. Last in the chain are clinical outcomes and throughput.

In the context of the current research, outcome refers to the occurrence and resolution of DRPs. This causal chain of intervention and outcome illustrates that interventions to prevent or solve DRPs could be conducted at either the management process or the clinical process. The outcome of the interventions can be measured at the patient level or surrogate endpoint.

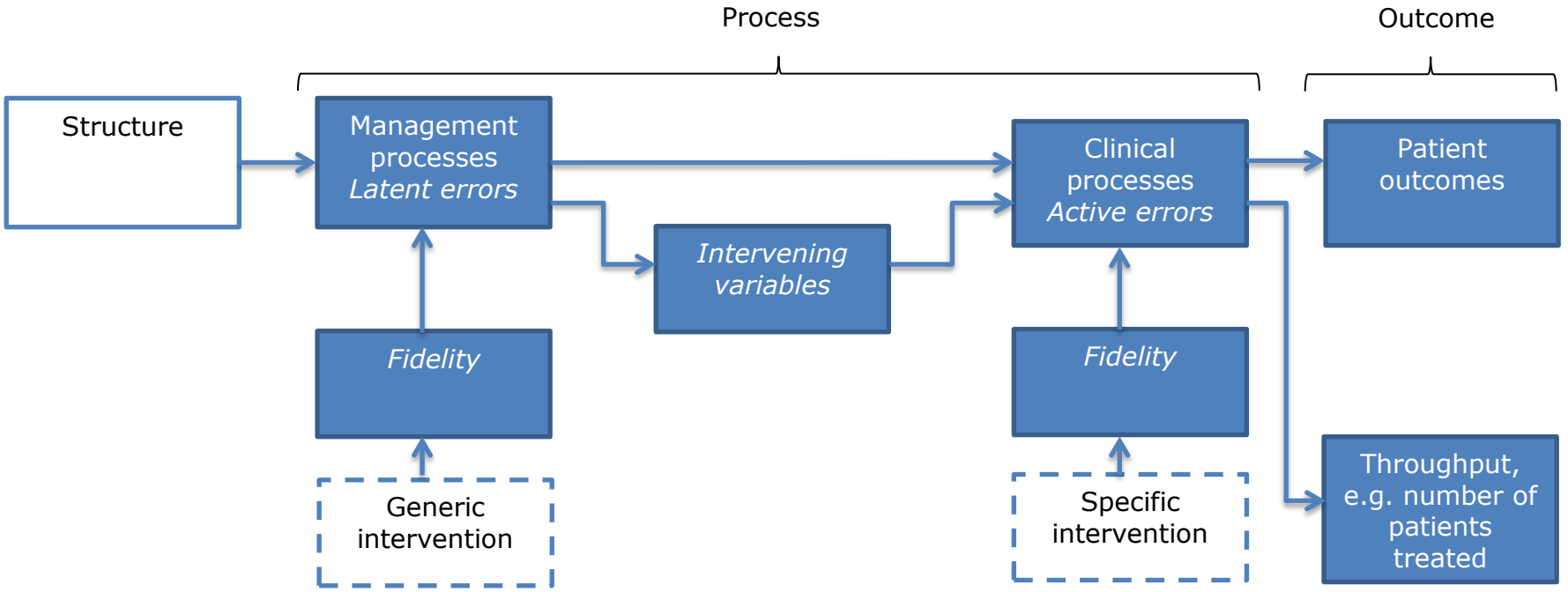


Figure 3.4 General and specific interventions across the system and evaluation end points. The coloured boxes represent the endpoint that could be measured in an evaluation of a patient safety intervention. Surrogate end point are shown in italics (Figure from Brown et al., 2008a)

3.4.2 Measuring outcomes in patient safety research

Within the aforementioned causal link model, endpoints can be measured at either the patient level, i.e. patient outcomes, or at any level prior to the final patient outcome, i.e. surrogate end points.

3.4.2.1 Patient outcomes

Patient outcomes can be either clinical or patient derived. Examples of clinical patient outcomes are morbidity, mortality or specific objective parameters to indicate improvements in disease management, e.g. blood pressure and low-density lipoprotein levels for hypertension and hypercholesterolemia respectively. Other examples are: patients' quality of life and satisfaction. Two issues that arise when patient outcomes are used as an end point are precision and bias (Brown et al., 2008c).

It is difficult to precisely evaluate an improvement caused by an intervention because outcomes may also be influenced by other factors such as the prescribing pattern, clinical judgement among healthcare providers and the disease progression (Brown et al., 2008c). The other factors that influenced patient outcome are also called signal to noise ratio. Signal is the indicator of improvement caused by the intervention and noise is the confounding factors that cause variance in the outcome. There is a tendency towards false positive statistical error in using patient outcome as the end point in an evaluation of a patient safety intervention.

As an example, a patient who has a high level of serum phosphate is treated with a phosphate-binding agent. The reduction of the phosphate

level is the intended clinical outcome and optimising the dose of the phosphate-binding agent would be most sensible to achieve this outcome. If the drug was omitted by error, it is speculated that there will be a poor outcome by showing no improvement or worsening of the serum phosphate level. However, the poor outcome may also be influenced by other factors, for instance progressive kidney failure requiring dialysis (dialysis eliminates excessive serum phosphate) or alteration in patient's diet to high phosphate content. Therefore, measuring the serum phosphate level as a signal to assess the negative implication of omission error would be an imprecise endpoint.

One of the strategies to improve signal to noise ratio is by choosing an outcome that arises exclusively from error as the signal, but the choice of these outcomes is limited (Brown et al., 2008a). Another strategy is to select the signal of cases of poor outcomes that were caused by poor care. This requires the identification of poor outcomes and then examination of the process of care to select the instances when the poor outcome was the result of deficiencies in care. The limitation to the second strategy is bias in making judgement about preventable poor outcomes. Clinical outcome in pharmacy practice research is also difficult to measure in a consistent way. In the context of research, it is important to ensure that the same observer makes the measurement if possible. This is to ensure that the results will not be biased due to inter-observer difference even when applying a standard definition and protocol (Kumar, 2011).

3.4.2.2 Surrogate endpoints

Surrogate end points are measured from the process level of the causal pathway. There are three types of surrogate end points: errors in clinical process, fidelity and intervening variables.

3.4.2.2.1 Errors in clinical process

Errors in the clinical process are the closest surrogate end point to patient outcome. They can be described as (1) failure to apply the correct standard of care, (2) failure to carry out a planned intervention as intended and (3) application of an incorrect plan.

3.4.2.2.2 Fidelity

Fidelity endpoints measure whether the system was implemented as intended. An example is to measure whether the installation of the ePS reduces prescribing errors; or the introduction of a new pharmacy service in the clinic reduces drug-related problems.

3.4.2.2.3 Intervening variable

Intervening variable is a surrogate end point to measure interventions targeted at a specific patient threat; it is aimed at strengthening the organisation. For example, implementing human resources policies are expected to impact on errors by means of effects on staff motivation and morale and reduced absence due to sickness.

3.5 Methods for the detection of DRPs

There is currently no gold standard in the method for detecting DRP, PE or ADE (Cardone et al., 2010; Dean et al., 2005; Franklin et al., 2009). Many works have been carried out to evaluate the methods for detecting errors, particularly PE (Dean et al., 2005; Franklin et al., 2009; Franklin et al., 2010; Ghaleb et al., 2010). It is not known how the concept in the methodological approach for PE would suit studies on DRPs or other ADEs (Dean et al., 2005) but it would be the closest method that is deemed suitable for the current research. There are four methods for PE detection that could be adapted for detecting DRPs, which are: (1) medical chart review, (2) pharmacists' documentation, (3) analysis of incident reports and (4) trigger tools (Brown et al., 2008c; Franklin et al., 2009). The medical chart review and pharmacists' documentation methods were applied for the detection of DRPs in the current research.

3.5.1 Medical chart review

Retrospective medical chart review can be conducted using the implicit or explicit methods. The implicit method involves experts making clinical judgement about the provided quality of care. Structured implicit methods require a set of questions prepared for the experts in order to extract a comprehensive review of the important phases of care. Researchers rather than expert clinicians can conduct the explicit chart review. It is more reproducible compared to the implicit method because the detection of events is guided by predetermined criteria. Nevertheless, documentation in medical charts may not be complete enough to assess the outcomes of

interest because information was not recorded for the purpose of research. The strengths and limitations of both methods are summarised in Table 3.2.

3.5.2 Pharmacists' documentation

Errors that are detected from pharmacists' documentation are usually in prospective studies. In this method, the pharmacists identify and record the errors during daily clinical practice on the wards. The limitation to this method is that little is known about the number of errors that have been identified and rectified by the pharmacists but not recorded. This may contribute to underreporting of the actual incidence of PE (Aucoin et al. 2005; Bertsche et al., 2010).

The types and numbers of problems identified by the pharmacists varies depending on the location of the data collection. This depends on the types of pharmacy services in operation. For example, ward pharmacists will have access to broader information about a patient's treatment and clinical condition, would identify more ADEs compared to the pharmacists at the dispensary. Furthermore, a pharmacist, as a member of the clinical team, has the advantage of being more aware of the extra information in the context of patients' treatment, which may facilitate the identification of ADEs (Dean et al., 2005). This may contribute to the variations in the types of ADEs identified by the pharmacists and researcher.

Table 3.2 Strengths and limitations of implicit and explicit retrospective review (Adapted from Brown et al., 2008c)

Methods of medical chart review	Strengths	Limitations
Implicit	• Easy to develop and administer • High face validity, since experts define 'good' and 'bad' care • Self-updating through use of experts • Reflects full scope of clinical decisions for a particular patient • Involves physicians and other experts in the quality of care	• Require (expensive) clinical experts • More arbitrary than evidence based • Poor reproducibility of judgement
Explicit	• Evidence-based criteria reproducible • Easy to explain low score in terms of criteria – which may narrow score of improvement efforts • Can be conducted by researchers rather than expert clinicians (reduce costs)	• Require training of reviewers • Limited scope of content and context • Need to be updated constantly • Potential for gaming • Need to decide how to analyse multiple criteria

3.5.1.1 Electronic medical chart review

The emerging use of technologies in healthcare would eventually shift the detection of DRP and other ADEs from paper-based to electronic medical record (eMR) (Holroyd-Leduc et al., 2011). The eMR holds rich information from multidisciplinary medical records and is seen as a valuable source of information to facilitate medicine management (Eguale et al., 2008). However, no studies have been published comparing the effectiveness of electronic and paper-based medical charts review in detecting ADEs at the hospital setting. A systematic review on the impact of eMR on the structure, process and outcomes within primary care which included case-control studies involving 71 primary care practitioners in the UK reported that, although eMR contained more words in documentation, there were no differences in the terms of proportion of chart entries (Holroyd-Leduc et al., 2011).

A study on detecting DRPs by screening the eMR at an inpatient setting of a geriatric ward reported that the use of eMR in hospital pharmacy practice facilitated the CPs in prioritising medication reviews and optimising workload. This study also suggested the use of a trigger tool as a strategy to aid in the detection of DRPs using the eMR (Roten et al., 2010*)*. A similar strategy was implemented to identify drug safety signals and ADEs from the eMRs of primary care clinics in New Zealand (Tomlin et al., 2012*).*

3.5.3 Analysis of incident reporting

A spontaneous reporting system is the easiest to establish and the cheapest to run but can suffer from poor-quality reports and underreporting (Pal et

al., 2013). A UK-based study by Franklin et al. (2009) comparing four methods in detecting PE reported that spontaneous reporting identified less than 1% of all errors. In the aforementioned study, other detection methods were trigger tool, pharmacists' documentation and retrospective case review. Any change in the reported events does not reflect the true change in the underlying problem (Brown et al., 2008c). It is difficult to estimate rates and frequencies of events through spontaneous reporting because it does not have a standard denominator (Dean et al., 2009; Pal et al., 2013).

3.5.4 Trigger tools

A trigger tool is used to highlight information in medical records such as medication stop orders or abnormal laboratory results, which point to an adverse event that may have harmed a patient (James, 2013). A positive trigger then leads to more extensive investigation to identify whether or not harm has occurred (Resar et al., 2003). Since detailed case note review is only required with the detection of a positive trigger, the method is less resource-intensive than a detailed case note review (Brown et al., 2008c). Also, this method could not assess the temporal relationship of event or risk factors. For example, a medication chart containing prescriptions for a combination of antihistamine, corticosteroid and adrenaline following administration of an antibiotic might trigger the occurrence of acute anaphylaxis, an allergic reaction to the antibiotic. But it could not be ascertained if other drugs manifested the allergic reaction unless such

information was recorded in the medical notes. Plus, it could also indicate an anaphylactic shock following a chronic systemic infection.

The limitations of using trigger tools are low sensitivity and low specificity, which lead to low positive predictive values and the risk of false positive outcomes. The proportion of adverse events detected by triggers describes sensitivity. However, it is difficult to assess sensitivity because there is no gold standard method of detecting these events (Brown et al., 2008c; Franklin et al., 2009; Franklin et al., 2010). For example, in the study by Franklin (2009) previously described, the trigger tool identified less than 10% of all errors. The trigger tool also identified half of the harmful errors but these were likely false positive.

In research, results from studies using the trigger tool are not likely to be comparable unless it is possible to standardise the denominator to construct the event rates and factors that affect the sensitivity and specificity of the tool, such as completeness of information on the database and the algorithm used to cross-examine the database (Brown et al., 2008c).

3.6 Classification systems to characterise DRPs

It was previously explained in Chapter 1 that the characterisation of DRPs depends on the definition and the classification systems adapted in a particular study. The two DRP classifications that were adapted in this research were the PCNE version 6.2 and the Gordon classifications (Gordon et al., 2005; PCNE, 2010). The PCNE classification was adapted as the main

data collection proforma in Study 1 and Study 2. The Gordon classification was adapted and added into the proforma for Study 2.

3.6.1 PCNE classification system (version 6.2)

For the standardisation of data evaluation in this present research, the drugs associated with DRPs were documented according to the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification (WHO-ATC) system. The definition and the classification system for DRPs were adopted from the PCNE. The PCNE defines DRP as:

"An event or circumstances involving drug therapy that actually or potentially interferes with desired health outcomes"

The PCNE DRP classification system version 6.2 attributes four categories to each observation: (1) coding for the types of problem, (2) the actual or suspected cause of the problem, (3) the intervention required to resolve the problem and (4) its outcome. Figure 3.5 shows the codes of the four categories in the PCNE DRP classification system. An example to illustrate how the codes were used in evaluating the characteristics of a DRP is given in Figure 3.6.

PCNE Classification scheme for Drug-Related Problems V6.2 - Page 1

The basic classification

	Code V6.2	Primary domains
Problems	**P1**	**Treatment effectiveness** There is a (potential) problem with the (lack of) effect of the pharmacotherapy
	P2	**Adverse reactions** Patient suffers, or will possibly suffer, from an adverse drug event
	P3	**Treatment costs** The drug treatment is more expensive than necessary
	P4	**Others**
Causes	**C1**	**Drug selection** The cause of the DRP can be related to the selection of the drug
	C2	**Drug form** The cause of the DRP is related to the selection of the drug form
	C3	**Dose selection** The cause of the DRP can be related to the selection of the dosage schedule
	C4	**Treatment duration** The cause of the DRP is related to the duration of therapy
	C5	**Drug use/administration process** The cause of the DRP can be related to the way the patient uses the drug or gets the drug administered, in spite of proper instructions (on the label, package or leaflet)
	C6	**Logistics** The cause of the DRP can be related to the logistics of the prescribing and dispensing process
	C7	**Patient** The cause of the DRP can be related to the personality or behaviour of the patient.
	C8	**Other**
Interventions	**I0**	**No intervention**
	I1	**At prescriber level**
	I2	**At patient (or carer) level**
	I3	**At drug level**
	I4	**Other**
Outcome of intervention	**O0**	**Outcome intervention unknown**
	O1	**Problem totally solved**
	O2	**Problem partially solved**
	O3	**Problem not solved**

Figure 3.5 PCNE classification scheme for DRP version 6.2 (Page 1/4)

PCNE Classification scheme for Drug-Related Problems V6.2 - Page 2

The Problems

Primary Domain	Code V6.2	Problem
1.Treatment effectiveness There is a (potential) problem with the (lack of) effect of the pharmacotherapy	**P1.1**	No effect of drug treatment/ therapy failure
	P1.2	Effect of drug treatment not optimal
	P1.3	Wrong effect of drug treatment
	P1.4	Untreated indication
2. Adverse reactions Patient suffers, or will possibly suffer, from an adverse drug event	**P2.1**	Adverse drug event (non-allergic)
	P2.2	Adverse drug event (allergic)
	P2.3	Toxic adverse drug-event
3. Treatment costs The drug treatment is more expensive than necessary	**P3.1**	Drug treatment more costly than necessary
	P3.2	Unnecessary drug-treatment
4. Others	**P4.1**	Patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes
	P4.2	*Unclear problem/complaint. Further clarification necessary (please use as escape only)*

❑ Potential Problem

❑ Manifest Problem

Figure 3.5 PCNE classification scheme for DRP version 6.2 (Page 2/4)

PCNE Classification scheme for Drug-Related Problems V6.2 -Page 3

The Causes

N.B. One problem can have more causes

Primary Domain	Code V6.2	Cause
1. Drug selection The cause of the DRP is related to the selection of the drug	**C1.1**	Inappropriate drug (incl. contra-indicated)
	C1.2	No indication for drug
	C1.3	Inappropriate combination of drugs, or drugs and food
	C1.4	Inappropriate duplication of therapeutic group or active ingredient
	C1.5	Indication for drug-treatment not noticed
	C1.6	Too many drugs prescribed for indication
	C1.7	More cost-effective drug available
	C1.8	Synergistic/preventive drug required and not given
	C1.9	New indication for drug treatment presented
2. Drug form The cause of the DRP is related to the selection of the drug form	**C2.1**	Inappropriate drug form
3. Dose selection The cause of the DRP is related to the selection of the dosage schedule	**C3.1**	Drug dose too low
	C3.2	Drug dose too high
	C3.3	Dosage regimen not frequent enough
	C3.4	Dosage regimen too frequent
	C3.5	No therapeutic drug monitoring
	C3.6	Pharmacokinetic problem requiring dose adjustment
	C3.7	Deterioration/improvement of disease state requiring dose adjustment
4. Treatment duration The cause of the DRP is related to the duration of therapy	**C4.1**	Duration of treatment too short
	C4.2	Duration of treatment too long
5. Drug use process The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label)	**C5.1**	Inappropriate timing of administration and/or dosing intervals
	C5.2	Drug underused/ under-administered (deliberately)
	C5.3	Drug overused/ over-administered (deliberately)
	C5.4	Drug not taken/administered at all
	C5.5	Wrong drug taken/administered
	C5.6	Drug abused (unregulated overuse)
	C5.7	Patient unable to use drug/form as directed
6. Logistics The cause of the DRP can be related to the logistics of the prescribing and dispensing process	**C6.1**	Prescribed drug not available
	C6.2	Prescribing error (necessary information missing)
	C6.3	Dispensing error (wrong drug or dose dispensed)
7. Patient The cause of the DRP can be related to the personality or behaviour of the patient.	**C7.1**	Patient forgets to use/take drug
	C7.2	Patient uses unnecessary drug
	C7.3	Patient takes food that interacts
	C7.4	Patient stored drug inappropriately
8. Other	**C8.1**	Other cause; specify
	C8.2	No obvious cause

Figure 3.5 PCNE classification scheme for DRP version 6.2 (Page 3/4)

PCNE Classification scheme for Drug-Related Problems V6.2 -Page 4

The Interventions

N.B. One problem can lead to more interventions

Primary Domain	Code V6.2	Intervention
No intervention	**I0.0**	No Intervention
1. At prescriber level	**I1.1**	Prescriber informed only
	I1.2	Prescriber asked for information
	I1.3	Intervention proposed, **approved** by Prescriber
	I1.4	Intervention proposed, **not approved** by Prescriber
	I1.5	Intervention proposed, outcome unknown
2. At patient/carer level	**I2.1**	Patient (medication) counselling
	I2.2	Written information provided only
	I2.3	Patient referred to prescriber
	I2.4	Spoken to family member/caregiver
3. At drug level	**I3.1**	Drug changed to …
	I3.2	Dosage changed to …
	I3.3	Formulation changed to …
	I3.4	Instructions for use changed to …
	I3.5	Drug stopped
	I3.6	New drug started
4. Other intervention or activity	**I4.1**	Other intervention (specify)
	I4.2	Side effect reported to authorities

The Outcome of the Interventions

N.B. One problem (or the combination of interventions) can only lead to one level of solving the problem

Primary Domain	Code V6.2	Outcome of intervention
0. Not known	**O0.0**	Outcome intervention not known
1. Solved	**O1.0**	Problem totally solved
2. Partially solved	**O2.0**	Problem partially solved
3. Not solved	**O3.1**	Problem not solved, lack of cooperation of patient
	O3.2	Problem not solved, lack of cooperation of prescriber
	O3.3	Problem not solved, intervention not effective
	O3.4	No need or possibility to solve problem

Figure 3.5 PCNE classification scheme for DRP version 6.2 (Page 4/4)

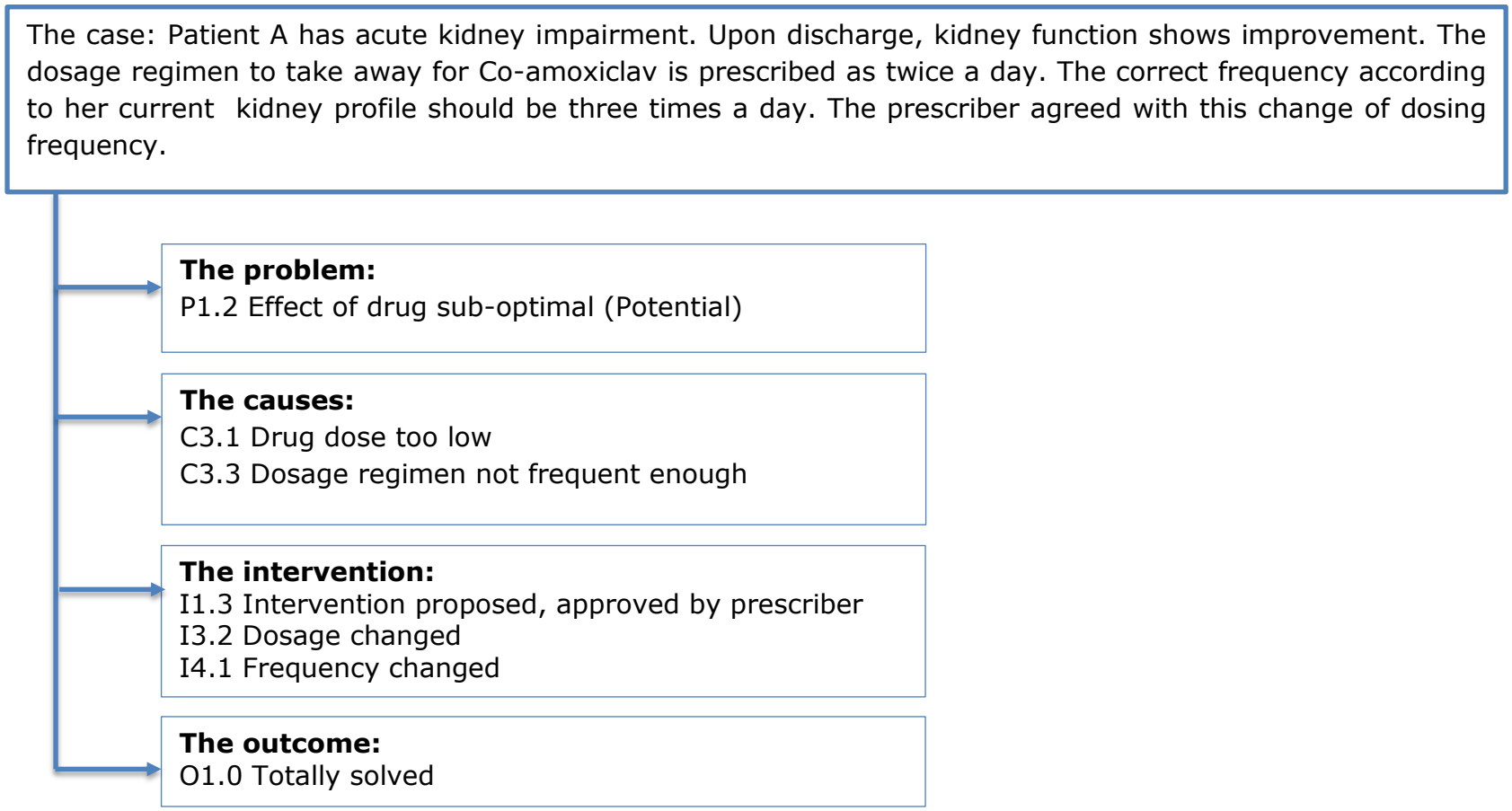


Figure 3.6 Example of classifying the characteristics of a DRP according to the PCNE classification system version 6.2

3.6.1.1 Considerations when using the PCNE classification system in research

Previous studies that used the PCNE system had difficulty in the selection of categories from the classification. Lampert et al. (2008) investigation on DRPs in the medical wards reported on the types of DRPs which could not be classified by the PCNE system. In another study, Eichenberger and colleagues (2010) suggested additional items to be added into the PCNE classification. Both of these studies used the earlier version of the PCNE classification. However, similar difficulties would arise using the current version because of the unavailability of a standard operational definition.

As an example, in Figure 3.6, the causes of DRP are (C3.1) drug dose too low and (C3.3) dosage regimen not frequent enough. It could be argued that these categories should be classified as prescribing error (i.e. drug and dosing error). In another example, of a patient who experiences dry cough after taking ACEi, the problem would most likely be categorised as (P1.3) wrong effect of drug treatment or (P2.1) adverse drug event (non-allergic)' subject to the assessor's understanding of the options available in the classification system.

Such circumstances could potentially cause internal and external variability in making decisions to classify the DRPs because decision making in clinical practice is complex and involves subjective assessment, which can be influenced by several factors such as the type of information available, knowledge and experience (Dean and Barber, 1999). Variability in the process of data collection can be minimised by having a standard operating definition for the variables (Kumar, 2011). An operating definition is a clear

and concise detailed definition of a measurement. The need for an operational definition for the PCNE classification system is fundamental to ensure the consistency of data collected throughout the current research. The development of the operational definition for the PCNE classification system is described in Chapter 4 (sub-section 4.2.4.2..

3.6.2 Gordon classification system

The introduction to the Gordon classification for DRPs was given in Chapter 1 (sub-section 1.3.2.4). In brief, the DRPs in this classification were identified by interviewing patients at the community pharmacies and surgeries using a standard screening tool.

The screening tool comprised a set of questions in regard to the use of medicines. The questions were divided into five sections:

1. Use of prescription and non-prescription medicines
2. Patients' demographic characteristics
3. Hospital admissions, consultations as an outpatient or with private healthcare providers
4. Self-reporting of non-compliance
5. Details related to contacts with consultants at the pharmacies and surgeries

Nine types of MRPs were reported by Gordon and these problems are listed in Table 3.3

Table 3.3 Classifications of medication-related problems (Gordon et al., 2005)

Medication-related problem	
MRP 1 :	Adverse drug reactions and drug interactions
MRP 2 :	Cognitive, physical and sensory problems (e.g. difficulty in remembering or reading a label)
MRP 3 :	Drug prescribing problems (e.g. patient concern regarding the need for a prescription)
MRP 4:	Intentional non-compliance (e.g. decision by the patient to alter the dose of a medicine)
MRP 5:	Monitoring and review of medicines including interface between primary and secondary care (e.g. monitoring for continued appropriateness of therapy or following a change)
MRP 6:	Problems with non-prescription medicines
MRP 7:	Lack of information or opportunity to discuss medication-related issues or concerns
MRP 8:	Problems with processes for obtaining repeat prescriptions through surgery or the pharmacy
MRP 9:	Problems with services from the surgery or the pharmacy (e.g. difficulty in obtaining appointment, uncertainty about generic products)
Definition of MRP: Any problem experienced by a patient that may impact on their ability to manage or take their medicines effectively	

The feasibility of the Gordon classification system and screening tool for DRP for Study 2 is presented in Chapter 4 (section 4.3).

3.7 Method for assessing the severity of DRPs

3.7.1 DRP severity rating

As there was no established tool to measure the severity of DRPs, this research adopted a validated severity-scoring tool for MEs from Dean and Barber (1999). This scale was validated using cases of drug administration errors (Dean and Barber, 1999) and prescribing errors (Kollo and Dean, 2000). The use of this scale in this research was justified based on the three points below:

1. This scale has been used to rate the severity of DRPs in an international multicentre on DRPs in the paediatric population hospitalised at the general medical wards; this study involved the paediatric population in the UK (Rashed et al., 2012b).
2. The indirect relationship between ADE and ME with DRP. Some ADEs are associated with MEs, and DRPs are a type of ADEs (Ibrahim et al., 2013).
3. Other scales used in previous studies were not validated (Easton et al., 2004; Easton et al., 1998) and were developed to assess preventability of ADRs in the United States (Schumock and Thornton, 1992).

Four judges were selected to score the severity of the identified DRPs using this scale: two pharmacists (a paediatric pharmacy consultant and a medication safety pharmacist), one paediatric renal consultant and one paediatric renal specialist nurse. A list of DRP cases was sent electronically to the judges, who were requested to rate the severity of all cases within four weeks. Each judge scored the severity of each DRP case in terms of clinical significance with scores ranging from 0 to 10 in a visual analogue scale. The score 0 represents a case with no potential harm and 10 represents a case that would result in death. A DRP is considered minor (unlikely to have any adverse effects) if the score is less than 3, moderate (likely to cause some adverse effects or interfere with therapeutic goals but very unlikely to result in death or lasting impairment) if the score is between 3 to 7, or severe (likely to cause death or lasting impairment) if the score is more than 7 (Table 3.4).

In cases of no score being assigned by the judges, the researcher contacted the judges and requested a score. The average score for all judges was the final score assigned to each DRP. The visual analogue scale for the assessment of DRP severity is enclosed in Appendix 3.

Table 3.4 Score range and interpretation of clinical significance of DRPs (Dean and Barber, 1999)

Clinical significance	Score	Interpretation
Minor	0 – <3	Unlikely to have any adverse effects
Moderate	3 – <7	Likely to cause some adverse effects or interfere with therapeutic goals
Severe	7 – 10	Likely to cause death or lasting impairment

3.7.2 The recruitment of judges

As mentioned in the sub-section above, the Dean and Barber scale was developed to assess the severity of administration errors. The scale had also been validated to assess the severity of cases on administration errors in order to achieve generalisability coefficient of 0.8 or more. The value of the generalisability coefficient ranges from 0 to 1, with higher values indicating greater reliability or agreement respectively (Pallant, 2010). In general, an acceptable value is above 0.70 (Field, 2009); however, a value above 0.80 is considered to represent an acceptable reliability in clinical practice research (Smith et al., 1995).

Dean and Barber (1999) suggested that (1) increasing the number of occasion on which the cases were scored and the differences on the profession of the judges (i.e. doctors, nurses and pharmacists) had little impact on the generalisability coefficient and (2) a minimum of 4 judges were required to assess the severity of the cases in one occasion in order to

achieve generalisability coefficient above 0.8. The generalisability coefficient predicted with number of judges and the number of occasions the cases were assessed is shown in Table 3.5.

Table 3.5 Generalisability coefficient predicted with number of judges and the number of occasions cases were assessed (Dean and Barber, 1999)

Number of judges	Number of occasions the judges assessed the severity of cases	Generalisability coefficient
1	1	0.575
1	2	0.579
1	10	0.581
1	100	0.582
2	1	0.725
3	1	0.794
4	1	0.834
5	1	0.859
10	1	0.916
30	1	0.958

In another study, using the Dean and Barber severity scale for prescribing error, Kollo and Dean (2000) also suggested at least 4 judges in order to achieve generalisability coefficient above 0.8 (i.e. 2 judges of each of 2 professions selected from: doctors, nurses and pharmacists).

There is no evidence for the researcher to conclude the optimum number of judges required to assess the severity of DRPs using this severity scale. It is also challenging to determine how different DRPs would behave compared to medication errors (Franklin et al., 2009). The Dean and Barber scale had previously been used to assess the severity of DRPs identified in children hospitalised in general medical wards by three judges comprising of two doctors and a pharmacist (Rashed 2012b).

In the current research, a total of 4 judges were selected. The final number of judges (i.e. four) for this research was based on the fact that (1) generalisability coefficient increases with the number of judges and four judges would be able to generate generalisability coefficient above 0.8 (Dean and Barber, 1999; Kollo and Dean, 2000) and (2) if any 4 judges from the population of experienced UK pharmacists, medical staff and nursing staff are used, their mean scores would be generalised to any four judges selected from the same population (Dean and Barber, 1999).

3.7.3 Minimising bias in scoring for DRP severity

The following strategies were utilised to minimise the possibility of bias in scoring the DRPs' severity among the judges: (1) allowing the judges to evaluate the cases independently within an agreed time period (i.e. three weeks), (2) the judges were informed that scores would not be compared with other judges and the mean score of each DRP would be taken to represent the level of severity, and (3) all descriptions of DRPs were stated in a standard format to eliminate the 'reverse phrases' effect.

A 'reverse phrase' refers to statements that are not following the way all other statements were described (Field, 2009). The 'reverse phrases' effect would introduce response bias in scoring the severity level of DRPs, for example: IV Ciprofloxacin 5mg/kg twice a day was prescribed; the correct dose should have been 10-15mg/kg once a day. The reversed phrasing for the above DRP description: IV Ciprofloxacin correct dose was 10-15mg/kg once a day; but the prescribed dose was 5mg/kg twice a day.

3.8 Ethical Considerations

3.8.1 Ethical approvals

The ethical approvals for this research were obtained from the following committees:

- The London-Westminster Research Ethics Committee (Appendix 4)
- The London-Hampstead Research Ethics Committee (Appendix 5)
- The Research and Development (R&D) Committee of Guy's and St. Thomas' Hospitals NHS Foundation Trust (GSTT) and Great Ormond Street Hospital for Children (GOSH).

3.8.2 Patient confidentiality

Patients' confidentiality should be maintained during data assessment and data analysis. The researcher was required to obtain an honorary contract with both hospitals and followed the Trusts' policies and procedures for patient confidentiality and information governance. Data were anonymised

by assigning patients to unique patient identifiers rather than using their name, registration number or any other types of information that may be used for identity tracking. As part of protecting patients' confidentiality and the integrity of the participating Trusts, as agreed by the Research Ethics Committee (REC), results comparing DRPs between research sites should only be shared with healthcare providers within the Trusts.

3.8.3 Safety implication

The CPs involved in this research have a minimum of ten years' experience in renal pharmacy practice and they were also members of the renal team responsible for the care of study subjects. The researcher had attended Child Protection training and obtained honorary contracts from both Trusts. The researcher was also a pharmacist, trained in renal pharmacy and not a staff member of the participating Trusts. Therefore, in the event that the CPs or the clinical team had not identified a DRP with potential harm to patients, then the researcher would be responsible for alerting them to this.

3.9 Summary

Thus far, the fundamentals of the methodological approach have been discussed. The following chapter presents the feasibility studies that were conducted before the initiation of the prospective observation study in the inpatient setting and the RCT in the renal outpatient clinics.

CHAPTER 4

Feasibility studies

4.1 Introduction

It was briefly mentioned in Chapter 2 and Chapter 3 that this research encompasses two main studies in investigating DRPs in children with kidney disease. Feasibility Study (1) was conducted prior to Study 1 and Feasibility Study (II) was conducted prior to Study 2. These feasibility studies were conducted to address the potential challenges in applying the proposed study designs and the DRP classification systems.

4.2 Feasibility Study (I)

4.2.1 Background

The PCNE classification system for DRPs has been previously used by Rashed and colleagues in investigating the epidemiology of DRPs in hospitalised children but this excluded renal patients (Rashed et al., 201b). Feasibility Study (I) was conducted to identify challenges in the process of data collection for a prospective cohort study and to identify the suitability of the PCNE DRP classification system for research in paediatric nephrology patients. Ethical approval was not required because this study was conducted as an evaluation for pharmacy services at ELCH and GOSH.

4.2.2 Objectives

1) To test the feasibility of a prospective observational cohort study on the renal wards of ELCH and GOSH.

2) To develop a standard operational definition for the PCNE classification (version 6.2) in characterising DRPs in children with kidney disease.

4.2.3 Method

4.2.3.1 Sites and study period

This study was conducted in the renal wards of the ELCH and GOSH. The study was conducted for two weeks, one week at each hospital. Data collection at GOSH was from 4th to 9th July 2011 and at ELCH from 11th to 15th July 2011.

4.2.3.2 Sample size

Sample size calculation was not required because this was a feasibility study.

4.2.3.3 Inclusion criteria for study patients

All children aged 2 to 16 years who were admitted to the renal wards during the study period with the following criteria were included:

1. Received at least one drug during their period of hospitalisation.
2. Admitted to the ward for more than 24 hours.

4.2.3.4 Process of data collection

The researcher was a non-participant observer during the study period. One CP was involved in the data collection at each hospital. At ELCH, the CP visited the ward and identified the DRPs from paper-based prescription chart review during routine ward pharmacy practice. At GOSH, the CP utilised the ePS and manually checked medication order entry for each patient. At both hospitals, the medical notes were reviewed when further details on DRPs were required.

Recommendations on the resolution of the identified DRPs were discussed with the clinical team during clinical rounds, as previously described in Chapter 3 (sub-section 3.2.1). The CPs recorded all DRPs onto a proforma according to the PCNE classification system, as previously described in Chapter 3 (sub-section 3.6.1). During the observation period, the researcher documented patients' profiles and this included their clinical progress, medication list and the event that led to the identification of the DRPs by the CPs. The process of data collection is illustrated in Figure 4.1.

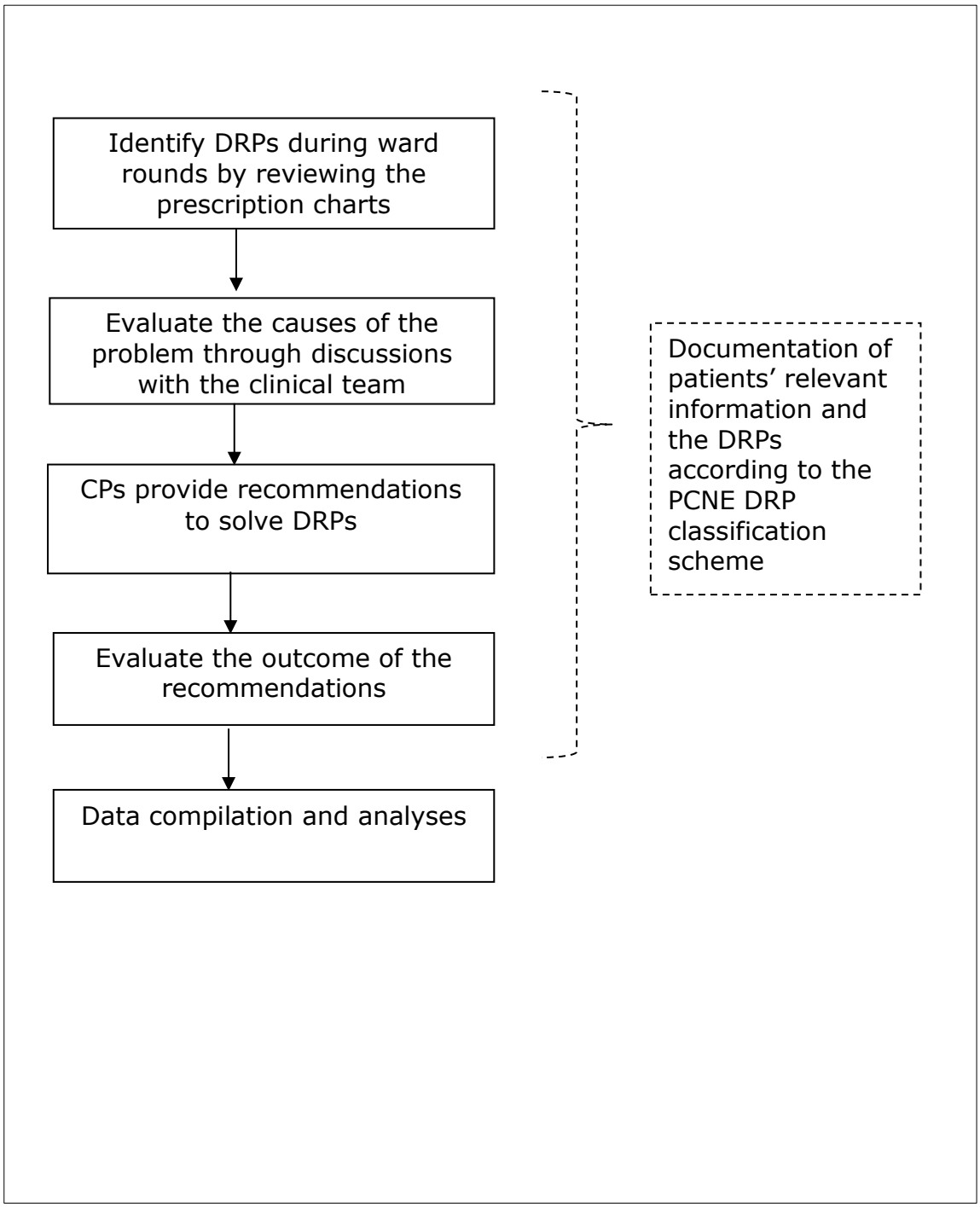


Figure 4.1 Flowchart for the process of data collection

4.2.3.5 Data analysis

At the end of the data collection period in each hospital, the researcher and the CP evaluated all patients' profiles and the identified DRPs. The CPs were also asked to determine the types and contributory factors for the DRP in the case study. The DRP identified from both hospitals were selected for the case study. Challenges in characterising the DRP using the PCNE classification version 6.2 were recorded in order to develop a standard operational definition. Any disagreement was solved by consensus between the researcher and the CPs.

4.2.4 Results

The results are presented in two sections. Sub-section 4.2.4.1 is the findings to improve the study design and sub-section 4.2.4.2 presents the challenges in using the PCNE classification system for research.

4.2.4.1 Considerations for study design

4.2.4.1.1 Characteristics of the potential study patients

The CPs reviewed a total of 31 patients but only 9 fulfilled the pre-determined inclusion criteria (ELCH, n=3; GOSH, n=6). The main reason for patients being excluded was because of the predetermined age limit. All patients who were included in the analysis had at least one DRP during hospitalisation. The majority of patients were male (69%). Overall, patients were in the average age of 5.67 (range 2.97 - 9.05) years old and were

prescribed with an average of 6 (range 3 – 16) medications at the point DRPs were identified.

4.2.4.1.2 Data collection schedule

At the beginning, it was planned that data would be collected concurrently at both study sites. Due to logistical reasons and staff constraints, this was not possible. It was suggested that the researcher be stationed at each hospital for a specified period of time rather than alternating the days for data collection between both hospitals. Such an arrangement would be able to (1) facilitate the CPs' rota for ward pharmacy service, (2) ensure uninterrupted observation of pharmacy practice throughout patients' hospital stay and (3) minimise missing data due to unavailability of the medical notes on the wards after patients had been discharged from the hospital. This arrangement was applied for scheduling the data collection in the main prospective cohort study.

4.2.4.2 Considerations for using the PCNE classification system in research

4.2.4.2.1 Decision-making in using the PCNE DRP classification system

The main challenge in using the PCNE classification for research was the unavailability of operational definitions for the constructs in the system. This contributed to inconsistency in classifying the characteristics of DRPs (i.e. the types of problem and contributory factors). As an example, the evaluation of the decision made by the CPs in classifying the characteristics

of DRPs using the case study showed discrepancies. As illustrated in Figure 4.2. The CPs agreed that the unavailability of a standard operational definition gave a wide variability in the interpretation of DRPs because their management involves complex clinical assessment.

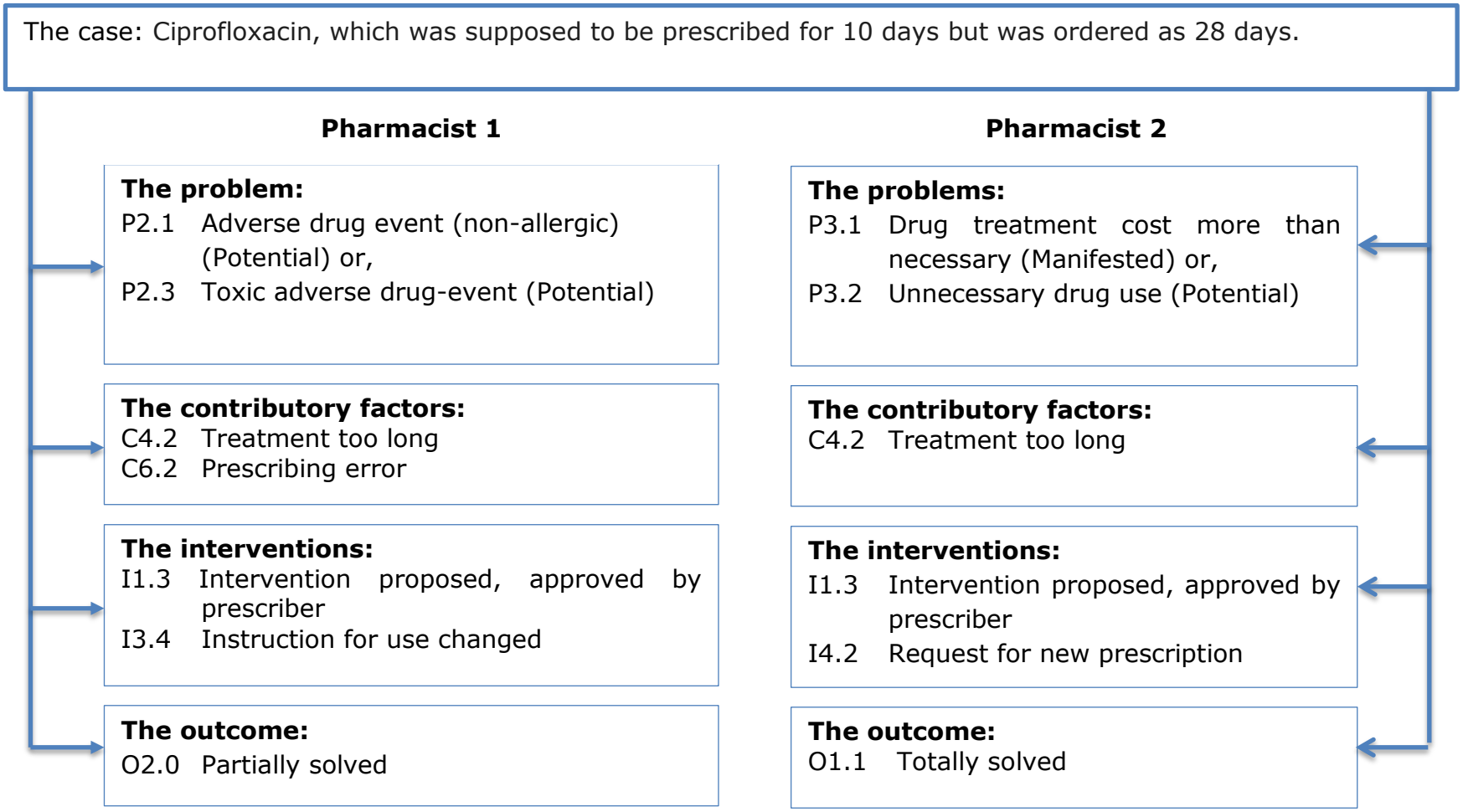


Figure 4.2 The characteristics of DRPs assessed by the pharmacists according to the PCNE classification system version 6.2

4.2.4.2.2 Operational definitions for DRPs and the constructs of the PCNE DRP classification system

The researcher and the CPs who were involved in identifying the DRPs developed the operational definition for the constructs in the PCNE DRP classification system. Based on the PCNE definition of DRP, the operational definitions are as follows:

"An event or circumstances involving drug therapy[1] that actually or potentially[2] interferes with desired health outcomes[3]"

In the definition stated above, the operational definition for the underlined phrases in the context of this research is explained in the following points:

1. 'An event or circumstances involving drug therapy[1]...' includes any problems related to the use of medicines that occur in the drug-use or drug-treatment process. This research was not designed to separate DRPs from the element of ADEs, ADRs, and MEs thus, these elements were interpreted as either a type of DRP or its contributory factors.
2. '…actually or potentially[2]…' refers to the nature of a DRP. An Actual DRP, which is also referred to as a Manifested DRP, is a problem identified after it has reached the patient. Whereby, a Potential DRP is a problem that is identified before it reaches the patient.
3. '…desired health outcomes[3]…' refers to the intended outcome desired from a drug that is prescribed for the patient.

The summary of the modifications made to the original PCNE classification system are shown in Table 4.1 and the details are presented in Appendix 7. The modified PCNE DRP classification version 6.2 was developed into a proforma, i.e. the DRP-Registration Form (DRP-Rf) that was used for collecting data throughout the present research (Appendix 8).

Table 4.1 Summary of the modification to the PCNE DRP classification version 6.2

Section	New codes in main categories	New codes in sub-categories
Types of DRPs	P4 Other	P4.2 Drug administration problems
Contributory factors for DRPs	C5 Medication errors C6 Drug supply	C3.8 Dose difficult to measure C5a Prescribing error in decision making C5.10 Dilution error C8.1 Poor medication reconciliation C8.2 Unwanted side effects C8.3 Inappropriate drug administration site/route
Intervention		I2.7 Dosing frequency changed to…

4.2.4.2.3 Modifications to the PCNE DRP classification

The following sub-sections explain the modification done to sections: contributory factors and pharmacist interventions for DRPs.

4.2.4.2.3.1 DRP contributory factors

In the PCNE classification (Figure 3.5), category (C5) drug use process refers to causes of DRPs related to the way the patient uses the drug, in spite of proper dosage instructions on the label. For instance, the patient 'took the drug at the inappropriate time' or the patient 'taking or being administered the wrong drug'. The aforementioned examples are mishaps in the process of drug use – this is also recognised as medication errors. In order to narrow down the scope of DRPs' contributory factors, category (C5) drug use process was modified to (C5) medication errors.

In the PCNE classification , category (C6) logistics, refers to causes of DRPs related to the management of the prescribing and dispensing process, which includes sub-categories of (C6.1) prescribed drug not available, (C6.2) prescribing errors and (C6.3) dispensing errors. Category (C6.2) and (C6.3) were shifted to (C5) medication errors. Category (C6) logistics was modified to (C6) drug supply.

4.2.5.2.3.2 Pharmacists' interventions

Category I1 for Intervention 'At prescriber level' in the PCNE classification was classified as pharmacist-prescriber encounters rather than a type of intervention. In clinical practice involving multidisciplinary healthcare

professionals, the process of notifying or seeking such acknowledgment is obtained through inter-professional discussions and good rapport within the clinical team. In view of this understanding, the act of a clinical pharmacist communicating with the prescribers (and vice versa) is appropriately seen as a process that precedes an intervention rather than a type of intervention.

4.2.5 Discussions

4.2.5.1 Amendments to the inclusion criteria

The age restriction of between 2 to 16 years limited the recruitment of patients. The researcher initially suggested this age limit based on the age group included for data analysis in the UKRR Annual Reports. The UKRR reports exclude data for patients aged 16 to 18 for from the majority of analyses, which includes the prevalence and incidence rates, because of incomplete data in the medical records as children in this age group may receive their medical care either in a paediatric or in an adult nephrology centre (Lewis et al., 2010).

This feasibility study found that children aged 16 to 18 years who were admitted to the wards at the study sites remained to be seen by the Paediatric Renal Team and incomplete data in their medical records were not an issue. This study also found that approximately 30% of the potential study population were less than 2 years old, an age group beyond the pre-determined inclusion criteria for this research. As this was an epidemiology

study, all patients aged 18 years and younger (instead of only in the range between 2 to 16 years old) were included. The inclusion criterion for the final research was amended to include all patients aged 18 years and younger.

4.2.5.2 Limitations of the PCNE classification system

One of the limitations in using the PCNE classification was the unavailability of extra information (or guideline) to facilitate users in selecting the most appropriate category and sub-category for the characteristics of DRPs. This challenge has been reported by previous studies (Eichenberger et al., 2010, Lampert et al., 2008). Similar finding has been found in the current study.

Another consideration in using the PCNE classification was the assessment to determine the causes of DRPs. The causes for a DRP can be multifactorial and interact with each. On many occasions, a DRP could not be attributed to a single cause. As an example of this, Lampert investigated DRPs identified in pharmacy practice in a Swiss hospital and found a total of 213 causes were reported for 207 DRPs (Lampert et al., 2008). A latter study on DRPs in the paediatric population found that a total of 674 causes were reported for 478 identified DRPs (Rashed et al., 2012b). Both of the aforementioned studies adapted the PCNE classification system and agreed that the causes of DRP were multifactorial; however the methods that had been used to assess the causes were not explained. Similar findings were obtained from the case study illustrated in Figure 4.2.

There is also no gold standard on the maximum number of causes that could be assigned to a DRP. For research purposes, the PCNE suggested a maximum of three causes for each DRP. The suggestion to limit the causes of DRPs to a maximum of three was accepted for the current research, however the term 'contributory factors' was the preferred term rather than 'causes'.

In the process of developing the operational definition, several modifications were made to the original PCNE system. The main reason for modifying the original classification was to capture the variables required for data evaluation. Permission to adapt the PCNE classification with modifications was obtained from the PCNE representative by email (Ibrahim, 2012a). The adapted PCNE classification version 6.2 was developed as the proforma used in data collection for this research. This proforma was referred to as the DRP-Registration Form (DRP-Rf) and is enclosed in Appendix 8.

4.2.6 Summary

It was feasible to conduct the observational study design on the wards of both hospitals. A limitation in this study was that, although the CPs (data collectors) were involved in developing the operational definition for the modified PCNE DRP classification system, no inter-rater test was performed to evaluate their agreement on using the operational definition for real-life clinical cases.

4.3 Feasibility Study (II)

4.3.1 Background

Pharmacy practice research involving interventions on PC and medicines management is complex (Wong, 2004). It requires a strategic methodological approach to solve the difficulty in defining the component of intervention, identifying plausible endpoints and the practicality of the chosen study design at the clinical setting. Therefore, the aim of this feasibility study was to examine the difficulties in the data collection process for an RCT at the renal outpatient clinic before embarking on the major trial. Ethical approval was obtained from the London-Hampstead Research Ethics Committee and the Guy's and St. Thomas' R&D Committee, UK.

4.3.2 Objective

1. To determine the types of CPs' interventions that are feasible to be carried out at the renal outpatient clinics.

2. To identify the circumstances that may contribute to non-adherence to trial protocol and identify measures that may limit them.

3. To test the feasibility of the modified PCNE classification and the Gordon classification for DRPs identified at the renal outpatient setting.

4.3.3 Methods

4.3.3.1 Study design

This was a single centre, simple randomisation, parallel group-study. The study design is illustrated in Figure 4.3.

4.3.3.2 Site and study period

This study was conducted from 18th February to 11th April 2013 at the ELCH renal outpatient clinics.

4.3.3.3 Sample size

Sample size calculation was not required because this was a feasibility study.

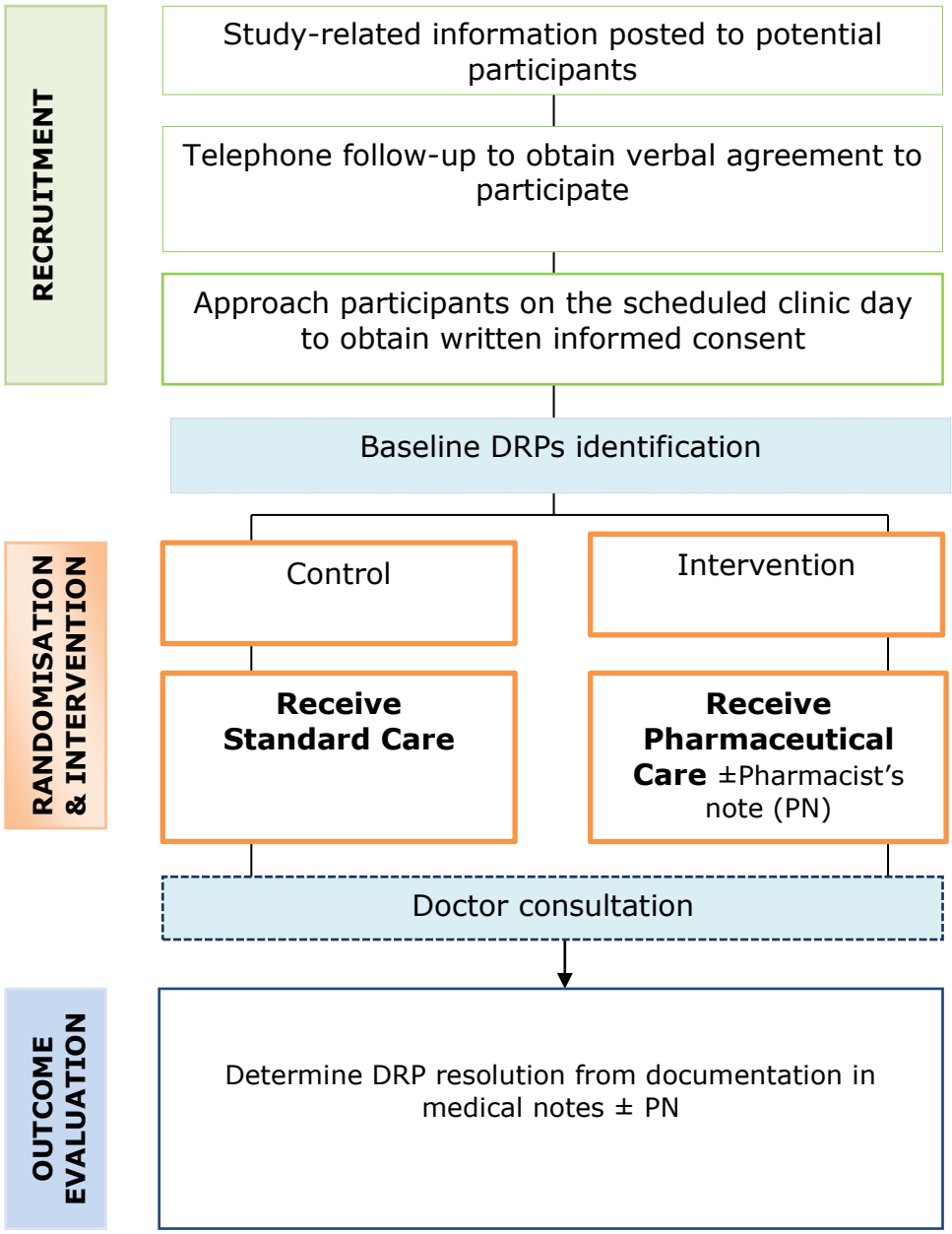


Figure 4.3 Outline of the study design

4.3.3.4 Study protocol

4.3.3.4.1 Inclusion criteria

All children under the care of the Paediatric Nephrology Department at ELCH aged 18 years and younger who attended the renal outpatient clinic and gave written informed consent were included. Children who were not on any medications and children who had received a doctor's consultation on the day of clinic were excluded.

4.3.3.4.2 Recruitment

In this study, the term 'participants' refers to the children (the patients) and their parent(s). The list of patients who would be attending the renal clinic was obtained from the clinic receptionist at three week prior to the appointment date. All patients were screened for their eligibility. Study-related materials were posted out to all patients who were deemed eligible as study participants. The child and their family therefore had an opportunity to review the study information before their next clinic appointment to decide whether or not to participate in the study.

Approximately two weeks after posting out the study information, the researcher made a telephone follow-up call to the potential participants to confirm if the materials had been received and to discuss consent-related issues. The study materials would be posted again following any parents' request if the initial information had not been received. The telephone calls were made at 1100 and 1200 and between 1500 and 1600 on weekdays. If

potential participants could not be contacted (unanswered, inactive telephone number) after three attempts on three different occasions, no further attempts to contact the family were made prior to their upcoming clinic appointment.

Once verbal agreement to participate in the study had been obtained, the patient's name was entered in the study database and arrangements made to schedule an appointment at the time of their next clinic visit. The schedule for enrolment is a shared electronic email calendar within the Trust accessible to the researcher and the CPs. At this point, the patient's group allocation had not yet been assigned. On the day of the scheduled clinic appointment, the researcher approached all potential participants including those who had not been contactable via the phone to discuss the study in more detail and obtain informed consent (and assent where age appropriate). The participants were given the chance to ask further questions about the study before giving consent, whilst waiting for the clinic to start. They were also encouraged to discuss the study with other healthcare providers if they wished, and were informed that they could withdraw from the study at any point and this would not affect their treatment. Once informed consent had been obtained, the researcher identified the DRPs at baseline for all patients. The study information leaflets and consent forms are enclosed in the Appendices (Appendix 10 to Appendix 17).

4.3.3.4.3 Identifying DRPs at baseline

The researcher identified DRPs at baseline for all patients in both arms. Baseline DRPs refers to active and inactive problems related to the use of drugs that occurred before patients were enrolled into the trial. Active DRPs refer problems that the researcher newly identified from eMR documentation and not which were unsolved at the point of enrolment. Inactive DRPs refer to problems that the researcher identified from the eMR and were already solved at the point of enrolment.

The baseline DRPs were detected using the explicit retrospective review of the eMR from the past six months prior to trial enrolment. Even though the effectiveness of detecting DRPs using this method has not been previously studied, it was the most feasible method to use for this study because of the following reasons:

1. The renal clinic notes were already uploaded onto the eMR when this study was initiated and the electronic charting of the clinic consultation notes was fully utilised by the renal team in managing patients at the outpatient clinic.
2. The paper-based medical notes were fully utilised by the nurses for phlebotomy measurement. During this feasibility study, most of the time the CPs were not able to get hold of the paper medical notes and this contributed to patients not receiving the intended intervention. The eMR was accessible to the researcher and the CPs; and this was important to standardise the source of information in detecting DRPs.

3. Research has shown that information entered onto the eMR was similar to paper-based notes at the primary care (explained in sub-section 3.5.2.1). The ELCH renal consultants agreed with this, furthermore, the clinic notes are short and brief compared to the inpatient notes. The researcher tested this assumption by comparing the types of DRPs detected from both resources in five patients selected at random; and they were found to be similar.

All DRPs were recorded onto the DRP-Rf proforma (Appendix 8). During the detection of baseline DRPs, the researcher was not supposed to intervene, however, if a problem(s) with significant potential for harm were identified, from the ethical point, the researcher would have to inform the doctor. The researcher is a qualified pharmacist trained in renal pharmacy but not working in the capacity of a clinical pharmacist within the Trust.

4.3.3.4.4 Randomisation

Once the baseline DRPs had been documented, the patients were then allocated into either the Control or the Intervention arm by simple randomisation.

Two tables of unique numbers were generated using the online random number generator (Social Psychology Network, 2013). Each table contained a list of 100 unique random numbers for the Control and the Intervention arm respectively. These numbers were printed on individual 10cm x 20cm white cards, which were then folded inwards and sealed in an A4 envelope. The envelope was kept in a locked cabinet in the ELCH Pharmacy

Department. This procedure was part of the allocation concealment steps. Determination of whether a patient would be in the Control or the Intervention arm was made by taking out one card at random for each patient. If the number on the card belonged to the table of the Intervention group, the researcher would notify the CP on duty and the CP would attend the clinic to perform the intervention.

4.3.3.4.5 Control group

Participants in the Control arm received the standard care from the study site. Standard care refers to the usual care all patients would have received when attending their routine renal clinic appointment, as previously described in the outpatient setting of the outpatient care in sub-section 3.2.2.

4.3.3.4.6 Intervention group

Patients who were enrolled into the Intervention arm received the CP interventions whilst waiting to see the doctor for their renal clinic appointment. Other than seeing the CP, the participants were not expected to do anything extra during their usual clinical review appointment.

4.3.3.4.7 CPs' interventions

Patients in the Intervention group received the CP interventions during their clinic visit. Two CPs were responsible for conducting the interventions on a weekly schedule basis. The interventions that were agreed and deemed

feasible by the CPs comprised two components: (1) conducted semi-structured interviews with the patients to screen for DRPs and (2) provided recommendations to the doctors on the resolution of any identified DRPs from the interview sessions.

4.3.3.4.7.1 Semi-structured interview

The CPs conducted the semi-structured interview with the patients using the Gordon DRP screening tool for DRP (Gordon et al., 2005). This screening tool is enclosed in Appendix 19. The interview was conducted in a 20-minute session before subjects were seen by their doctor. During that session, the CP reviewed patient's medications which were on a list obtained from the most recent clinic note in the eMR and determined whether there were any problems in taking them as prescribed. Throughout the interview session, participants were involved as a full partner and, therefore, any suggestions to solve the identified problems were communicated with the parent (and child when age appropriate).

4.3.3.4.7.2 Provide recommendations to solve DRPs

At the end of the session with the participant, the CP summarised the DRPs and provided recommendations to solve the problems by issuing a Pharmacist Note (PN) to the doctor. The PN was delivered together with the patient's medical notes prior to the clinical consultation (Appendix 20).

4.3.3.4.8 Blinding

Due to the nature of the intervention, blinding was not possible.

4.3.3.4.9 Outcome measures

The primary outcome is to measure the effect of CP interventions in resolving active DRPs identified at baseline by the researcher. This outcome was defined as the number of active DRPs that were solved after the clinic sessions divided by total number of active DRPs identified at baseline by the researcher multiplied by 100. The formula is shown below:

$$\text{The precentage of DRP resolution in each arm } (\%) = \frac{\text{Number of active DRPs after clinic consultation}}{\text{Total number of active DRPs at baseline}} \; x \; 100$$

The resolution of active DRPs was identified by evaluating the doctor's clinical notes on actions taken toward the identified problems. The concept of surrogate endpoint in patient safety research has been explained in sub-section 3.4.2.2. The researcher gathered information on the changes to patients' medication management with respect to the DRPs from the medical notes at the end of the clinic day. The resolution of a baseline active DRP was categorised as 'Solved' (if actions were taken to solve the identified DRP) or 'Not solved' (if no actions were taken to solve the identified DRP or if the implementation of the suggestion or action to solve the problems by CPs was not documented).

The secondary outcomes were as follows:

1. The severity of the DRPs: assessed by four judges

2. The drugs associated with DRPs: classified using the WHO-ATC classification system.
3. The characteristics of DRPs: characterised according the adapted PCNE classification system using the proforma DRP-Rf (Appendix 8).

As this study aimed to examine the feasibility of data collection process for an RCT, the primary and secondary outcomes were not evaluated. The methods used in measuring the outcomes have been explained in Chapter 3.

4.3.4 Results

4.3.4.1 Recruitment

A total of 75 patients were screened during this feasibility study, of which 26 fulfilled the inclusion criteria. Out of 26 potential participants to whom the study-related materials were posted at three weeks prior to their renal clinic appointment, only 7 were successfully followed-up by telephone for verbal agreement (3 agreed to participate, 3 were undecided, and 1 declined). Telephone calls to the remaining 19 potential participants were not successful despite three attempts. On the scheduled clinic days, all 3 patients who had given verbal consent were enrolled in the study and another 3 patients who were initially undecided during telephone follow-ups opted to participate. Written consents were obtained from all 6 patients (4 Intervention and 2 Control). Of the 4 patients who were allocated into the

Intervention arm, 1 did not receive the intervention. The result of recruitment is summarised in Figure 4.4.

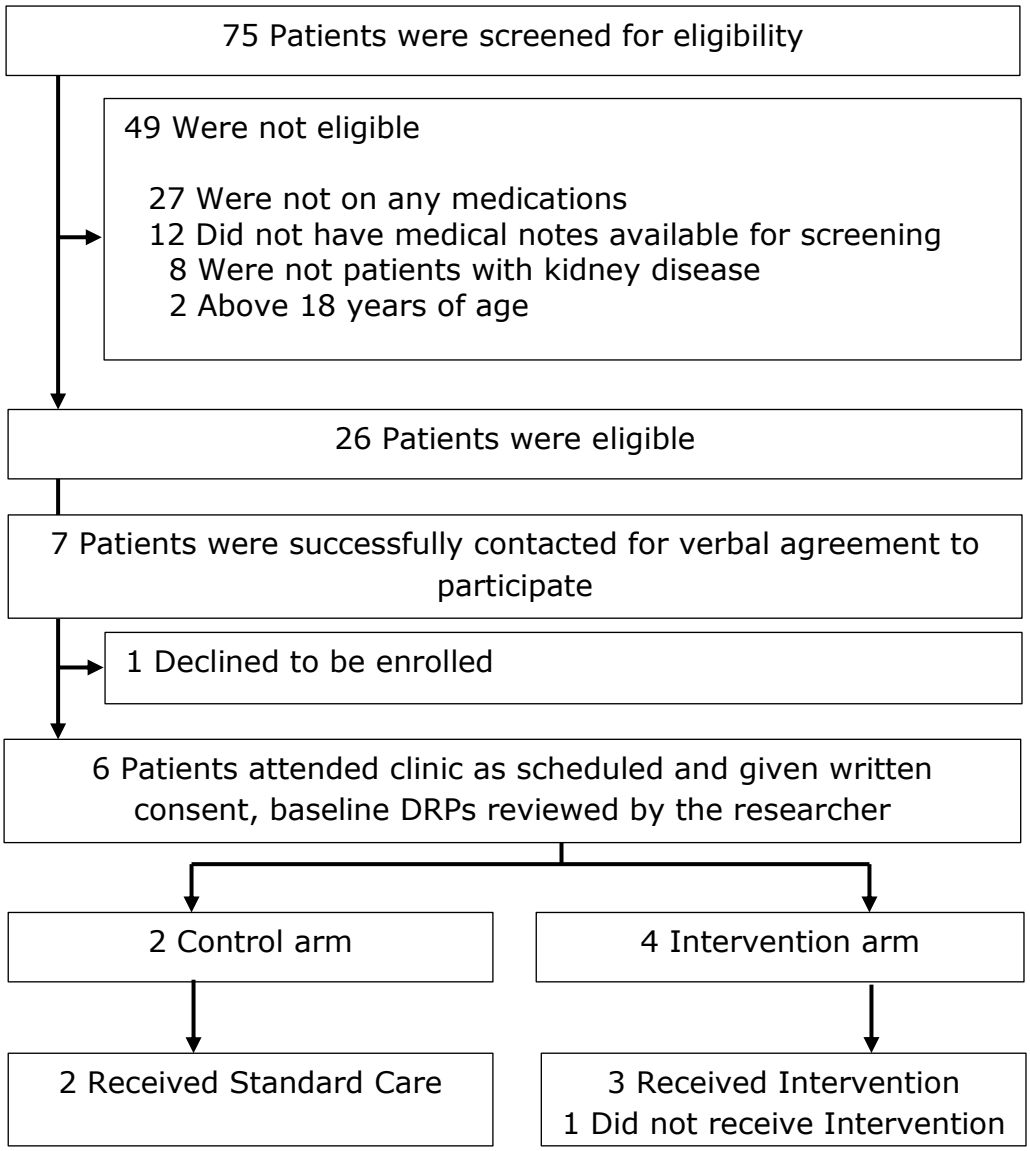


Figure 4.4 Flowchart of patient recruitment and random allocation

4.3.4.2 Non-adherence to protocol

One patient who was allocated into the Intervention arm did not receive the intended intervention. The reason for this scenario was that the CPs involved in the study were also the staff within the Trust and they were bound to commitments of their daily job descriptions especially during the shortage of staff. This situation limited the chances of all participants in the Intervention arm receiving the intervention according to the trial protocol.

4.3.4.3 Opportunity window to conduct the intervention

Identifying an appropriate opportunity to introduce interventions in the standard practice was a challenging task. Nevertheless, referring back to setting of the outpatient standard care as described in sub-section 3.2.2, there was a 10-20 minutes waiting period after phlebotomy assessment, prior to doctor's consultation. This time period was seen as a window of opportunity to implement new healthcare intervention by pharmacists (see Figure 4.5).

It was also feasible to create a window of opportunity at the point of dispensing rather than at the clinic; but this was not chosen for the present study because:

1. The characteristics of DRPs identified would vary depending on the location of the data collection (Dean et al., 2005). At the point of dispensing, the service is focused on dispensing the right medicine to the right patient at the most appropriate time. Therefore, data would

be bias towards prescription errors (Dean et al., 2005) and this would not represent the actual DRPs occurring at the renal clinic.

2. The dispensing role at the dispensary is shared amongst a bigger team of pharmacists with different level of training in paediatric pharmacy practice - this would contribute to wide data variability.
3. Not all potential participants could be included into the study because not all patients would receive prescriptions for new medications to be collected from the hospital pharmacy.
4. The evaluation on the resolution of DRPs in this research is obtained from clinic notes entered at two time points: at baseline and after clinic session. Therefore, identifying DRPs at the point of dispensing would not be appropriate because collecting medicines from the hospital dispensary is the final stage in the outpatient clinic procedure.

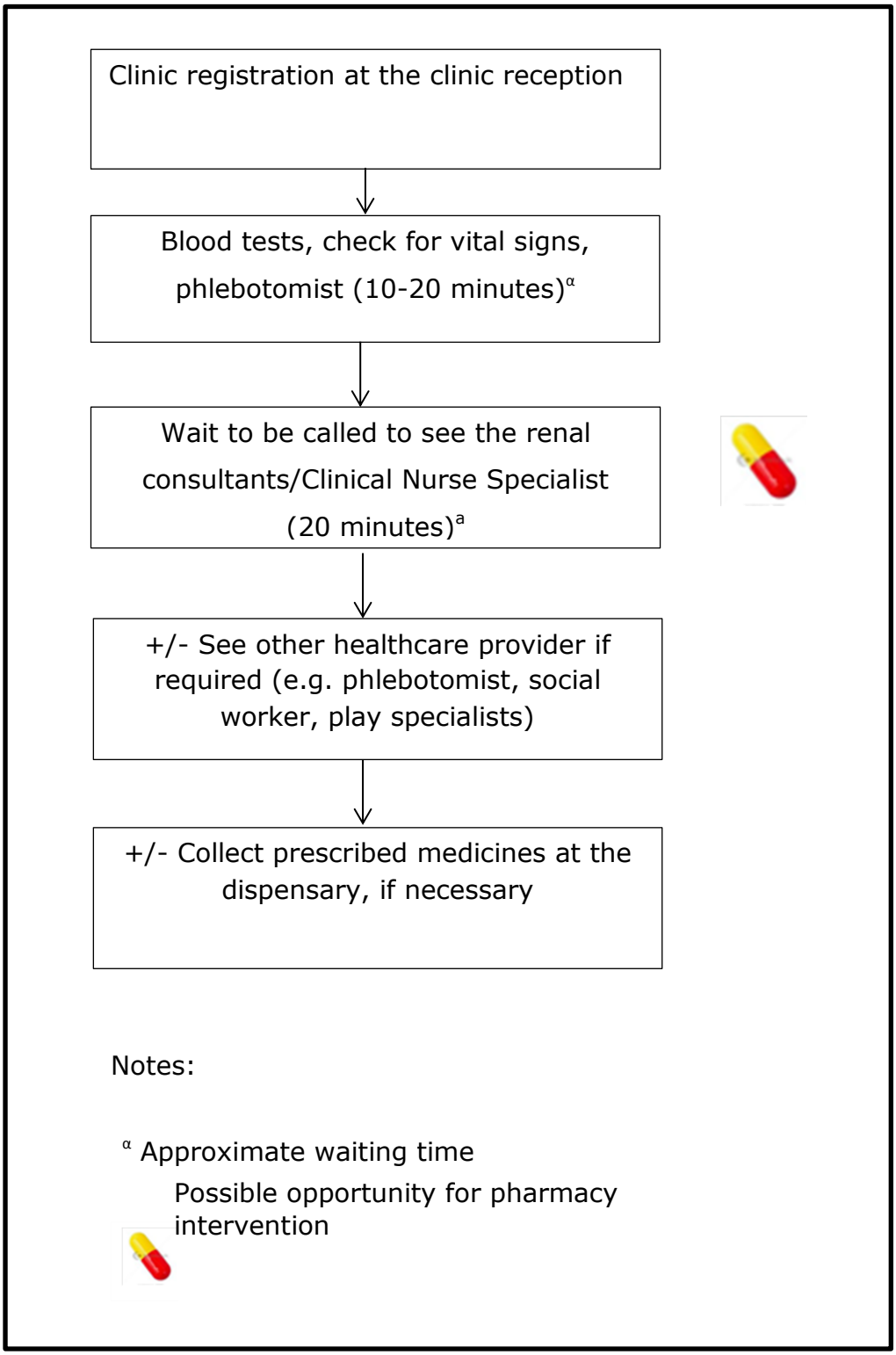


Figure 4.5 Window of opportunity to conduct pharmacist intervention at the renal outpatient clinic

4.3.4.4 Consideration in using the modified PCNE classification system for DRP

The modified version of the PCNE classification system that was developed during the Feasibility Study (I) at the inpatient setting was practical for use in the outpatient setting. However, several new codes were added based on the characteristics of the identified DRPs (Table 4.2).

4.3.4.5 Consideration in using the Gordon screening tool for identifying DRP

The median time taken to identify DRPs from patient interviews using the Gordon screening tool at the renal outpatient clinic was 15 minutes per patient (range 10-20 minutes).

As the allocated time for CPs interventions was 20 minutes, a simplified version of the tool was preferred as it allowed more time for the CPs to summarise and resolve the identified DRPs. Thus, the researcher and the CPs developed the Patient Interview Form by consensus. The form was divided into two parts. The first part contained a table for the CPs to write down patients' medication during medication review. The second part of the form contained questions adapted from the Gordon screening tool for DRP. The form was developed as an additional proforma to the DRP-Rf (Appendix 21).

Table 4.2 Codes added to the modified version of the PCNE classification system for DRPs

Codes	Sub-categories	Operational definition
P4.3	Delay in treatment	*
C6.2	Difficulty in obtaining repeat prescription from the community	*There is a problem in obtaining repeat prescription(s) from the general practitioner (GP) or the community pharmacy*
C7.7	Patient (parent/carer) forgets to obtain repeat prescription(s) from the community	*
C7.8	Poor understanding of treatment plan and medications	The patient (or parent/carer) had poor understanding of treatment plan and medications
C8.4	Dependent on enteral feed tubes	*The patient is dependant on enteral feeding tubes for the administration of medicines*
C8.5	Difficulty in obtaining information from the general practitioner	*
C8.6	New dose not altered by the general practitioner	*
*Self-explanatory		

4.3.5 Discussion

There were only six recruitments during this study. Further evaluation revealed that the list of patients who were expected to attend the renal clinics that was obtained at three weeks prior to the appointment did not portray the actual expected clinic attendance. Furthermore, there were also a number of patients who were newly added onto the clinic list but were not available to the researcher. In order to overcome this problem, the researcher would have to obtain an updated list for appointments that were scheduled at two weeks prior to the clinic date. Patients who were newly added to the latest list were screened for eligibility as potential participants and followed a similar procedure for recruitment. However, this group of patients may be contacted less than two weeks after receiving the study-related materials. The clinical supervisors for the study suggested that all patients who have been posted the study materials should be approached regardless of whether or not they were able to be contacted by telephone. This is because failure to be contacted was not a definite indicator of not agreeing to participate in the study.

In regard to the interview session using the Gordon screening tool for DRPs, the questions were originally designed for adult patients. In almost all cases, the questions were answered by the parent or carer. Hence, not all questions would be suitable to be adapted into the research proforma. In this study, the median time for an interview session was 15 minutes and longer interview times were required for patients with a more complex treatment. Gordon et al. reported an average of 12 minutes was required to conduct an interview using the same tool at the surgeries (Gordon et al.,

2005). Therefore, a simplified version of the tool was preferred in order to achieve the objective. The process of using the original screening tool during this feasibility study offered a training ground to standardise the thought process for the CPs.

4.3.6 Summary

The RCT and the proposed CP interventions were deemed feasible. However, this study identified several limitations in the conduct of the trial: (1) the CPs' commitments to their duty within the Trust may result in a number of patients in the Intervention arm not receiving the intended interventions, (2) as the researcher was the only person responsible for recruitment, there would be possibility that participants who have received the study material were not approached and (3) no agreement test was conducted to evaluate the agreement between the CPs in categorising the DRPs using the adapted screening tool.

4.4 Conclusion

The present feasibility studies managed to address the strategies to overcome the potential challenges in the proposed study designs. The standard operation definition developed for the modified PCNE classification system and the simplified Gordon classification would be able to standardise the process of data collection throughout the subsequent studies. The next chapter describes the work conducted to establish the incidence and nature of DRPs in children with kidney disease at the inpatient setting.

CHAPTER 5

Prospective Observational Study on the Characteristic of DRPs in Hospitalised Children with Kidney Disease

5.1 Introduction

The systematic literature review in Chapter 2 concluded that there is a lack of data on the epidemiology of DRPs in children with kidney disease and supports the need for further research. In Chapter 4, the Feasibility Study (I) showed that the characteristics of DRPs in this patient group can be evaluated using the modified PCNE classification system version 6.2. This chapter describes the work carried out to investigate the incidence, characteristics and the potential predictors for the occurrence of DRPs in hospitalised children with kidney disease. The ethical approvals were obtained from (1) the London-Westminster Research Ethics Committee and (2) the R&D Committee of Guy's and St. Thomas' Hospitals NHS Foundation Trust (GSTT) and Great Ormond Street Hospital for Children (GOSH).

5.2 Hypothesis

"Hospitalised children with CKD have higher DRP incidence compared to the general paediatric population, in whom the incidence is 33%"

When this study was about to commence in 2010, the most recent data on the incidence of DRPs in children in the UK was reported as 33% (Rashed et al., 2011). Personal correspondence with the paediatric renal consultants and renal nurses at the participating hospitals came to an agreement that the incidence of DRPs in children with CKD could possibly be higher than in

the general paediatric population, and therefore the hypothesised the clinical estimates of DRP incidence in children with CKD was 50%.

5.3 Aim and objectives

This study aimed to determine the epidemiology of DRPs in hospitalised children with kidney disease. The study objectives were as follows:

1. To identify the risk factors
2. To measure the severity
3. To identify the characteristics

Of DRPs that developed during hospital stay in children with kidney disease at the inpatient setting.

5.4 Methods

5.4.1 Study design

Prospective observational cohort study. The outline of the study design is illustrated in Figure 5.1.

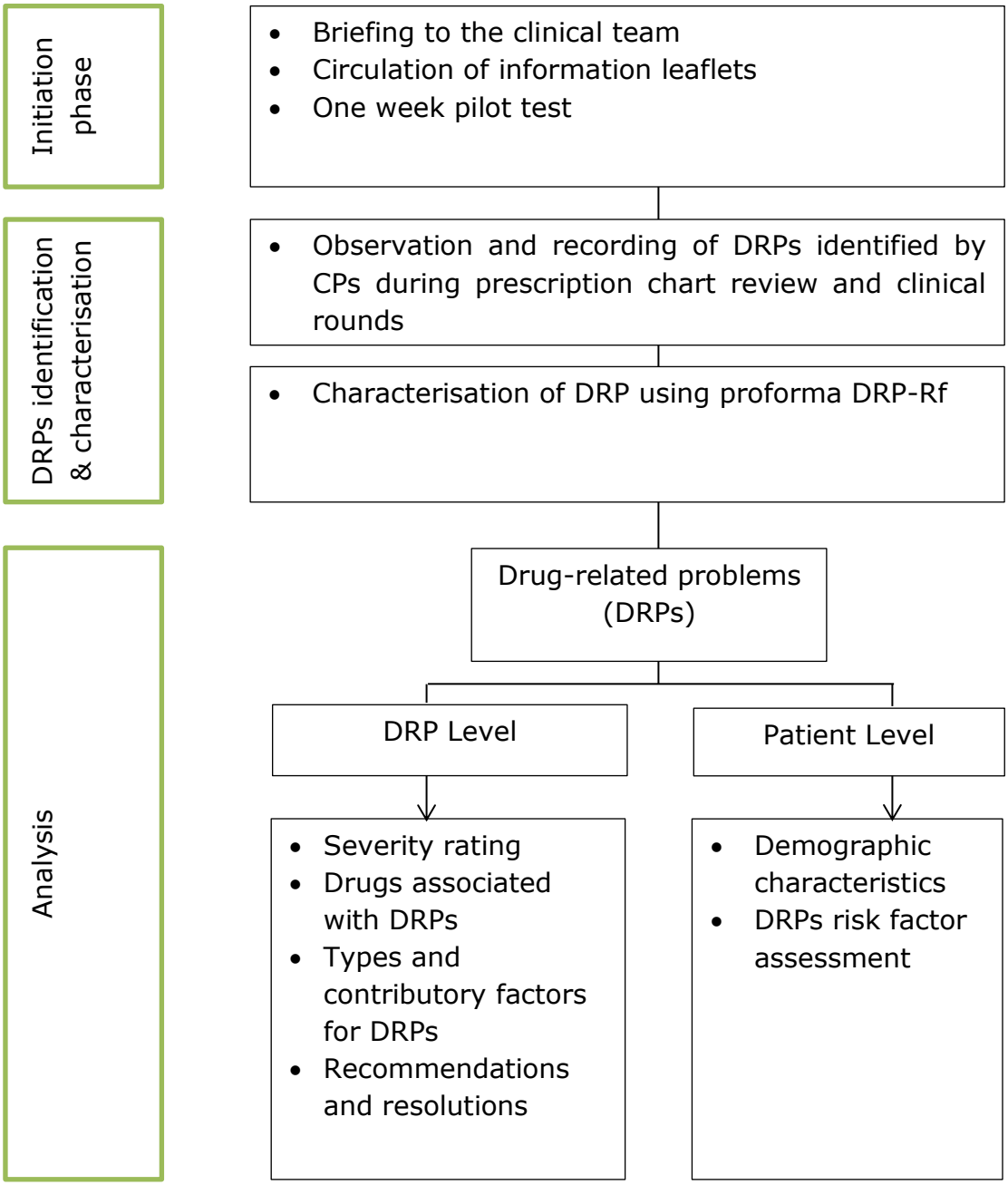


Figure 5.1 Flowchart for data collection process and analysis

5.4.2 Sites and study period

Data collection was performed over a ten-month period at the renal wards of ELCH and GOSH, London, UK. The data collection period at each study sites was as follows:

- 1st December 2011 to 30th April 2012: GOSH
- 1st May 2012 to 1st September 2012: ELCH

The model of standard care in the inpatient setting in both hospitals has been described in sub-section 3.2.1. The main differences in the setting of the inpatient care between the two hospitals were (1) paper-based prescription charts at ELCH and (2) the use of the ePS at GOSH.

5.4.3 Sample size calculation

The clinical estimate of DRPs' incidence in hospitalised children with CKD was 50%. The calculated sample size to detect the 95% confidence interval between 42% and 58% was a minimum of 156 patients. The sample size was calculated using the formula below:

$$N = \frac{4P\ (1-P)}{x^2}$$

$$N = \frac{4(0.5)\ (1-0.5)}{0.08^2}$$

= 156 patients

Where,

N = Sample size

P = The proportion of the study population with at least one DRP during hospitalisation, which was 50% from clinical estimation.

x = The precision of 8%

5.4.4 Inclusion criteria for study patients

All children aged 18 years and younger who were admitted to the renal wards during the study period with the following criteria were included:

1. Received at least one drug during their period of hospitalisation.
2. Admitted to the ward for more than 24 hours.

5.4.5 Study initiation phase

5.4.5.1 Briefing to clinical team

The researcher was given a 30-minute session for a PowerPoint presentation in the monthly Nephrology Department meeting at GOSH and ELCH. The renal consultants, registrars, ward staffs and the CPs attended the briefing sessions. The briefing at both hospitals was conducted on the first week of the data collection period at each site. The briefing session also included an introductory session to the concept of DRPs and the outline of

the study design. The study information leaflet on how the study was to be conducted was distributed to all ward staff (Appendix 9).

5.4.5.2 Pilot test

A pilot test was conducted for a week at each hospital prior to the initiation of data collection together with the feasibility study in conjunction with the pharmacy services evaluation. The pilot test was conducted to test the feasibility of the prospective observation study design and the data collection forms. The conduction of the feasibility test is described in section 4.2.

5.4.5.3 Training for CPs

The CPs were involved in identifying and characterising the DRPs. During the pilot test, a one-hour session was allocated to train the CPs on the use of the study proforma (i.e. DRP-Rf) and the application of its operational definition. The CPs involved in collecting the data were also involved in the development of the operational definition and were familiar with the content of the DRP-Rf (Appendix 7).

5.4.6 Detection of DRPs

DRPs were detected using the prospective prescription chart review method by the CPs during routine clinical pharmacy practice on the wards. The recommendations for resolution were made through discussion with the clinical team during clinical rounds. For standardisation across the two

participating study sites, all identified DRPs were documented into the DRP-Rf. Briefly, this proforma has main categories and sub-categories for types of DRPs, contributory factors of DRPs, recommendations to resolve the DRPs and outcomes for the recommendations. An example of how a DRP was characterised using the DRP-Rf was previously illustrated in Figure 3.5. The drugs involved with the DRPs were classified using the WHO-ATC system.

Throughout the process of DRP identification, the researcher remained as a non-participant observer. Non-participant observation in the data collection process may be subjected to the 'Hawthorne effect' (Kumar, 2011). The presence of the observer could potentially decrease or increase the identification of DRPs and the resultant actions taken. Within the scope of this project, it was not possible to totally exclude this effect but it was minimised by adopting the participant observation approach. The researcher introduced herself as a student and did not make any conclusion or suggest any form of recommendations during the observation period. This was to ensure that the presence of the observer was as discreet as possible so as not to interfere with the work of the CPs and ward staff.

The presence of the observer was necessary to ensure consistency in data collection, especially in the early stages when pharmacists were still getting used to the proforma and the operational definitions.

5.4.7 Data analyses

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows® and presented as percentages (%), median (Md), interquartile range (IQR 1-3) and odd ratios (OR) with 95% confidence interval (CI). In all statistical tests *p* values of less than 0.05 were considered statistically significant. For the descriptive analysis of patients and DRP characteristics, Chi-squared (χ^2), Kruskal-Wallis Rank and Mann-Whitney tests were used as appropriate.

5.4.7.1 Incidence of and risk factors in DRPs

The overall incidence of DRPs in the cohort was defined as the number of patients with at least one DRP during hospitalisation divided by the total number of patients reviewed by the CPs multiplied by 100.

$$DRP\ incidence = \frac{Number\ of\ patients\ with\ at\ least\ one\ DRP\ during\ hospitalisation}{Total\ number\ of\ patients\ reviewed\ by\ the\ CPs} x100$$

For DRPs' incidence and risk factor calculations, only the first admission during the study period was considered for investigating the association between DRPs' incidence and potential risk factors.

5.4.7.2 Logistic regression for assessing predictors of DRPs

Logistic regression was performed to assess the impact of a number of predictors on the likelihood that DRPs would occur among the study

population during a hospital stay. Logistic regression allows the testing of binary outcomes for the presence of at least one DRP throughout hospitalisation; and the independent variables can be a mixture of categorical or continuous (Pallant, 2010). The backward stepwise model was chosen because it is less likely to eliminate predictors involved in suppressor effects and thus has a lower risk of making a Type II error (false negative). The differences between the forward and backward stepwise methods are summarised in Table 5.1.

Table 5.1 Differences in the process of the Logistic Regression Stepwise model (Peacock and Peacock, 2013)

Forward Stepwise

- Put each variable into the model alone
- Discard variables that are not statistically significant
- Of the remaining variables, the one which is most strongly related to the outcome variable is selected
- Add the remaining variables one at a time in order of their strength of relationship with the outcome, until adding an extra variable does not contribute significantly to the model

Backward Stepwise

- Remove the first variable that has the weakest relationship with the outcome, one variable at a time
- Of the remaining variables, the one which has the weakest relationship with the outcome is removed
- The process is repeated until all the remaining variables are significantly related to the outcome.

The regression analysis was conducted in three steps. First, preliminary analyses were conducted to ensure the assumptions of independence of errors, multicollinearity and linearity for logistic regression were adhered. Then, the univariate logistic regression was conducted to test the significance of individual predictors. Finally, the multivariate logistic regression model was conducted. The regression worked around one binary outcome (at least one DRP during hospital stay: Yes/No) and 6 independent variables:

(Age): Age in years

(G): Gender (female versus male)

(LOS): Length of hospital stay (days)

(Rx): Numbers of medicines prescribed per child during hospital stay

(Adm): Types of ward admission (elective versus non-elective)

(RRT): RRT modality (Dialysis, Transplant and non-RRT)

The factors that were analysed in the multivariable analyses included those found to be relevant in the literature and others of significance from the data in the current study or of pathophysiological significance (Grabe et al., 1997; Hogg et al., 2003; Ibrahim et al., 2013; Kaplan et al. 1994a; Manley et al., 2003; Rashed et al., 2012b).

5.4.7.3 Inter-rater agreement for severity assessment of DRPs

The Intraclass Correlation Coefficient (ICC) measures the degree to which the four judges achieved identical ratings of DRPs' severity under similar assessment conditions. The type of ICC method used was the two-way random effect ANOVA for absolute agreement. The two-way random effect model treats both the DRPs and the judges' scores as random measures asserting that the DRPs assessed in this study represent problems from the hospitalised population of which the results should be generalised. The test also treats the judges' scores as random factors as if the scores represent the measure of DRPs' severity in hospitalised children with kidney disease.

The value of ICC ranges from 0 to 1, with higher values indicating greater reliability or agreement respectively (Field, 2009).

5.5 Results

A total of 132 patients were recruited (ELCH n=60, GOSH n=72). Of the 132 patients, 5 were admitted as a cause of a DRP and thus were excluded from analysis.

A total of 127 patients fulfilled the inclusion criteria and were included in the cohort. Of the 127 patients, 22 had multiple ward admissions (range 2-6) contributing to a total of 166 admissions during the study period. A total of 203 DRPs were recorded from the 166 admissions. The study results are presented based on data analysis at Patient level (sub-sections 5.5.1 and 5.5.2) and DRP level (sub-sections 5.3.3 to 5.5.7). Analyses at Patient level included the demographic characteristics and the risk factors for the DRPs in the 127 patients. Analyses at DRP level included the characteristics of the 203 problems (i.e. the severity of the DRPs, the medicines associated with DRPs, the types and contributory factors of DRPs). The codes for the characteristics of DRPs presented in this chapter is according to the modified PCNE classification system for DRPs in Table 4.1.

5.5.1 Patient characteristics

A total of 127 patients were included in the analyses (ELCH n=57, GOSH n=70). Of the 127 patients, 65 (51.2%) had at least one DRP throughout hospitalisation. The incidence of DRPs in the study cohort was 51.2% (95%

CI 43.2-60.6%) of patients reviewed by the CPs. Of the 127 patients, 68 (53.5%) were male. The median age of the study population was 6.6 years (IQR 1.8-12.5). The overall median length of hospital stay was 6 days (IQR 3-12). The median length of hospital stay when the initial DRP was identified was 4 (IQR 1-12.5). There was a statistically significant difference in the number of patients who developed DRPs during hospitalisation compared to those who did not in regard to the length of hospital stay ($p<0.001$) and RRT modality ($p=0.001$). The total number of medicines prescribed in the study cohort was 3341 and the median number of medicines per child was 17 (IQR 9-31). Table 5.2 presents the demographic characteristics of the study cohort.

Demographic characteristics of children from each hospital are shown in Table 5.2. GOSH reported significantly more number of patients who had DRPs ($p<0.001$), had longer length of hospital stay ($p=0.02$), receiving dialysis treatment ($p=0.04$) and more numbers of medicines prescribed per child ($p<0.001$).

Table 5.2 Patient demographic characteristics by occurrence of DRPs (n=127)

Characteristics	All	DRPs*	No DRPs	p value[α]
Total patients	127 (100)	65 (51.2)	62 (48.8)	0.78
Gender				
Male	68 (53.5)	37	31	0.44
Female	59 (46.5)	28	31	
Median age	6.6 (1.8-12.5)	5.0 (1.3-11.9)	8.1 (2.1-13.2)	0.22
Number of patients by age group				
0-1 month	2 (1.6)	1	1	
>1 month to ≤ 2 years	34 (26.8)	20	14	
>2 years to ≤ 6 years	27 (21.3)	13	14	0.27
>6 years to ≤ 12 years	29 (22.8)	16	13	
>12 years to ≤ 18 years	35 (27.6)	15	20	
Median length of hospital stay (days)	6.0 (3-12)	9 (4-20)	4 (3-7)	
Length of hospital stay				
1-7 days	74 (58.3)	27	47	**<0.001**
8 days and longer	53 (41.7)	38	15	
Type of ward admission				
Elective	76 (59.4)	41	35	0.45
Non-elective	51 (40.2)	24	27	

Characteristics	All	DRPs*	No DRPs	p value[α]
Renal replacement therapy				**0.001**
Dialysis	28 (22.0)	20	8	
Kidney transplant	29 (22.8)	18	11	
No RRT	70 (55.1)	27	43	

Data are median and (IQR 1-3) or frequency (%),
*Number of patients with at least one DRP during hospitalisation; [α]Mann-Whitney Test

Table 5.3 Demographic characteristics of patients with at least one DRP throughout hospitalisation by study sites (n=65)

Characteristics	DRPs*	ELCH	GOSH	*p* value[α]
Total patients with at least one DRP throughout hospitalisation	65 (100)	26 (40)	39 (60)	**<0.001**
Gender				0.54
Male	37	16	21	
Female	28	10	18	
Median age	5.0 (1.3-11.9)	5.7 (0.9-12.5)	5.0 (2.0-10.6)	0.85
Number of patients by age group				0.99
0-1 month	1	0	1	
>1 month to ≤ 2 years	20	11	9	
>2 years to ≤ 6 years	13	2	11	
>6 years to ≤ 12 years	16	5	11	
>12 years to ≤ 18 years	15	8	7	
Median length of hospital stay (days)	9 (4-20)	6 (3-11.3)	12 (7-28)	**0.02**
Length of hospital stay				**0.03**
1-7 days	27	15	12	
8 days and longer	38	11	27	

Characteristics	DRPs*	ELCH	GOSH	*p* value[α]
Renal replacement therapy				**0.04**
Haemodialysis	20	3	17	
Kidney transplant	18	10	8	
No RRT	27	13	14	
Types of ward admission				0.21
Elective	41	14	27	
Non-elective	24	12	12	
Median number of medicines prescribed per patient	28 (13-50)	15 (11-27)	37 (21-66)	**<0.001**

Data are median and (IQR 1-3) or frequency (%); [α]Mann-Whitney Test

5.5.2 Risk factors for DRP

5.5.2.1 Regression analysis

The univariate regression showed a significant association between the occurrence of DRPs with dialysis (Dx), transplantation (Tx), longer hospital stay (LOS) and more number of medicines prescribed (Rx). In the multivariate modelling, only Rx remained significant (OR 1.06, 95% CI 1.02-1.10, p=0.002) (Table 5.4). The odd ratio of 1.06 for variable Rx indicates that the chance of having a DRP is 6% higher with the addition of one medicine in the treatment on the wards, controlling for all other factors. The effect was calculated as follows: (1.06–1) x 100 = 6%.

Table 5.4 Risk factors for DRPs in hospitalised children in the study cohort (n=132)

	Univariable OR (95% CI)	p-value	Full model OR[α] (95% CI)	*p* value
Gender (female vs. male)	0.76 (0.38-1.52)	0.44	1.03 (0.43-2.44)	0.95
Age (year)	0.96 (0.90-1.02)	0.17	0.96 (0.89-1.03)	0.24
Type of ward admission (elective vs. on elective)	1.32 (0.65-2.68)	0.45	1.76 (0.70-4.42)	0.23
Renal replacement therapy				
Not on dialysis or transplant	1.00 (Reference)	-	1.00 (Reference)	-
Dialysis	3.98 (1.54-10.30)	**0.004**	2.10 (0.68-5.52)	0.22
Post-transplant	2.61 (1.07-6.35)	**0.04**	1.93 (0.68-5.48)	0.20
Length of hospital stay (days)	1.11 (1.05-1.17)	**<0.001**	1.05 (0.99-1.10)	0.10
Number of medicines prescribed per child	1.07 (1.04-1.11)	**<0.001**	1.06 (1.02-1.10)	**0.002**

Note:
[α]Full model using Backward Stepwise Regression
Odd ratio (OR) at 95% confidence interval (CI)

5.5.3 Severity assessment of DRPs

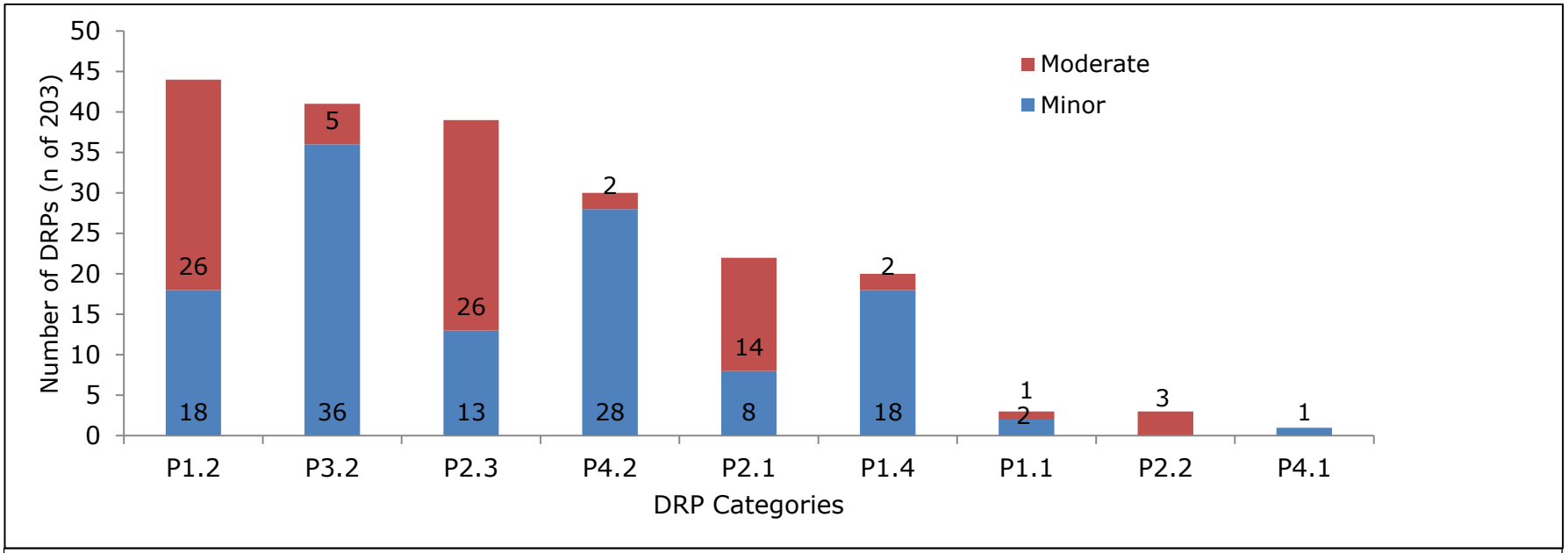
All 203 DRPs were listed for severity assessment. The completed scoring sheets were obtained from all four judges, four weeks after the sheets were sent out.

5.5.3.1 Inter-rater level of agreement in rating the DRP severity

The ICC coefficient was 0.69 (95% CI 0.57-0.78, $p<0.001$), indicating that there was moderate agreement among the four judges relative to each other on average in rating the DRP severity.

5.5.3.2 Analysis of severity

The mean severity scores ranged from 0.1 to 6.8 and none of the DRPs were scored as severe. Of the 203 DRPs, 138 (68%) were scored as minor and 65 (32%) were moderate in clinical significance (Figure 5.2). The majority of DRPs that were scored as minor was (P3.2) unnecessary drug treatment (26.1%, n=36/138). Category (P2.3) toxic adverse reaction were mostly scored as moderate (40%, n= 26/65). An example description of a minor DRP is when a patient has completed treatment with broad-spectrum antibiotics but nystatin for candidiasis prophylaxis not stopped (DRP no. 36). Moderate significance DRP cases included the administration of 500mcg of intravenous prazosin when the prescribed dose was 50mcg in a neonate with compromised renal function (DRP no. 133). The full description of the DRPs are enclosed in Appendix 24.

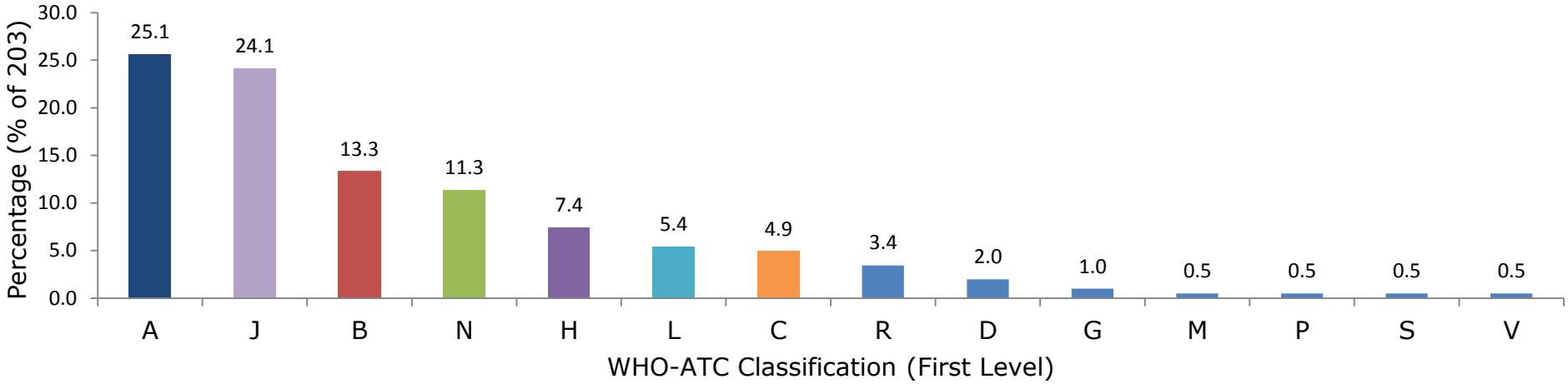


P1.2 Sub-optimal drug effect
P3.2 Unnecessary drug treatment
P2.3 Toxic adverse reaction
P4.2 Drug administration problem
P2.1 Non-allergic adverse reaction
P1.4 Untreated indication
P1.1 No effect of drug treatment
P2.2 Allergic adverse reaction
P4.1 Patient dissatisfied with therapy

Figure 5.2 Number of DRPs by severity rating according to DRP categories (N=203)

5.5.4 Drugs associated with DRPs

Using the first level of the WHO-ATC classification system for medications, the groups of medication most often associated with DRPs were '(A) Alimentary tract and metabolism' (n=52/203, 25.6%), followed by '(J) Systemic anti-infectives' (n= 49/203, 24.1%), and '(B) Blood and blood forming organs' (n=27/203, 13.3%) (Figure 5.3). There was no significant difference in the types of medicines associated with DRPs between study sites. The full list of the drugs involved is presented in Appendix 23.



(A) Alimentary tract and metabolism
(J) Antiinfectives for systemic use
(B) Blood and blood-forming organs
(N) Nervous system
(H) Systemic hormonal preparations, Excluding sex hormones and insulins
(L) Antineoplastic and immunomodulating agents
(C) Cardiovascular system
(R) Respiratory system
(D) Dermatologicals
(G) Genito-urinary system and sex hormones
(M) Musculo-skeletal system
(P) Antiparasitic products, insecticides and repellents
(S) Sensory organs
(V) Various

Figure 5.3 The drugs associated with DRPs by WHO-ATC classification system (N=203)

5.5.5 Types of DRPs

A total of 203 DRPs were identified from 166 admissions during the study period. More than half of the total DRPs were potential in nature (55.1%, n=112/203). The most frequently reported DRPs were (P1) drug effect (33.1%, n=67/203), followed (P2) adverse drug event (31.5%, n=64/203) and (P3) treatment cost (20.2%, n=41/203). At the sub-category level, the most frequently recorded problems were (P1.2) sub-optimal drug effect (21.7%, n=44/203), followed by (P3.1) unnecessary treatment (20.2%, n=39/203) and (P2.3) toxic adverse reaction (19.2%, n=39/203).

At the hospital level, the number of DRPs identified at GOSH is 42.9% more than at ELCH (75.4% versus 32.5%). All DRPs pertaining to (P1.1) no drug effect was only reported at GOSH whilst (P2.2) allergic reaction were reported from ELCH. An example of ineffective treatment is a case of medicine prescribed for the wrong site e.g. Maxitrol eye ointment preparation, which was intended for topical application at the gastrostomy site, was prescribed for administration on both eyes (DRP no. 135). All three cases of allergic drug reaction at ELCH did not have history of drug allergy recorded on the medication chart. An example is a case with the manifestation of an allergic reaction to cyclizine injection in a patient who had a history of allergy to cyclizine in previous hospital admissions but this had not been documented on the patient's medication chart (DRP no. 23). The description of the DRPs cases are presented in Appendix 24. The summary of the main categories and sub-categories in the types of DRPs is given in Table 5.5.

Table 5.5 Types of DRPs identified in the study cohort by main and sub-categories (N=203)

Main category for Types of DRPs	Sub-categories[δ]	Total (% of N)	Potential DRPs* (n of N)	ELCH (n of N)	GOSH (n of N)
Total DRPs		203 (100)	112 (55.1)	66 (32.5)	153 (75.4)
P1 Drug effect (n=67, 33.1%)	P1.1 No effect of drug treatment	3 (1.5)	1	0	3
	P1.2 Sub-optimal effect	44 (21.7)	33	16	28
	P1.4 Untreated indication	20 (9.9)	6	4	16
P2 Adverse drug event (n=64, 31.5%)	P2.1 Non-allergic reaction	22 (10.8)	13	8	14
	P2.2 Allergic drug reaction	3 (1.5)	2	3	0
	P2.3 Toxic adverse reaction	39 (19.2)	32	8	31
P3 Treatment cost (n=41, 20.2%)	P3.1 Unnecessary treatment	41 (20.2)	4	6	35
P4 Others (n=31, 15.3%)	P4.2 Drug administration problems	30 (14.8)	21	11	19
	P4.1 Patient dissatisfaction	1 (0.5)	0	1	0

*Potential DRPs refers to drug problems that were identified before the patient experienced harm

5.5.6 Contributory factors in DRPs

A total of 387 contributory factors were reported from 203 DRPs. Of the 387 contributory factors, the most recorded categories were (C5) medication errors (46.8%, n=181/387), followed by (C3) dose selection (22%, n=97/399) and (C1) drug selection (18.6%, n=72/399). At the sub-category level, the most recorded were (C5.8) prescribing errors (45.5%, n=176/399), followed by (C3.2) doses too high (5.9%, n=23/399) and (C1.7) required synergistic/preventive drug not prescribed (5.2%, n=20/399). Table 5.6 summarises the full description of contributory factors.

Evaluation of DRPs' contributory factors between the study sites showed relatively different trend. The three most frequent categories reported from ELCH were (C5) medication error followed by (C3) dose selection and (C1) drug selection. At GOSH, the predominant categories were (C5) medication error, (C2) dose selection and (C8) other factors (i.e. mainly poor medication reconciliation). This could be due to the use of ePS in the screening of prescription charts which was only available at GOSH.

Table 5.6 Contributory factors of DRPs by study sites (n=399)

	Contributory factors main category / sub-category	N (%)		ELCH (n of N)	GOSH (n of N)
Treatment	**C1 Drug selection**	**72**	**18.0**	**13**	**59**
process	C1.7 Synergistic/Preventive drug not prescribed	20	**5.0**	1	19
	C1.9 No indication	13	**3.3**	2	11
	C1.1 Inappropriate drug	10	**2.5**	3	7
	C1.3 Inappropriate drug duplication	9	**2.3**	1	8
	C1.4 Indication for drug not noticed	7	**1.8**	0	7
	C1.5 Too many drugs unnecessarily for same indication	6	**1.5**	1	5
	C1.2 Inappropriate drug combination	5	**1.3**	3	2
	C1.6 More cost-effective alternative available	1	**0.3**	1	0
	C1.8 New indication	1	**0.3**	1	0
	C2 Inappropriate drug form	**7**	**1.8**	**5**	**2**
	C3 Drug dosage	**97**	**24.3**	**30**	**67**
	C3.2 Dose too high	23	**5.8**	5	18
	C3.1 Dose too low	17	**4.3**	7	10

	Contributory factors main category / sub-category	N (%)		ELCH (n of N)	GOSH (n of N)
	C3.4 Dosage regimen too frequent	15	**3.8**	5	10
	C3.7 Deterioration/improvement of disease state	10	**2.5**	4	6
	C3.3 Dosage regimen not frequent enough	8	**2.0**	3	5
	C3.6 Pharmacokinetic problem requiring dosage adjustment	8	**2.0**	3	5
	C3.5 No therapeutic monitoring	3	**0.8**	1	2
	C3.8 Dose difficult to measure	13	**3.3**	2	11
	C4 Treatment duration	**15**	**3.8**	**2**	**13**
	C4.2 Too long	13	**3.3**	1	12
	C4.1 Too short	2	**0.5**	1	1
Drug use process	**C5 Medication errors**	**181**	**45.4**	**46**	**135**
	C5.8a Prescribing error in decision making	104	**26.1**	23	81
	C5.8b Prescribing error in prescription writing	72	**18.0**	20	52
	C5.2 Drug over administered	2	**0.5**	2	0
	C5.1Inappropriate timing of drug administration/dosing intervals	2	**0.5**	1	1

Contributory factors main category / sub-category	N (%)		ELCH (n of N)	GOSH (n of N)
C5.9 Dispensing error	1	**0.3**	0	1
C7 Patient factors	**1**	**0.3**	**0**	**1**
C7.5 Refuse to take medicines	1	**0.3**	0	1
C8 Other factors	**26**	**6.5**	**12**	**14**
C8.2 Unwanted side effects	14	**3.5**	8	6
C8.1 Poor medication reconciliation	12	**3.0**	4	8

From the 203 DRPs, 45 (22.2%) had a single contributory factor, 126 (62.1%) had two and 32 (15.8%) had three contributory factors. It is worth noting that, in most occasions, the contributory factors were multifactorial and interacted with each other. Of the 203 DRPs, 29 (14.3%) had PE as the only contributory factor, and 147 DRPs (72.4%) had PE as one of the contributory factors. Of the 147 DRPs that had two or more contributory factors, the most frequent combination factors were (C5.8) prescribing error with (C3) dose selection, 51.7% (n=76/147) and, (C5.8) prescribing error with (C1) drug selection, 29.9% (n=44/147).

5.5.7 Recommendations and resolutions for DRPs

The CPs provided a total of 228 recommendations to solve the 203 DRPs. The majority of recommendations to solve the DRPs were at the Drug Level, which included changes to the drug doses, dosing frequency and selection of drug treatment. DRPs that received the highest numbers of recommendations were (P1.2) sub-optimal drug effect, (P2.3) toxic adverse reaction and (P3.2) unnecessary drug treatment. Table 5.7 shows the types of recommendations at different levels.

The acceptance rate for the provided recommendations was 99.5%% (n=227/228). Of the 228 recommendations, the clinical team did not agree to only one and this is referred to as DRP number 187. In this case, the recommendation was to stop prescribing lactulose in a patient who was reluctant to take the drug as prescribed. The problem was acknowledged by the clinical team but they insisted on trying to persuade the patient to adhere to treatment.

The recommendations solved 96% (n=195/203) of the DRPs as a result of ward pharmacy practice. Out of the remaining 8 DRPs, 5 (2.5%) DRPs were partially solved and required follow-ups at the outpatient clinics (DRP no. 31, 89, 91, 103 and 116). Another 3 DRPs (1.5%) were unsolved because of lack of patients' cooperation on taking the medicines as prescribed (DRP no. 67, 187and 190). The descriptions of the DRP cases mentioned above are presented in Appendix 24.

Table 5.7 Recommendations to solve DRPs by clinical pharmacists (n, % of 228)

Main category for recommendations to solve DRPs	Sub-categories	Total n (%)
I2 Recommendations at drug level (n=196, 86%)	I2.2 Dosage changed	59 (25.8)
	I2.7 Dosing frequency changed	36 (15.8)
	I2.5 Drug stopped	31 (13.6)
	I2.6 New drug started	23 (10.1)
	I2.1 Drug changed	12 (5.3)
	I2.4 Instructions for use changed	11 (4.8)
	I2.9 Treatment duration changed	10 (4.4)
	I2.3 Drug form/formulation changed	9 (3.9)
	I2.8 Route/site of administration changed	5 (2.2)
I3 Recommendations at patient/carer level (n=12, 5.3%)	I3.1 Patient (medication) counselling	9 (3.9)
	I3.3 Referred patient to prescriber	3 (1.5)
I4 Recommendations at other level (n=20, 8.8%)	I4.1 Request for new prescriptions	10 (4.4)
	Update information on prescription charts	10 (4.4)

5.6 Discussion

The findings in this study support the hypothesis that hospitalised children with kidney disease have higher incidence of DRPs compared to the general paediatric population. While not all predicted risk factors for DRPs were significant, the overall characteristics of DRPs in the study cohort shared some similarities to the children hospitalised in the medical wards. These results also supported previous studies that have shown the effectiveness of ward pharmacy practice and the potential benefit of ePS in managing DRPs.

5.6.1 Incidence of DRPs in children with CKD

The incidence of DRPs observed in this study cohort was 51.2% (95% CI 43.2-60.6%) of patients. This incidence is higher compared to the incidence reported in children hospitalised in other specialties including those receiving care in the paediatric intensive care units, which was reported as 45.2% (95% CI, 41.5-48.8) of children (Rashed et al., 2012b). The same study also reported the DRP incidence in the UK cohort was 39.4% (Rashed et al., 2012b). One possible explanation for higher incidence in the renal units is the complexity of cases seen. Furthermore, in patients with kidney disease, the drug doses and frequency require frequent adjustment according to the estimated GFR. A drug dosing service in a renal unit has shown to minimise DRPs (Daschner, 2005; Hassan et al., 2009).

Data from the five patients who required admission because of a DRP were excluded from analysis because this study was designed to only evaluate DRPs that occurred during inpatient treatment. The information on DRPs

that led to admission for these five patients was a finding by chance and did not represent the study population.

5.6.2 Risk factors for DRPs

The number of drugs prescribed per child was the only factor that was statistically significant in the full model logistic regression analysis. The current study shows that an addition of one medicine increases the chance of DRPs' occurrence during hospital treatment by 6%. The cut-off point for DRPs or MEs at which there is no clinical significance is not known. Ideally, safe and effective treatment should be free of DRPs or errors of any sort. As most DRPs in this study were found to be minor (severity score 0-2.9) and potential in nature, it is unlikely that the DRPs would be associated with fatal consequences (i.e. severity score 7-10).

In this study population, the median prescription per patient was 17 and ranges between 10 and 31. Studies of adult renal patients acknowledged the use of five or more drugs and a regimen involving twelve or more doses a day as factors associated with DRPs (Grabe et al., 1997; Kaplan et al., 1994b; Koecheler et al., 1989; Manley et al., 2003). Polypharmacy with complex regimen has been recognised to be a risk factor for adverse drug events and other types of DRPs in previous studies of children and adults (Bates et al., 1999; Fattinger et al., 2000; Koh et al., 2005; Mason, 2011; Rashed et al., 2012a; Rashed et al., 2012c).

5.6.3 Severity of DRPs

The majority (68%) of DRPs identified in the current study were minor in clinical significance. It is a challenge to compare the severity of DRPs in the current study to others because of the variation in definitions of levels of severity and in the methods used for the severity assessment. As an example, the majority of DRPs (74%) in hospitalised children in general medical wards were also found to be minor in significance (Rashed et al., 2012b). This aforementioned study also adapted the Dean & Barber (1999) scale to assess the severity of DRPs; however, the evaluation on the degree of severity for the DRPs was conducted by face-to-face discussions (rather than individual scoring) among three (rather than four) judges.

Castelino et al. (2011) studied the clinical significance of DRPs in adult renal patients and reported that the majority of DRPs were minor (72%). In the aforementioned study, the assessment was made using the Alderman Criteria which was developed to describe clinical pharmacy interventions in a psychiatric unit. The Alderman criteria defined minor DRPs as problems requiring small adjustments and optimisation to therapy which were not expected to significantly alter hospital stay, resource utilisation or clinical outcome. The Dean and Barber scale (1999) which was used in the present study defined minor DRPs as problems that were unlikely to have any adverse effects.

5.6.4 Drugs associated with DRPs

Drugs in the class of 'alimentary tract and metabolism' (n=51/203) and 'systemic anti-infective' (n=49/203) were the most frequently associated

with DRPs in this study. These two classes of medicines were also reported to be the most frequently associated with DRPs in children in the UK (Rashed et al, 2012b). Anti-infectives were reported as the predominant class of drugs associated with DRPs in other research on medicine use in children (Kaushal et al., 2001; Kunac and Reith, 2008). Infection is known to be one of the main causes of mortality in children with kidney disease (Harambat et al., 2012; Warady and Chadha, 2007; Pruthi et al., 2012b). This could possibly explain the high usage of anti-infective in the study cohort.

Anti-infective were also reported to be associated with DRPs in the adult renal patients but were not as common as cardiovascular agents and anti-diabetics (Castelino et al., 2011; Kaplan et al., 1994a; Manley et al., 2005). The difference in the types of drugs associated with DRPs between children and adult patients with CKD could be due to the aetiology of the disease. Kidney disease in adult patients is secondary to long standing of metabolic disorders such as hypertension and diabetes mellitus. In the paediatric population, almost one-half of all CKD cases are due to congenital kidney disorders (Kim et al., 2013; Warady and Chadha, 2007).

5.6.5 Types and contributory factors of DRPs

The most common DRPs in the study cohort were sub-optimal drug effect and unnecessary treatment (Table 5.5). These DRPs were associated with drug selections and dosage errors. Similar findings were reported in other studies focusing on medication errors and have reported that dosing errors

as the most common errors affecting the paediatric population (Ghaleb et al., 2006; Ghaleb et al., 2010; Jani et al., 2008; Kaushal et al., 2001).

One reason for the high frequency of dosing problems identified in the study cohort might be due to the effect of dialysis on the pharmacokinetic properties of medicines (Hassan et al., 2009; Veerback and Musuamba, 2009). Dialysis increase drug elimination and result in sub-optimal drug effect (Verbeeck and Musuamba, 2009). This scenario complicates the calculation for a dose in children that is known to be dependant on many factors such as the weight, age, BSA and associated clinical conditions (Conroy and Carroll, 2009; Ghaleb et al., 2010).

Problems pertaining to unnecessary drug treatment in the study cohort reflects that medications should not only be adjusted according to the estimated GFR (Corsonello et al., 2012) but also frequently monitored according to the patients' updated clinical condition to prevent the occurrence of adverse drug events (Hassan et al., 2010).

Frequent monitoring of medications also involves medication reconciliation on admission and at hospital discharge which can reduce discrepancies that may cause potential harm. Medication discrepancies in children were reported to range from 22% to 72.3% (Huynh et al., 2013b). Future research is required to address problems in medication discrepancies for patients with kidney disease, especially those who are dialysis-dependent (Pai et al., 2013).

5.6.6 Recommendations and resolutions for DRPs

The high acceptance rate (99.5%) towards CPs' recommendations in resolving DRPs by the clinical team may have been attributed by several factors. Other than the integration on clinical pharmacy practice at the inpatient setting, the clinical skills and experience of the CPs also played an important role. The CPs involved in this study had more than 10 years of experience in renal pharmacy practice. Furthermore, the professional relationship built between the CPs and other member of the clinical team had established the role of CPs in decision making for patient care. Professional interpersonal relationships between pharmacists and physicians has shown to contribute to higher acceptance rates towards pharmacists' recommendations and improve treatment outcomes in previous studies (Altavela et al., 2008; Bodgen et al., 1998; Leape et al., 1999).

Although the present study did not measure whether acceptance of recommendations led to the resolutions of DRPs resulted in improved clinical outcomes, but it did reflect positive multidisciplinary decision making in managing DRPs.

5.7 Strengths and limitations

The strength of this study lies in the prospective measures of DRPs in the current clinical practice; and it is the first study to evaluate the characteristics of DRPs in children with kidney disease at the inpatient setting. Certain limitations must be considered when interpreting the findings, including the difference in the data collection time period and the

use of ePS which may introduce variability to characteristics of DRPs identified in ELCH and GOSH. Although data-collection training was given to the CPs to optimise the consistency of the collected data using a standardised proforma, no inter-rater test was performed to evaluate the agreement on classifying the characteristics of DRPs.

5.8 Summary

This study was able to explain the underlying reasons of higher incidence of DRPs in hospitalised children with kidney disease compared to those in the general medical inpatient settings. Sub-optimal drug effect is the predominant DRP in the study cohort and the majority of the problems were contributed by drug and dosing errors. Whilst many factors may be associated with DRPs in children and their associations may be cumulative and interdependent, the only independent predictor for the occurrence of DRPs in this study group was the greater number of medicines prescribed per child during hospital treatment. The majority of the DRPs were minor in significance and were solved as a result of ward pharmacy services. Findings from this study provide a starting point for future studies on DRPs at the renal outpatient clinic setting, which would give more information on consideration of providing clinical pharmacy services to paediatric nephrology patients. The next chapter describes the work on investigating the characteristics of DRPs and the impact of CP interventions in resolving DRPs at the renal outpatient clinic.

CHAPTER 6

The effect of clinical pharmacist interventions in resolving DRPs at the renal outpatient clinic: A randomised control trial

6.1 Introduction

In Chapter 5, an observational study in hospitalised children showed that the occurrence of DRPs in those with kidney disease is 11.8% (51.2% vs 39.4%) higher compared to those admitted to other specialties (i.e. Medical and Paediatric intensive care units) in the UK reported by Rashed et al., (2012b). This chapter describes the work to investigate the nature of DRPs in outpatient settings in a busy tertiary paediatric nephrology clinic and the impact of CP interventions in these circumstances. This study obtained ethical approval from the London-Hampstead Research Ethics Committee, London, UK.

6.2 Hypothesis

"The baseline incidence of patients with active DRPs at the paediatric renal outpatient clinics is 40% of patients and intervention resolves the baseline DRPs by at least 15% more than the Standard Care"

6.3 Aim and objectives

This study aimed to evaluate the impact of CP interventions on the resolution of DRPs and to determine the epidemiology of DRPs in children attending the renal outpatient clinic.

6.3.1 Primary objective

To determine whether CPs' intervention at the outpatient clinic setting were effective in resolving at least 25% of the active DRPs identified in the Control versus Intervention arm at baseline. Active DRPs were identified at baseline from eMR documentation and referred to problems which were not yet solved at the point of enrolment.

6.3.2 Secondary objectives

1. To determine the risk factors
2. To measure the severity
3. To identify the characteristics

Of DRPs documented in the medical records of children with kidney disease who were attending the renal outpatient clinics.

6.4 Methods

6.4.1 Study design

This was a single centre, simple randomisation, parallel group-study.

6.4.2 Site and study period

This trial was conducted at the ELCH paediatric outpatient renal clinic from 18th February to 18th September 2013. The setting of the study site has been explained in Chapter 3.

6.4.3 Sample size calculation

The clinical estimate of the event rate in the Control arm was 40%. It was not possible to determine the desired effect size of pharmacists' intervention based on previous studies in the CKD population due to heterogeneous outcomes and variability in the quality of published research (Salgado et al., 2012). Assuming an intervention difference of 25 percentage points (40% in control arm and 15% in intervention arm), with 105 in each arm, this trial would have enough participants to estimate the difference in proportion of patients with DRPs with 95% confidence interval ± 25 percentage points. The width of the confidence interval used in the sample size calculation was selected such that the number per arm was feasible to recruit and it would enable the researcher to estimate the intervention difference with a desired degree of accuracy. The calculated sample size was 210 patients (105 patients per arm). The sample size was calculated assuming α=0.05, power=0.95 and equal samples in both arms using the following formula (Schulz and Grimes, 2005):

$$n = \frac{1}{2}\frac{\left[10.51\left[(R+1) - P(R^2+1)\right]\right]}{Q(1-R)^2}$$

$$n = \frac{1}{2}\frac{\left[10.51\left[(0.38+1) - 0.15(0.38^2+1)\right]\right]}{0.4(1-0.38)^2}$$

$$n = 105\ subjects\ per\ arm$$

Where,

n = the sample size in each arm

P = event rate in the Intervention arm = 0.15

Q = event rate in the Control arm = 0.40

R = risk ratio ($\frac{P}{Q}$) = 0.15/0.40 = 0.38

6.4.3.1 Interim analysis

An interim analysis was performed when 47.6% (n=100/210) of patients had been recruited. The achieved difference in the event rate between the Control and Intervention arms was calculated to determine the actual sample size that was required to estimate the intervention difference with a desired degree of accuracy.

6.4.4 Trial protocol

The trial protocol has been explained in Chapter 4 (Feasibility Study (II)) and the following is a brief summary. Baseline DRPs (i.e. active and inactive DRPs) were identified by the researcher for all patients in the Control and Intervention arms. After baseline DRPs were identified, patients were assigned into one of two groups at random. Patients in the Control group received the standard care and those in the Intervention group received CPs' interventions. At the end of the clinic day, the resolution of the active DRPs at baseline for participants in both arms were identified from the doctor's notes. The diagram of the study design is shown in Figure 4.3.

Active DRPs refers to problems that were not yet solved when the patients were enrolled. Inactive DRPs refers to problems that had been solved when the patients were enrolled.

6.4.5 Study initiation phase

The timeline for the study initiation phase is shown in Figure 6.1.

6.4.5.1 Briefings to clinical team

Three briefings were conducted. In the first briefing (14th February 2013), the researcher was given a one-hour session for a PowerPoint presentation which introduced the concept of DRPs, the results of the observational cohort study (Chapter 5), the proposed method for the current RCT and the potential effect of the trial on the work process at the renal clinic. The second and third briefings (3rd and 18th April 2013) were requested by the renal consultants for an update on the patient recruitment process. All briefings were held during the monthly Nephrology Department meeting at ELCH and were attended by all renal consultants, registrars and CPs.

Information leaflets on the study method were distributed to all clinical team members after the briefings (Appendix 22). This strategy increased the likelihood of documenting information related to the use of medicines in patients' case notes. A similar approach was applied previously (Eguale et al. 2008).

6.4.5.2 Briefings to clinical pharmacists

In the first briefing (14th February 2013), an additional one-hour session with the CPs was conducted. During this session, the CPs were briefed on the conduct of interventions proposed (and agreed by the CPs) in the trial protocol. The operational definitions of DRPs and the components of the study proformas were also explained.

6.4.5.3 Piloting the study proformas

The researcher and the CPs piloted the study proforma on three occasions (19th & 27th February and 2nd March 2013). The proforma for the semi-structured patient interview was piloted during clinic session in the doctor's consultation room. During this session, the doctor had a trial of interviewing two patients on their medicine-taking behaviour using the proforma. The proformas for medication review were piloted by having the researcher and the CPs review the eMR of a test patient. Minor changes to the proformas were mainly on the layout of the form rather than the content, and therefore ethics approval for the amendments was not required.

6.4.5.3 Feasibility study

The report of the feasibility study has been described in Chapter 4 (Feasibility Study (II)). It is important to note that a strategic approach is required to determine the practicality of the chosen study design at the clinical setting (Wong, 2004). Therefore, the aim of the feasibility study (18th February to 11th April 2014) was to identify difficulties in the data-

collection process for an RCT. The feasibility study was to assess the process rather than the outcome of the trial. By the 26th March 2014 (Figure 6.1), the difficulties in the process of data collection were rectified. The initial recruitment process involved a two-week period of posting study information packages to eligible patients via clinic letters. Therefore, it was necessary to start the recruitment process early (from 26th March to 11th April), to ensure that all potential participants were recruited. The first attempt to approach patients at the clinic started on 14th April, which was after the feasibility study.

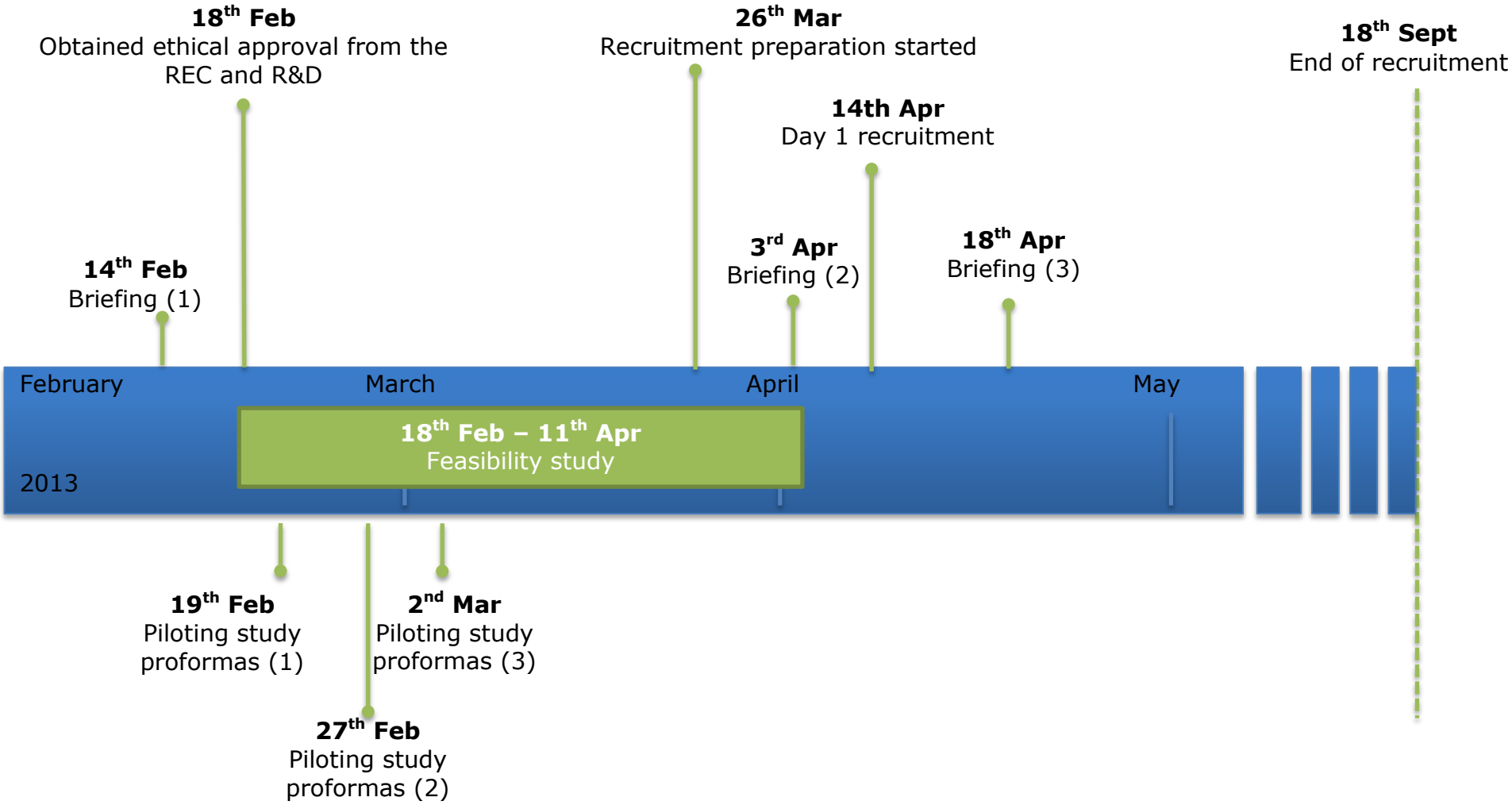


Figure 6.1 Timeline for the study at the outpatient renal clinic from 14th February to 18th September 2013

6.4.6 Data analyses

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows® and presented as percentages (%), median, interquartile range (IQR 1-3) and odd ratios (OR) with 95% confidence interval (CI). In all statistical tests *p* values of less than 0.05 were considered statistically significant. For the descriptive analysis of patients and DRP characteristics, Chi-squared (χ^2), Kruskal-Wallis Rank and Mann-Whitney tests were used as appropriate.

6.4.6.1 Intention-to-treat and Per protocol analysis

The effect of intervention on the resolution of active DRPs between both group were analysed using the ITT and the Per protocol principles. In the Per Protocol analysis, patients in the Intervention arm who did not receive intervention were treated as Controls. To report the significance difference between the resolution of DRPs in subject Control versus Intervention arm, the difference in the number of unresolved active DRPs before and after intervention was compared using Mann-Whitney test.

6.4.6.2 Logistic Regression for assessing predictors of DRPs

The principle of Logistic Regression was explained in the data analysis section of Chapter 5. The potential risk factors that were tested comprise of: age in years (Age), gender (G), total number of medicines prescribed (Rx) and stages of CKD (CKD).

6.4.6.3 Inter-rater agreement for severity assessment of DRPs

The Intraclass Correlation Coefficient (ICC) measures the degree to which the four judges achieve identical ratings of DRPs' severity under similar assessment conditions. The principle of ICC was previously described in sub-section 5.4.7.3.

6.4.6.4 Descriptive analysis

6.4.6.4.1 Incidence of patients with newly identified active DRPs

The incidence of patients who were newly identified with active DRPs at baseline was defined as the number of patients with at least one active DRP when attending the clinic divided by the total number of patients reviewed by the researcher at baseline multiplied by 100. For the calculation of DRP incidence, only patients with active DRPs that were newly identified at baseline were included.

$$DRP\ incidence = \frac{Number\ of\ patients\ with\ at\ least\ one\ \ active\ DRP\ when\ attending\ the\ clinic}{The\ total\ number\ of\ patients\ reviewed\ at\ baseline\ by\ the\ researcher}\ x\ 100$$

6.4.6.4.2 Characteristics of DRPs

The descriptive analysis for the characteristics of DRPs includes:

1. Drugs associated with DRPs
2. Types, contributory factors and severity scores of DRPs

6.5 Results

This trial had an early termination based on the interim analysis that showed small possible effect and a large number of patients were required to estimate the true effect of the interventions. Thus, the statistical tests would lack power to detect the true estimation of the endpoint. Whilst statistical comparison showed no significance difference between the Control and Intervention groups, findings on the characteristics of DRPs offer a new insight for the management of DRPs in children attending the renal clinic. Table 6.1 summarises the sequence of results presentation. The codes for the characteristics of DRPs presented in this chapter is according to the modified PCNE classification system for DRPs in Table 4.1 and Table 4.2.

Table 6.1 Sequence of result presentation

Sub-sections	Result presentation
6.5.1	Interim analysis
6.5.2	Recruitment
6.5.3	Patients' characteristics
6.5.4	Effect of interventions on the resolution of active DRPs between the Control and Intervention group. This result was analysed using the IT and per Protocol principle
6.5.5	Risk factors for DRPs. This analysis evaluated the risk factors for the occurrence of all DRPs (active and inactive) that were identified at baseline from retrospective review of eMR using regression analysis
6.5.6	Severity scores of all DRPs (N=64) assessed by four judges
6.5.7	Drugs associated with DRPs
6.5.8	Characteristics of DRPs (N=64). This section described the types and contributory factors of the DRPs

6.5.1 Interim analysis

An interim analysis was conducted when almost half of the expected number of participants were recruited (47.6%, n=100/210). The achieved intervention difference was 2%, calculated as follows: event rate in Control minus event rate in Intervention (0.19-0.17=0.02). Based on this percentage point, the sample size that was required to show a significant difference in the proportion of resolved DRPs between the Control and Intervention arm was calculated. The trial was terminated based on the interim analysis that showed a large number of patients (N=8500) were required. The calculated sample size in the interim analysis is as follows:

$$n = \frac{1}{2}\frac{\left[10.51\left[(R+1) - P(R^2+1)\right]\right]}{Q(1-R)^2}$$

$$n = \frac{1}{2}\frac{\left[10.51\left[(0.89+1) - 0.17(0.89^2+1)\right]\right]}{0.19(1-0.0.89)^2}$$

$$n = 4250\ subjects\ per\ arm$$

Where,

n = the sample size in each arm

P = achieved event rate in the Intervention arm = 0.17

Q = achieved event rate in the Control arm = 0.19

R = risk ratio ($\frac{P}{Q}$) = 0.17/0.19 = 0.89

6.5.2 Recruitment

A total of 659 patients were screened for eligibility as potential participants. Of the 659 patients, 317 (48.1%) were excluded. The main reason for exclusion was because the patients were not on any medications. Of the remaining 342 (51.9%, N=659) patients, 148 (43.3%, N=342) were approached during the trial period. The reasons for not being able to approach all 342 eligible patients were because either they were already called to see the doctor before being invited into the trial, had their clinic appointments rescheduled, or did not attend the clinic.

From the 148 patients who were approached, 100 were recruited from 26th March to 10th September 2013 in 39 clinic days (280 clinic sessions). Of the 148 patients, consents were not obtained from 48 patients. Sixty-five percent (n=31/48) of the 48 patients were boys and the median age (IQR) was 10.9 (5.4-15.1) years. Forty-four percent (n=21/48) of those who declined to participate were not interested to take part in research of which five mentioned that they had participated in research within the past 12 months. The 21 patients whose parent/carer was not interested tin them taking part in any research were five years and younger, with median (IQR 3 -3.5).

All the 100 patients, before randomised into one of the two groups, had their medical notes reviewed retrospectively using the eMR by the researcher in order to identify DRPs at baseline. In the Intervention arm, 23.4% of patients (n=11/47 patients) did not receive intervention because they were called for a doctor's consultation before being seen by the CPs. The trial participant flow is shown in Figure 6.2.

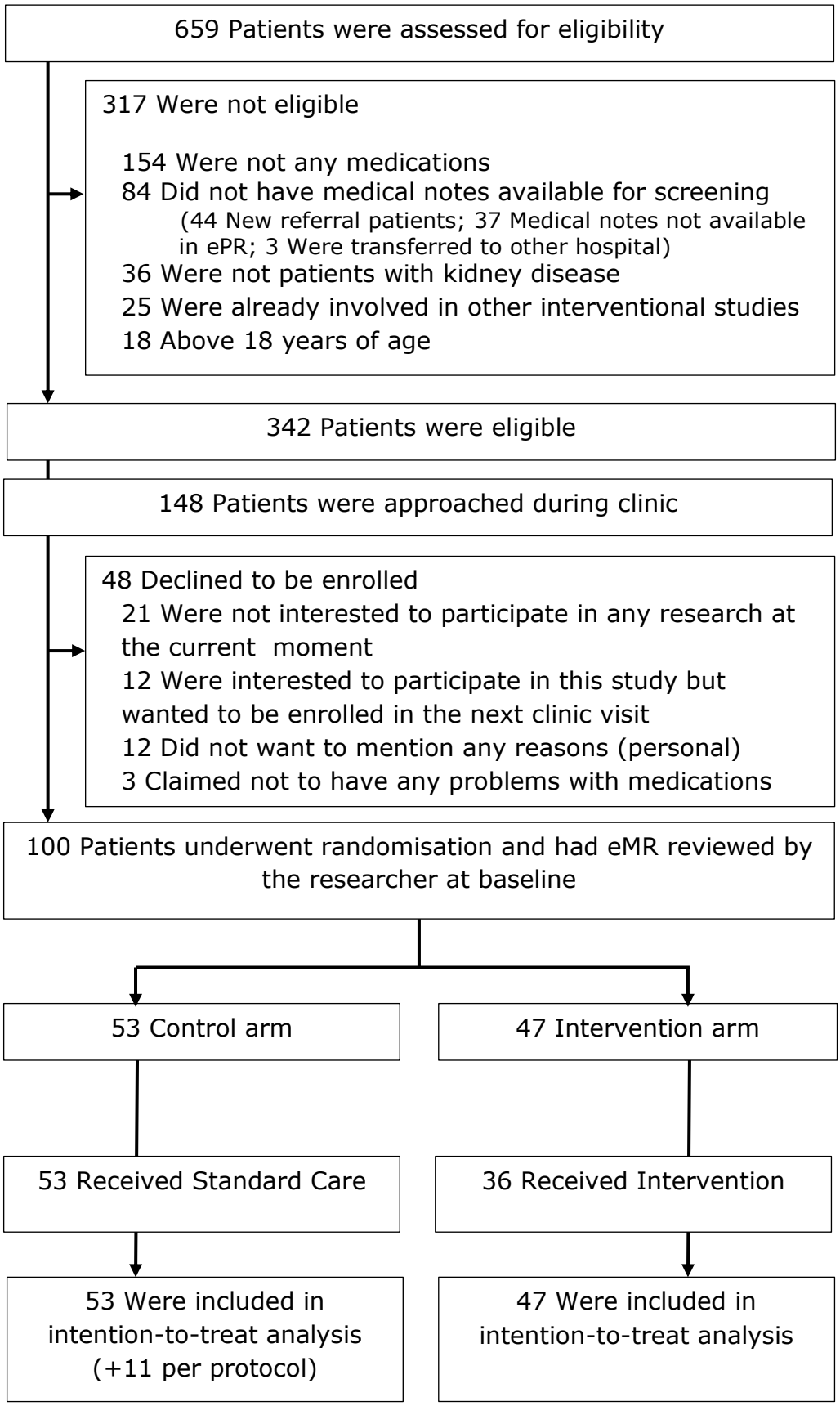


Figure 6.2 Participant flow

6.5.3 Patient characteristics

The characteristics of the randomised patients were similar in both arms (Table 6.3). The median age of the randomised patients was 9.7 (SD 4.8) years, 55% (n=55/100) were male and a mean of 5 (SD 3) medicines were prescribed per patient. Nine of the patients did not have CKD staging recorded in the medical notes and their serum creatinine levels were also not available to calculate the GFR value. A total of 32 patients had at least one DRP recorded in their medical notes in the previous six months of which 18 of them still had active DRPs on the day of recruitment (Control, n=10/53; Intervention, n=8/47). The incidence of patients with active DRPs was 18% (95% CI 11.3-26.7%) (Table 6.2).

Table 6.2 Characteristics of patients' demography

	Control (N=53)	Intervention (N=47)	p value
Age (years)	8.9 (5.7-13.8)	8.7 (5.3-15.1)	0.76
Gender (Boys)	29 (54.7)	26 (55.3)	0.41
CKD Staging (GFR mL/min/1.73m^2):			0.90
Stage 1 (>90)	12 (22.6)	6 (12.8)	
Stage 2 (60-89)	6 (11.3)	4 (8.5)	
Stage 3A (59-45)	4 (7.5)	3 (6.4)	
Stage 3B (44-30)	6 (11.3)	7 (14.9)	
Stage 4 (15-29)	7 (13.2)	9 (19.1)	
Stage 5 (<15)	5 (9.4)	3 (6.4)	
Post kidney transplant	10 (18.9)	9 (19.1)	
Not recorded in medical notes	3 (5.7)	6 (12.8)	
Medicines prescribed per patient	5 (3-7)	5 (3-7)	0.65
Patients with at least one active DRPs identified	10 (18.9)	8 (17.0)$^{\alpha}$	0.33
Number of DRPs identified			
Active DRPs	14 (10 patients)	17 (8 patients)$^{\beta}$	
Inactive DRPs	19 (11 patients)	14 (7 patients)	

Data are median and (IQR 1-3) or frequency (%)
$^{\alpha}$Of the 8 patients, 1 did not receive intervention;
$^{\beta}$Of the 17 active DRPs, 1 belonged to the patient who did not receive the intervention

6.5.4 Resolution of active DRPs between patients in Control and Intervention arms

In the Control group, 10 patients were identified with a total of 14 active DRPs. In the Intervention group, 8 patients were identified with a total of 17 active DRPs. Using the ITT and Per Protocol analysis, there was no significant difference in the resolution of DRPs between both groups (ITT: p=0.96; Per Protocol: p= 0.81) (Table 6.3 and Table 6.4).

Table 6.3 Resolution of active DRPs between patients in Control and Intervention arms (ITT analysis)

	Resolution of active DRPs before and after intervention			
	Before	After	Δ (before-after)	*P* value
Control (n=10)	14	11	3	0.96
Intervention (n=8)	17	14	3	

Δ The number of resolved active DRPs before and after intervention

Table 6.4 Resolution of active DRPs between patients in Control and Intervention arms (Per Protocol analysis)*

	Resolution of active DRPs before and after intervention			
	Before	After	Δ (before-after)	*P* value
Control (n=11)	15	12	3	0.81
Intervention (n=7)	16	13	3	

*One patient in the Intervention who did not received the intervention was treated as Control in the Per Protocol analysis

Δ The number of resolved active DRPs before and after intervention

In total, 6 active DRPs were solved (3 DRPs in each arm). Table 6.5 shows that 5 out of the 6 resolved active DRPs were (P1.2) sub-optimal drug effect (Control, n=2; Intervention, n=3) and mostly contributed by patients' poor understanding of treatment plan and medications. It is worth noting that for DRP (P4.2) drug administration problems in the Control group, even though (C8.4) was the main contributory factor, the resolved problem in this category was contributed to (C6.2) difficulty in the process of obtaining refill prescription from the community.

Table 6.5 Types of Active DRPs identified at baseline in the Intervention and Control arm (n=31)

	Intervention (n=16)		Control (n=15)	
Main and sub-categories for types of DRPs	n (solved)	Most common contributory factors	n (solved)	Most common contributory factors
P1 Drug effect				
P1.2 Sub-optimal effect (n=16, 51.6%)	9 (2)	C7.1 Patient forgot to take the prescribed medications	7 (3)	C7.8 Poor understanding of treatment plan and medications
P1.3 Untreated indication (n=1, 3.2%)	1 (0)	C7.5 Patient refused to take the prescribed medications	0	
P2 Adverse drug event				
P2.1 Non-allergic ADR (n=5, 16.1%)	1 (0)	C8.2 Unwanted side effect	4 (0)	C8.2 Unwanted side effect
P4 Others				
P4.2 Drug administration problems (n=9, 29%)	5 (1)	C8.4 Dependent on NG or PEG tubes for enteral feeding including oral medications[δ]	4 (0)	C6.2 Difficulty in the process of obtaining refill prescription from the community

[δ] Nasogastric (NG), Percutaneous Endoscopic Gastrostomy (PEG)
The descriptions of the DRPs are presented in Appendix 25
Control group: Case number 37, 93, 94; Intervention group: Case number 57, 70, 72 in Appendix 25

6.5.5 Risk factors for DRP

The multivariate binary logistic regression showed that none of the predicted risk factors were associated with the occurrence of DRPs at the renal outpatient clinic (all $p>0.05$). The CKD staging was listed in Table 6.6 because the results from the DRP study at the inpatient setting (Chapter 5) that showed a trend of higher DRPs in children on dialysis. This analysis showed that higher stages of CKD did not contribute to the occurrence of DRPs at the renal outpatient clinic.

Table 6.6 Multivariate logistic regression predicting likelihood of DRPs occurring in renal outpatient clinics (N=100)

Potential predictors	Full model OR (95% CI)	p-value
Gender (female vs. male)	1.12 (0.48-2.60)	0.80
Age (year)	1.01 (0.93-1.10)	0.83
CKD Staging		
Stage 1 – 3A	1.45 (0.59-3.53)	0.42
Stage 3B – 5	1.00 (reference)	-
Number of drugs prescribed	1.05 (0.91-1.21)	0.53

Odd ratio (OR) at 95% confidence interval (CI)

6.5.6 Severity assessment of DRPs

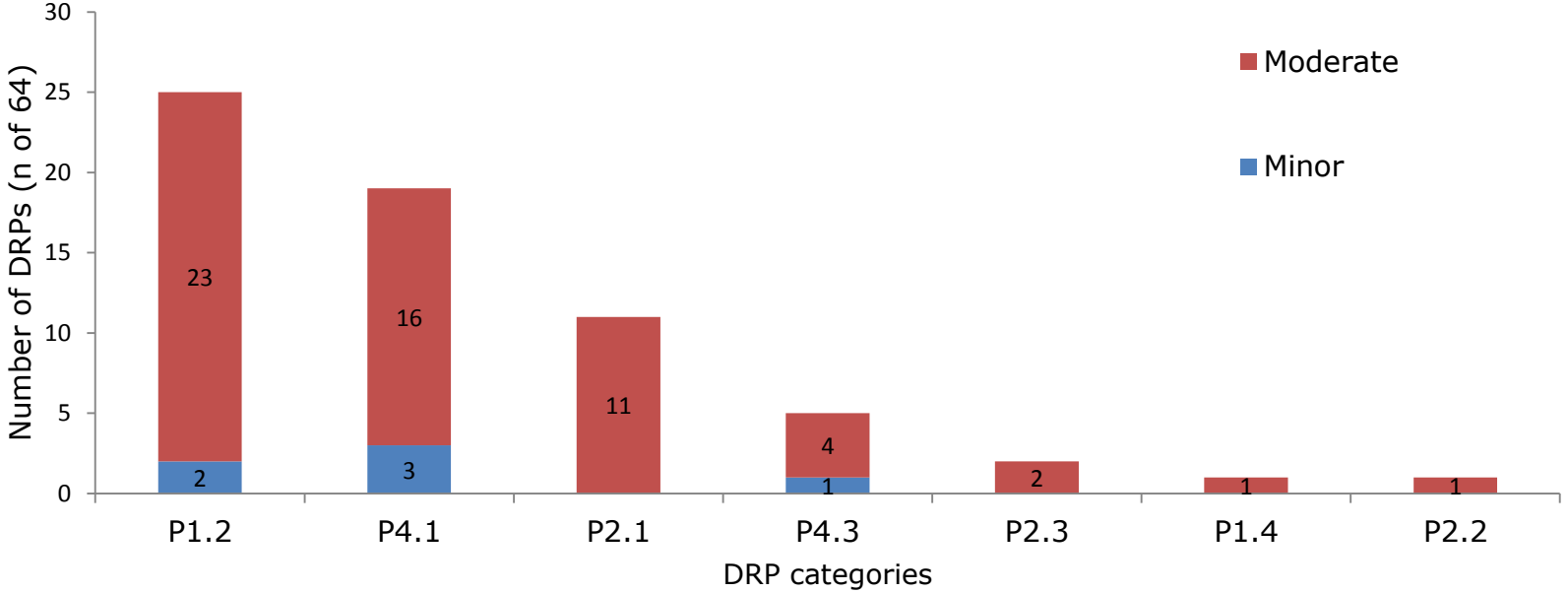
A total of 64 DRPs were listed in the scoring sheet for severity assessment. Four judges who were involved in the assessment of DRP severity in the previous observational study (Chapter 5) were invited to participate. The fourth judge was not able to participate due to work commitments and recommended a colleague in the same specialty as a replacement. The new selected judge has been involved in the initial work of the current study. The researcher provided training on the scoring method to the new judge before the list of DRPs were distributed.

6.5.6.1 Inter-rater agreement for severity assessment

The ICC coefficient was 0.43 (95% CI 0.10-0.65, p<0.001) indicating low agreement among the four judges relative to each other on average in rating the severity of DRPs.

6.5.6.2 Analysis of severity

Majority of the DRPs were classified as moderate in severity (90.6%, n=58/64) and minor problems accounted for 9.4% (n=6/64). The median (IQR) severity score was 4.1 (1.2). There was no significant difference in the severity score between the active and inactive DRPs (p=0.58). Most problems were manifested in nature (64.1%, n=41/64) but had not caused any harm.

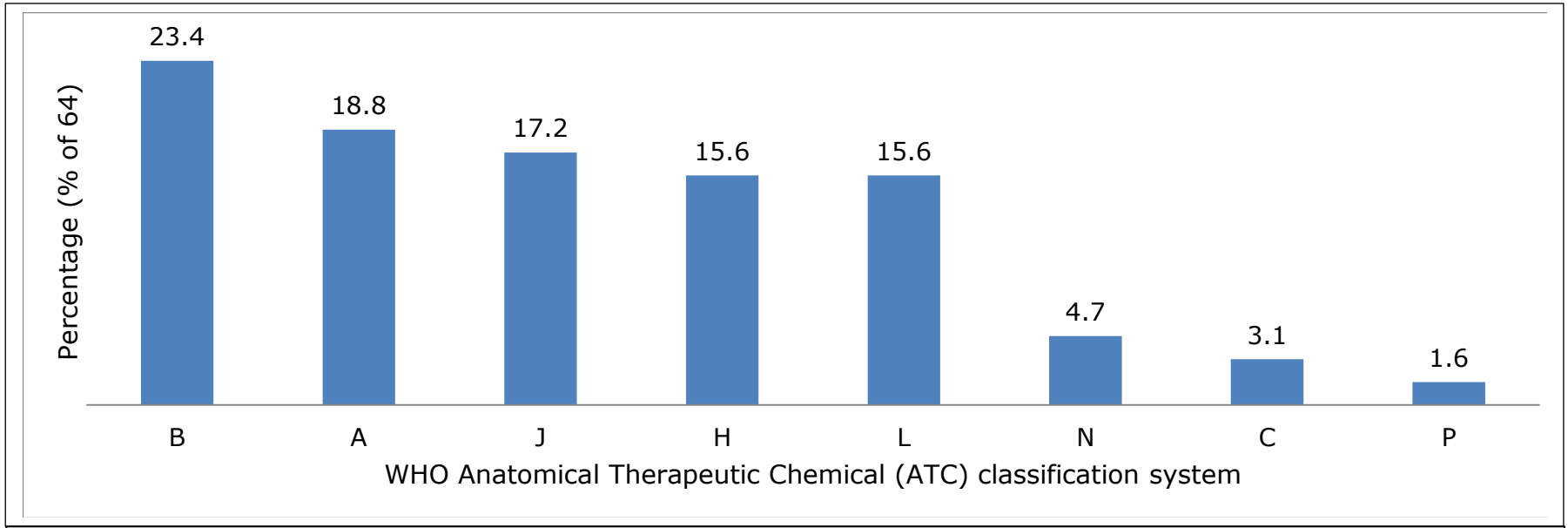


P1.2 Sub-optimal drug effect
P4.1 Patient dissatisfied with therapy
P2.1 Non-allergic adverse reaction
P4.3 Delay in treatment
P2.3 Toxic adverse reaction
P1.4 Untreated indication
P4.2 Drug administration problem
P2.2 Allergic adverse reaction

Figure 6.3 Number of DRPs by severity according to categories (N=64)

6.5.7 Drugs involved in the occurrence of DRP

Using the first level of the WHO ATC classification system for medications, the three most often involved in DRPs were medicines in the '(B) blood and blood forming organ' (24.3%, n=15/64), followed by '(A) alimentary tract and metabolism' (18.8%, n=12/64) and '(J) anti-infectives for systemic use' (17.2%, n=11/64) (Figure 6.4). Prednisolone (15.6%, n=10/64) and Sodium bicarbonate (9.3%, n=6/64) were the two medicines frequently associated with DRPs in the study cohort. The full list of drugs associated with DRPs is presented in Appendix 26.



B	BLOOD AND BLOOD FORMING ORGAN AGENTS	L	ANTINEOPLASTIC AND IMMUNOMODULATING
A	ALIMENTARY TRACT AND METABOLISM	N	NERVOUS SYSTEM SYSTEM
J	ANTIINFECTIVES FOR SYSTEMIC	C	CARDIOVASCULAR
H	SYSTEMIC HORMONAL PREPARATIONS, EXCLUDING HORMONES	P	ANTIPARASITIC PRODUCTS, INSECTICIDES SEX AND REPELLENTS

Figure 6.4 Medicines associated with drug-related problems by the WHO ATC classification system (N=64)

6.5.8 Characteristics of DRPs (n=64)

6.5.8.1 Types of DRPs

A total of 64 DRPs were identified from retrospective eMR review. Of the 64 DRPs, 31 were active DRPs and 33 were inactive DRPs. Sixty-four percent (n=41/64) of the DRPs were Manifested and 36% (n=23/64) were Potential in nature.

The most frequently identified DRPs were (P1) drug effect (40.6%, n=26/64), followed by (P4) Other groups of DRPs (30.1%, n=25/64) and (P2) adverse drug event (21.9%, n=14/64). At the sub-category level, the most frequently documented problems were (P1.2) sub-optimal drug effect (39.1%, n=25/64), followed by (P4.2) drug administration problem (29.7%, n=19/64) and (P2.1) non-allergic adverse reaction (17.2%, n=11/64). The description of DRPs is presented in Appendix 25.

Participants' (i.e. parent/carer and child at appropriate age) poor understanding of treatment plan and medications was documented as the most common contributory factors for sub-optimal drug effect. Unwanted side effect was one of the factors contributing to adverse drug events and the use of feeding tubes contributed to difficulty in administering medications (Table 6.7).

From the total 64 identified DRPs, 11 were categorised as non-allergy ADR. Out of the 11 DRPs, 6 were associated with side effects of Prednisolone and the remaining 5 were associated with Azathioprine, Dexamphetamine, Ferrous Fumarate, Fluoxetine and Itraconazole. Prednisolone was documented to cause side effects affecting the skin (acne, facial stigmata),

central nervous system (mood swing), gastrointestinal tract (abdominal pain) and metabolic (cushingoid). All side effects of Prednisolone were assessed as moderate in severity by the judges and the scores ranged between 3.2 to 5.3. Prednisolone side effect with the highest score, 5.3, was abdominal pain when taken with Mycophenolic Acid without prophylaxis for steroid induced gastritis (DRP no. 107 in Appendix 25).

Table 6.7 Types of DRPs identified by the researcher at baseline by main and sub-categories (N=64)

Types of DRPs		Total (% of N)	Potential DRPs (n of Total)	Most common contributory factors
Main category	Sub-categories			
P1 Drug effect (n=26, 40.6%)	P1.2 Sub-optimal effect	25 (39.1)	14	C7.8 Poor understanding of treatment plan and medications
	P1.4 Untreated indication	1 (1.6)	0	
P2 Adverse drug event (n=14, 21.9%)	P2.1 Non-allergic ADR	11 (17.2)	3	C8.2 Experience unwanted side effect of the prescribed drug
	P2.2 Allergic ADR	1 (1.6)	0	
	P2.3 Toxic ADR	2 (3.1)	1	
P4 Others (n=25, 30.1%)	P4.2 Drug administration problems	19 (29.7)	1	C8.5 Dependent on NG$^{\alpha}$ or PEG$^{\alpha}$ tubes for enteral feeding including oral medications$^{\alpha}$
	P4.3 Delay in treatment	5 (7.8)	5	
	Total	64 (100)	23	

Data are in count (%)
$^{\alpha}$Nasogastric (NG), Percutaneous Endoscopic Gastrostomy (PEG)

6.5.8.2 Contributory factors of DRPs

A total of 73 contributory factors were documented from the 64 DRPs. Ninety percent of the DRPs identified at the renal outpatient clinics were largely contributed by factors of the drug use process i.e. (C7) patient factors (42.5%, n=31/73), (C8) other factors (35.6%, n=26/73) in which the majority were unwanted side effects and (C6) drug supply (11%, n=8/73) in which all were problems in obtaining repeat prescriptions from the community.

Prescribing error in the community contributed to a case of potential sub-optimal drug effect, which involved prescription of One Alpha Calcidol dispensed as Cholecalciferol (Vitamin D3). This error occurred for eight months before it was discovered and documented in the medical notes. This case was rated as moderately severe, but did not cause harm to the patient (DRP no. 11). The list of DRPs contributory factors is available in Table 6.8.

Table 6.8 Contributory factors for DRPs (n=73)

	Contributory factors main category / sub-category	n (% of N)	
Treatment process	**C1 Drug selection**	**3**	**(4.1)**
	C1.1 Inappropriate drug	1	(1.4)
	C1.3 Inappropriate drug combination	1	(1.4)
	C1.8 Synergistic/Preventive drug not prescribed	1	(1.4)
	C3 Drug dosage	**4**	**(5.5)**
	C3.1 Dose too low	2	(2.7)
	C3.2 Dose too high	1	(1.4)
	C3.5 No therapeutic drug monitoring	1	(1.4)
Drug use process	**C5 Medication errors**	**1**	**(1.4)**
	C5.8a Prescribing error in decision making	1	(1.4)
	C6 Drug supply	**8**	**(11.0)**
	C6.2 Problems with the process for obtaining repeat prescriptions from the community	8	(11.0)
	C7 Patient factors	**31**	**(42.5)**
	C7.1 Patient forgot to take the drug	10	(13.7)
	C7.5 Refused to take medicines	6	(8.2)
	C7.7 Forgot to ask for refill prescription from community	1	(1.4)
	C7.8 Poor understanding of treatment plan and medications	14	(19.2)
	C8 Other factors	**26**	**(35.6)**
	C8.2 Unwanted side effects	12	(16.4)

	Contributory factors main category / sub-category	n (% of N)
	C8.4 Dependent on NG/PEG for medications	8 (11.0)
	C8.5 Difficult to obtain information from GP	5 (6.8)
	C8.6 New dose not altered by the GP	1 (1.4)

Data are count or percentage (%)

6.6 Discussion

The primary objective of this study was to determine the effectiveness of CP interventions in resolving DRPs at the renal outpatient clinic. This study was terminated after the interim analysis showed that the possible effect was so small (2% difference) and required a huge number of patients (N=8500) to show statistical significance between Control and Intervention arm. The incidence of patients with DRPs was 33.2% lower than the incidence of DRP reported from the observational study at the inpatient setting in Chapter 5 (18% [95% CI: 11.3-26.7%] vs.51.2% [95% CI 43.2-60.6%]). There was no statistical significance in the resolution of DRPs between both arms and the predicted risk factors for DRPs. The medicines that were associated with DRPs the most were in the 'blood and blood forming organ' group. The predominant types of DRPs were sub-optimal drug effect and the most frequently reported contributory factor was related to patients' cognitive behaviour towards medications. The majority of DRPs (90.6%) had minor to moderate clinical significance.

6.6.1 Trial termination

This study recruited 100 out of the 210 patients and this was 52% less than the calculated sample size. The interim analysis showed that the required number to estimate a true difference on the effect of intervention was approximately 8500 patients, which was not feasible within the circumstances of this trial. Nevertheless, findings from this study contributed to new knowledge in understanding the medicine management

of children with kidney disease as well as to develop strategies in designing a pharmacy-based interventional study in the future.

6.6.2 Incidence of patients with DRPs attending the renal clinic

The incidence of patients with active DRPs when attending the renal clinic is 18% (95% CI 11.3-26.7%), which was lower than the incidence reported from the DRP study at the inpatients setting in Chapter 5 (51.2% [95% CI 43.2-60.6%). There could be several possibilities for the lower incidence of DRPs at the renal outpatient clinics setting than the inpatient setting.

Patients in the ambulatory care received fewer prescriptions, and had less complex complications compared to those who received treatment on the wards (median number of medications per child: inpatient 17, outpatient 5). Furthermore, problems that occurred more frequently but with less causality were not likely to be documented (Brown et al., 2008a). Interviewing the patients (and family) have shown to be a more effective method than medical charts review in identifying DRPs at the outpatient setting. Jameson and Vannwoord (2001) in a study at the ambulatory care setting, reported that 73% of pharmacotherapy problems were recognised through patient interview and the remaining problems were identified from medical chart reviews and health database.

The present study chose the retrospective eMR review method because the study objective was to identify the types of DRPs documented by the clinicians. Should this study use other methods, different characteristics of problems would be generated (Franklin et al., 2009).

6.6.3 Resolution of active DRPs

The interventions in this study did not show superiority over non-intervention in resolving DRPs in children attending the renal outpatient clinics.

The types and contributory factors for the 31 active DRPs (Table 6.5) shows that 5 out of 6 solved problems related to sub-optimal drug effect and these problems were contributed by patient factor. This finding supports the need for consultancy sessions on medicines to empower participants' knowledge on treatment, as reported by So et al (2011). In young patients undergoing long-term therapy, interventions to improve their cognitive behaviour towards medicines involve a complex psychological assessment that are not fully understood (Dean et al., 2010; Salema et al., 2011). More often than not, the strategies for such interventions require continuous assessment for at least 6 months (Haynes et al., 2008).

The second highest active DRPs were problems in administering the prescribed medications. This problem was mainly contributed by two factors: patients' dependency on using the feeding tubes (which was also used in the administration of medicines) and the difficulty in the process of obtaining repeat prescriptions from the community.

Children with CKD may show anorexia, vomiting and poor appetite which may result insufficient protein intake to maintain growth (Rees and Shaw, 2007). Enteral feeding is indicated when dietary manipulation and medication fail to optimise nutrition intake. Tube feeding is important when struggling with oral intake in an anorexic child causes intolerable strains within family; and is also used for the administration of medications in such

circumstance (Rees and Brandt, 2010). The stresses on the family trying to feed or administer medications to a struggling child using the feeding tube could be overwhelming. In the current study, problems in administering medications via the feeding tube were unsolved and patients with this problem were documented to be struggling with oral intake.

According to the causal chain linking interventions to outcomes in patient safety research (Brown et al., 2008c) previously described in Chapter 3, difficulties in the process of obtaining refill prescriptions from the community is related to the structure of the healthcare system. i.e. external factors that are beyond the control of the managers within a particular health organisation such as national directives, licensing products and budget constraints. This was reflected in the small proportion of DRPs that could be solved by the CPs in the current study.

From the pharmacy practice perspective, referring patients from the community back to the hospital for medicine supplies may not be the optimum solution. Alternative solutions include empowering the services in the community through programmes such as the New Medicine Service (NMS), Effective Shared Care Agreement (ESCAs) and homecare services (ESCAs, 2014; RPS, 2014a; RPS, 2014b).

The NMS focuses on patients with long-term conditions who have been prescribed with new medication or had changes made to their existing medication. The service involves an intervention in which the community pharmacists provide information and reassurance to address patients' concerns during the first month of a new medicine or new dosage regimen. At present, the service is only available for adults who have been prescribed

new medicines for asthma, chronic obstructive pulmonary disease, type 2 diabetes and high blood pressure (NHS, 2013).

An effective shared care agreement can assist in the seamless transfer of patient treatment from secondary care to general practice, as it provides information on the medication, together with guidance on the prescribing and monitoring responsibilities (ESCAs, 2014). Communication barriers in the transfer of patient care may result in serious harm to patients due to failure in continuity of care (NHS, 2014a). The medications listed for the ESCAs in childrenare limited and this is currently under review for future improvement (NHS, 2014b).

There is also considerable shift towards homecare services as a way of providing medication that is not suitable or available for shared care agreements. The medicines that are included in this scheme for patients with kidney disease (all ages) are renal dialysis solutions and epoetin. The post renal transplant immunosuppressants will eventually be delivered via homecare, but for the time being this change is on hold due to some technical problems with the service provider (NHS, 2014b). Different delivery options are being explored by the procurement experts with the expectation that homecare will be possible starting in April 2015 (NHS, 2014b).

Medicine management programmes at the community level, such as the examples above, can be seen as increasingly offering opportunities to redesign patient care pathways, which may have a positive impact in reducing DRPs.

6.6.4 Risk factors of DRPs

Children attending the renal outpatient clinics did not have similar risk factors to those hospitalised on the wards. Nevertheless, it would be valuable to investigate whether problems in obtaining drug supply from the community is a latent risk factor for DRPs in this group of patients. An adult study reported higher incidence of DRPs resulting in emergency department visits, which was 33% of patients; of whom approximately 20% were related to patients not receiving the required medications (Baena et al., 2006).

6.6.5 Severity of DRPs

The majority of the DRPs identified in this study were rated as moderate in significance to clinical practice, i.e. likely to cause adverse effects or interfere with therapeutic goals. Most of these problems contributed to patients' intentional and non-intentional non-adherence and difficulties in obtaining prescribed medications from the community (Table 6.5 and Table 6.7). The proportion of these problems that led to visits to healthcare professionals was not evaluated in this study. A study in the paediatric population showed that the incidence of DRPs in children at the emergency department was 21.7% but the concerns were related to dosing problems and ADR (Rashed et al., 2013).

6.6.6 Drugs associated with DRPs

The drug classes most frequently involved in DRPs were 'blood and blood forming organ', 'alimentary tract and metabolism' and 'anti-infectives for systemic use'. This is not surprising as these drug classes are usually prescribed for managing the complications of kidney impairment (Belaiche et al., 2013; Kaplan et al., 1994a; Manley et al., 2003). Prednisolone and Sodium bicarbonate were frequently reported with DRPs in this study cohort. These medicines are essential treatment in the management of kidney disorders.

Prednisolone is an anti-inflammatory agent which was mostly prescribed long term for the management of nephrotic syndrome and as an adjunct immunosuppressant in post-transplantation. Its long term use is usually accompanied with metabolic syndrome in childhood (Litwin and Niemirska, 2014). Metabolic syndrome leads to obesity, hypercholesterolemia, hypertension and impaired blood glucose control (Zimmet et al., 2007). All these complications increase the risk of cardiovascular disease in children with kidney disease (Litwin and Niemirska, 2014). Sodium bicarbonate is an alkaline agent for the management of metabolic acidosis, a common complication in patients with kidney disorders. Metabolic acidosis has been reported to accelerate CKD progression, impair nutritional status and, in children, cause growth disruption (Abramowitz et al., 2013; de Brito-Ashurst et al., 2009).

6.6.7 Types and contributory factors of DRPs

This study found that the most frequently identified DRPs documented in the clinical notes were (P1) drug effect, (P4) others and (P2) adverse drug event (Table 6.7). The types and contributory factors for the first two DRP categories were similar to the ones that had been previously discussed in 6.6.3 (i.e. sub-optimal drug effect and drug administration problems which were contributed by patient factors and difficulty in obtaining repeat prescriptions). Thus the discussion in this this sub-section is focused on (P2) adverse drug event.

Children were thought to be at higher risk for adverse drug events than their adult counterpart due to their physiology and immature mechanism of drug metabolism (Impicciatore et al., 2000). In children with kidney disease, adverse drug events are also affected by pharmacokinetic alteration in dialysis and changing GFR. This study showed that unwanted side effect of the prescribed medicines as the main contributing factors for the adverse drug events.

Six out of the 11 non-allergy ADRs were contributed by side effects from chronic use of Predisolone. Appendix 25 described the DRPs and the ones related to Prednisolone side effects were numbered 5, 28, 60, 77, 99 and 107 – these DRPs occurred in patients who required long term use of steroid. Side effects from chronic use of steroid cause complications such as severe infection and metabolic syndrome. The current clinical practice guideline for post renal transplantation and glomerular diseases are shifting towards minimum use of steroid immunosuppressive regimen. However, alternatives to minimise the use of corticosteroids are expensive and

require further research on safety and efficacy in children (Pravitsitthikul et al., 2013).

One case of an allergic adverse reaction reported in this study was associated with Amoxicillin. Anti-infective agents were described as most frequently associated with adverse drug reactions in children (Rashed et al., 2012a; Smyth et al., 2012). Two DRPs of toxic adverse drug reactions were associated with the use of Metformin for weight loss and Tacrolimus as immunosuppressant in post kidney transplant – both medicines are not licensed for use in children (BNFc, 2009). A meta-analysis of 17 articles on adverse drug reactions in paediatric at the inpatient and outpatient settings concluded that the use of unlicensed and off-label medicines in children increased the risk of adverse reactions (Impicciatore et al., 2001) however, there is still a lack of clarity on their risk factors (Mason et al., 2012).

6.7 Strengths and limitations

To the researcher's knowledge, this is the first RCT on CP interventions at the renal outpatient clinic for children. Findings in this study provide a better understanding on the characteristics of DRPs. The limitations of this study include low statistical power to show any significance of the interventions. The possible effect of the intervention was so small FOR statistical significance with the achieved sample size. Only one person (the researcher) was involved in recruiting potential patients and thus not all patients who were interested in participating were invited before they were called for a doctor's consultation. Although the identification of baseline DRPs from the eMR was conducted explicitly and guided by the DRP-Rf to

ensure consistency, the retrospective review method is still bound to interpretation bias because the hospital medical notes are not recorded for research purposes. The economic impact of clinical pharmacy services in resolving DRPs was not evaluated because it was beyond the scope of this research. However, it is important to consider the direct and indirect costs incurred by the NHS in future research

6.8 Summary

This study concludes that the majority of DRPs identified at the paediatric renal outpatient clinic are moderate in clinical significance to treatment outcomes; however, a more complex and long-term intervention is required to effectively resolve these problems. Sub-optimal drug effect and drug administration problems were the two most common DRPs identified – both were largely contributed by patients' medicine-taking behaviour and the structure of medication supply in the community. The proforma used to interview patients in this study could be a potential tool in practice to aid the DRP identification and documentation.

CHAPTER 7

Overall Discussion

7.1 Overview of the research key findings

The aims of this thesis were to investigate the epidemiology of DRPs using standardised definitions and methods, and the effect of CPs' interventions in resolving DRPs in paediatric nephrology patients. Multiple methodological approaches were used to describe the incidence, the risk factors, the characteristics and the resolution rate of DRPs in children with kidney disease at the tertiary healthcare settings in two paediatric hospitals in London.

7.1.1 DRPs in children with kidney disease: Inpatient setting

In hospitalised children with CKD, the incidence of DRPs was 51.2% (95% CI 43.2-60.6) of patients reviewed and the number of medicines prescribed per child was the only predominant risk factor for DRPs (OR 1.06, 95% CI: 1.02-1.10, p=0.002). The majority of the DRPs were scored as minor in clinical significance (68%, n=138/203). Medicines that were most commonly associated with DRPs was in the 'alimentary tract and metabolism' drug group (25.1%, n=51/203).

The predominant DRPs were sub-optimal drug effect (21.7%, n=44/203), followed by unnecessary drug treatment (20.2%, n=41/203) and toxic adverse reaction (19.2%, n=39/203). The most frequently reported contributory factors for these problems were inappropriate drug selection and dosage error. Almost all of CPs' recommendations in managing DRPs were accepted by the clinical team (99.5%, n=227/228) and 96% (n=195/203) of the identified DRPs were solved as a result of ward pharmacy practice.

7.1.2 DRPs in children with kidney disease: Outpatient renal clinics

The incidence of patients with active DRPs when attending the renal clinic during the study period was 18% (95% CI 11.3-26.7). There was no statistical significance in the resolution of DRPs between the Control and Intervention arms (ITT analysis, p=0.96; Per Protocol analysis, p=0.81). In addition, none of the predicted risk factors for DRPs were significant. Majority of the DRPs were classified as moderate in clinical significance (90.6%, n=58/64). The drug class most frequently involved in DRPs were 'blood and blood forming organ' (23.4%, n=15/64). The predominant DRPs was sub-optimal drug effect (39.1%, n=25/64), drug administration problem (29.7%, n=19/64) and non-allergic adverse reaction (17.2%, n=11/64).

The most frequently reported contributory factors for these problems were related to patients' cognitive behaviour, which is not easily corrected by healthcare professionals in tertiary care. Community-based medication reviews that are incorporated in the NMS, ESCAs and homecare schemes could improve medicine management at the community setting and subsequently reduce DRPs in children receiving outpatient treatment.

Direct comparison of data obtained in this research to what has been reported in other population could be discussed with consideration of the differences in the research methods and data evaluations.

7.2 Comparison of DRP data with adult renal patients

Compared to the adult patients, children with kidney disease had at least half the incidence of DRPs. Almost all studies on DRPs in adult populations reported that all renal patients have at least one DRP (Cardone et al., 2010; Castelino et al., 2011). This could be due to the difference in the selection of patients and the calculation of incidence. The majority of studies evaluating DRPs in the adult renal patients were conducted in those with ESKD on regular dialysis (Cardone et al., 2010; Salgado et al., 2012) but less than 30% of the study cohort of this research were on dialysis (Study 1: 22%, n=28/127; Study 2: 8%, n=8/100) . Furthermore, the calculation for the incidence of DRPs in the adult renal populations were not clearly defined and most probably included readmissions. In the present research, for the calculation of incidence of DRPs, only the first admissions during the study period were considered.

The predominant DRPs reported from studies in the adult renal populations at the inpatient setting were toxic adverse reactions due to inadequate monitoring of biochemistry markers and serum blood levels (Salgado et al., 2012). Whereby in children, the main problems were sub-optimal drug effect and unnecessary treatment due to inappropriate drug selection and prescribing error. Other than the difference in physiology and prescribing pattern between adults and children, the differences in the characteristics of DRPs are also due to the distinction of the DRPs' classification systems used. The majority of studies in the adult renal patients adapted the Hepler and Strand classification (1990) (Cardone et al., 2010; Salgado et al.,

2012) whereby the present research adapted the PCNE classification for DRPs.

Thus direct comparison of the characteristics of DRPs found in this research to the findings in the adult renal patients is challenging. Nevertheless, problems related to drug and dosing are a concern in renal patients, adults and children alike. In children, medication errors, particularly prescribing errors is a common contributory factor to the occurrence of DRPs. The study on the element of errors in the process of drug use for adult renal patients is limited and suggest for future research.

Appendix 27 summarises findings on the characteristics of DRPs between the two studies of the present research (Study 1 and Study 2) to three other studies: (1) a study on DRP in children hospitalised in the other specialties (Rashed et al., 2012b), (2) a study on DRPs in pre-dialysis adult CKD patients (Castelino et al., 2011) and (3) a systematic review on DRPs in adult renal patients in whom the majority were on dialysis (Cardone et al., 2010).

7.3 Comparison of DRP data with children in the general medical wards

The overall incidence of DRPs reported in children hospitalised in the medical and the paediatric intensive care units was 45.2% (95% CI 41.5-48.8) (Rashed et al., 2012b) and the incidence in the UK population was 39.5% (95% CI 34.4-44.6). The aforementioned study also reported the incidence of DRPs in the paediatric care unit as 59.7% (95% CI 47.0-71.5).

Thus, compared to the finding in the present research it can be concluded that even though the incidence of DRPs in hospitalised children is relatively higher than those hospitalised in the medical unit (51.2-45.2%=6% difference), but the incidence is lower than those who are critically ill (51.2-59.7%= - 8.5% difference).

Findings on the characteristics of DRPs in the present study at the inpatient setting were similar to those reported by Rashed et al. (2012b). Both studies reported 'alimentary tract and metabolism' and 'anti-infectives' as the main drug group causing DRPs – this reflects the prescribing pattern in paediatrics. Further analysis on the specific types of medicines associated with DRPs in the study cohort of the current research also indicate the prescribing pattern in managing kidney failure. Sub-optimal drug effect was the predominant DRPs and the problems were contributed by drug and dosing errors. Most of CPs recommendations in solving the DRPs in both studies were at the drug level and the majority of the DRPs were minor in clinical significance. The only dissimilarity in the characteristics between the DRPs of both studies was the significant risk factors. The number of medicines prescribed per child is the only risk factors for DRPs in the present study whereby, in children without kidney disease the additional risk factor is when transferred from another hospital or ward.

7.4 Comparison of DRP data in children with kidney disease at the inpatient and outpatient settings

It is worth mentioning on the differences in the demographic characteristics between study subjects involved in evaluating DRPs at the inpatient and outpatient setting in the current research. Even though both study populations were children with kidney disease, the majority of those seen at the renal clinics were in the predialysis stage. Whereby, children receiving inpatient treatment were more ill due to complications of the disease progression or the RRT. CKD children receiving inpatient treatment required three times more number of medicines compared to those attending the outpatient clinic (median 17 vs. 5 medicines per child).

Many studies have previously demonstrated that patients at the late stage of CKD and on dialysis require more complex drug therapy and which subsequently exposed them to higher chances of having DRPs (Cardone et al., 2010; Fernandez-Llimos et al., 2004; Salgado et al., 2012). The above circumstances explained the lower incidence of DRPs reported in children attending the renal outpatient clinics compared to those hospitalised on the renal wards (51.2% [95% CI: 43.2-60.6%] vs. 18% [95% CI: 11.3-26.7%]).

Interestingly, despite of having more serious clinical conditions, in hospitalised patients, the majority of DRPs were scored as minor in clinical significance (68%, n=138/203) compared to the DRPs identified at the outpatient setting in which 90.6% (n=58/64) were moderate. The possible reason to this circumstance could be explained using the model for causal chain linking interventions to outcome (Brown et al., 2008c) in the context

of medicines management. The concept of this model was explained in Chapter 3.

Drug problems occurring on the wards are 'active errors' in the clinical process of the model. The majority of the 'active errors' in the current research were caused by drug-dosing errors which could be rapidly rectified and the outcome could be carefully monitored by healthcare professionals. Thus, the errors are less likely to cause harm as a result from the interventions. As an example, sub-optimal Tacrolimus dose in the management of post kidney transplantation on the ward could be adjusted from post 12-hour Tacrolimus serum drug levels. Changes to drug regimen are directly monitored by multidisciplinary healthcare professionals and patients receiving inpatient treatment are likely to adhere to the prescribed therapy. In contrast, drug problems occurring at the outpatient clinic are 'latent error' in the management process; in which the majority of the errors were caused by exogenous processes that is beyond the control of healthcare professionals (e.g. difficulties in obtaining medications from the community) or require long-term interventions (e.g. patients' non-adherence). Furthermore the responsibility for managing the medications outside the hospital is down to the patients themselves (which includes parent and carer). Thus, medicine management services in the community could be beneficial in resolving DRPs occurring in the community.

7.5 Implications for practice

7.5.1 Clinical pharmacy practice

Clinical pharmacy practice on the paediatric renal wards appears to be effective in identifying and resolving DRPs that may lead to potential harm in the inpatient setting but remains to be proven in the outpatient seting. The DRPs identified on the wards have a higher resolution rate because CPs' involvement in managing medicines is integrated into the clinical team, coupled with simultaneous multidisciplinary care during hospitalisation, whereas such involvement is new at the outpatient setting. An important role for pharmacy practice on the wards is confirming medication histories on admission, as many studies have highlighted that errors are common at this stage (Brock and Franklin, 2007).

Medication reconciliation could be integrated as part of the ward pharmacy services for renal paediatric patients and this has been recently highlighted for the care of adult renal patients (Pai et al., 2013; St. Peter et al., 2013). At the inpatient setting, the CPs have the time and opportunity for face-to-face contact with the medical team and this is a factor associated with better implementation of clinical pharmacy services (Jameson and Vannoord, 2001). The results of the inpatient DRP study reported in Chapter 5 of this thesis strengthen the current evidence that medication reviews through clinical pharmacy services in hospitalised patients lead to improved treatment outcomes (Graabæk and Kjeldsen, 2013; Kaboli et al., 2006).

The RCT reported in Chapter 6 showed that pharmacy services at the outpatient clinic appear to have an insignificant effect in resolving the

problems due to the distinct nature and causes of the DRPs as well as the operating procedure of the standard care at the outpatient setting. However, an avenue that may gain benefit from pharmacy services at the out-patient clinics is again, medication reconciliation and programmes to facilitate parents/carers in managing their child's medications. A Cochrane review reported that adolescents would benefit from programmes focused on medicine-taking behaviour at the transition period to the adult unit (Haynes et al., 2008). The report suggested that the programme should be a continuous effort for at least 6 months. Effective medicine management in the community setting (e.g. NMS, ESCAs and homecare services) could be a possible solution to reduce the occurrence of DRPs.

At present in the UK and the US, clinical pharmacy services are not embedded into the standard care of the outpatient clinic (Brock and Franklin, 2007) and this circumstance would be highly similar in other countries. With regard to pharmacists' interventions at the renal out-patient clinics aimed to improve the clinical endpoints – such as the Pharmacist-Led clinics for calcium-phosphate products, blood pressure control and lipid management – the evidence regarding their effectiveness is sparse (Stemer and Lemmens-Gruber, 2011; Salgado et al., 2012). It is a challenge to prove the effectiveness of clinical pharmacy services at the out-patient setting in tertiary care because of various reasons as previously described. Furthermore, it also involves complicated study designs and, more often than not, the outcomes are surrogate markers of clinical endpoint which may be biased and underpowered (Stemer and Lemmens-Gruber, 2011; Salgado et al., 2012).

The lack of evidence on the significant impact of pharmacists' role in optimising clinical outcomes contributes to the reason why the clinical skills of pharmacists are unknown and under-recognised by the public, patients and policy makers (Royal Pharmaceutical Society, 2013a). In November 2013 the Royal Pharmaceutical Society (RPS) Faculty initiated a recognition programme for specialised pharmacy practice through professional assessment. At present, this opportunity is open for the RPS faculty members practising in the UK (Royal Pharmaceutical Society, 2013b). It is hoped that the RPS specialist recognition for the pharmacy profession would widen the horizons of the pharmacy profession at all level of care and its success could be adapted by other countries.

7.5.2 Monitoring of DRPs

It is apparent from the current research that the number of medicines a patient receives during inpatient treatment is an independent risk factor for DRPs at the in patient setting. Even though not statistically significant, hospitalisation of more than four days and the higher stages of kidney disease could be clinically important in monitoring for DRPs. This is supported by the fact that patients at the late stages of CKD (stage 3B and above) require more medications for the management of the complications related to the failing kidneys, hence continuous monitoring of DRPs would help to prevent poor treatment outcomes.

Children with kidney disease require lifelong treatment of complex pharmacotherapy. They are frequently hospitalised and medications are frequently altered throughout hospitalisation and at hospital discharge

(Warady and Chadha, 2007). In the UK, a survey among paediatric pharmacists found that 67% of the pharmacists reconciled medications on hospital admission for children; however, only 34% had a medication reconciliation policy in place (Huynh et al., 2013b). It is important that medication reconciliation is conducted at all level of care and this has been advocated by the NKF Guidelines for children and adolescents with kidney disease (Hogg et al., 2003). Medication reconciliation is an avenue to minimise discrepancies in the transfer of information (Rashed et al., 2012b).

Proper coordination for supplies of medication in the community is also essentially important because failure to receive medication has been reported as a cause of low adherence in patients with CKD (Cardone et al., 2010). An initiative that has been taken by the ELCH Pharmacy Department is introducing the Drug Information Centre where parents and patients can seek advice on problems related to medications by telephone calls. A similar service (i.e. drug information centre) could be set up in the community, where patients spend more time.

7.5.2.1 The application of electronic prescribing system in monitoring for DRPs

Electronic prescribing and medicine administration system has long been advocated to replace paper-based system. In the present research, the use of ePS by CPs in screening prescriptions at one of the two study sites to identify potential and manifested DRPs could have contributed to the types of DRPs reported in this thesis.

The hospital that uses ePS at the inpatient setting in the current research were seen to successfully prevented allergy reactions. This supports the benefit of ePS in improving the interception of potentially harmful prescribing errors (Caldwell and Power, 2012). In the conventional paper-based documentation, the screening of medication charts could only be conducted whenever the CPs visit the wards. The availability of ePS enables the CPs to review patients' medication lists remotely from the wards and support clinical pharmacy activities.

Nevertheless, pharmacists' role to ensure patient safety would be more challenging in hospitals that use ePS (Sanghera et al., 2006) because of the high possibility of information errors which include prescribing errors. The occurrence of prescribing errors in the use of ePS include: wrong drug being ordered by the prescribers because the lacked of detailed information concerning the choices of products available at the dispensary, failure to renew or stop a treatment leading to underuse or overuse of medicines and delay in charting immediate orders which may affect the schedule of drug administration (Koppel et al., 2005).

7.5.3 Interventions to solve DRPs

There is no cure for kidney disease. Children with kidney disease are a group of patients who require lifelong treatment and complex drug therapy. Surveillance for the prevention and resolution of problems in the use of medicines in children with CKD should be a continuous effort at all levels of care (Hogg et al., 2003). The nature of the disease progression and the required treatment expose these children to DRPs even though when

dosage adjustment recommendations are carefully followed (Verbeeck and Musuamba, 2009). The interventions to solve DRPs at the inpatient setting and the outpatient clinics should be approached with different strategies according to their characteristics.

In the inpatient setting, a majority of DRPs are largely contributed by prescribing errors. Prescribing errors have been reported to be preventable (Conroy and Carrol, 2009; Dean et al., 2010; Ghaleb et al., 2010) thus, having continuous awareness programmes on medication safety in paediatrics remains essential in practice (Conroy and Carrol, 2009; Rashed et al., 2012b).

At the outpatient clinics, services focused on changing patients' of cognitive behaviour towards medications and/or specific clinical outcomes as well as empowering patients' involvement in managing their medications have been proven to show benefits in the long term for patients with kidney disease (Cardone et al., 2010; So et al., 2011; Stemer and Lemmens-Gruber, 2011). The challenges to achieve such interventions are to formulate an indicator that is measurable and providing human as well as financial resources for the service. The DRP classifications and the DRP screening tool used in the present research could also be integrated into the physician's practice.

Interventions to identify and solve DRPs should be a shared responsibility of all healthcare providers. Mason and Bakus (2010) suggested eight structured process that can be adapted by all healthcare providers in identifying and resolving DRPs:

1. Obtaining an accurate medication list that truly reflects what the patient is taking.
2. Evaluating whether each medication is necessary or whether any other medication is required.
3. Determining whether each medication is the preferred one for its indication.
4. Assessing that the dosages and regimen are correct.
5. Reviewing the medications list for interactions or adverse effects.
6. Ensuring that proper monitoring takes place.
7. Assessing adherence and causes of non-adherence and
8. Resolving any discrepancies between the actual list and the one in the medical records.

For the paediatric population, the researcher suggests an addition of another two points to the process:

9. Facilitate parents/carers in the monitoring, prevention and resolution of DRPs and
10. Empower children (age appropriate) and especially adolescent with motivation to be confident to take charge of their medications.

7.6 Strengths and limitations

The strengths and limitations of each study in this thesis have been stated at the end of Chapter 5 and Chapter 6. In this section, the focus is on the overall research.

The strength of this Ph.D. research lies in the use of multiple methods to investigate the characteristics of DRPs in children with kidney disease during hospitalisation as well as at the renal outpatient clinics. In addition, this thesis also included the first randomised control trial to explore CP-led intervention in resolving DRPs among children attending the renal outpatient clinics. Even though the trial showed no significant difference in the resolution of DRPs in participants who received intervention, the epidemiology data from this research contributed new knowledge to clinical pharmacy practice. This research included two paediatric hospitals in London, and therefore the results are not necessarily generalised to other settings. However, as the two largest UK paediatric renal centres, it could be hypothesised that their care already reduces the DRPs, and other centres may well have increased rates.

The DRP classification system used in this study was adapted from the PCNE classification version 6.2 and hence the data interpreted in this research may generate some differences in the groups into which the DRPs are classified when using different versions of the PCNE classification

The DRP severity assessment tool used in this research was initially developed to evaluate the severity of administration errors; however, it was the most appropriate tool to be used in the present research. In using this tool, the degree of agreement amongst the judges in scoring the severity levels of DRPs identified in the inpatient setting was higher compared to the outpatient clinics (ICC coefficient: inpatient 0.69 versus outpatient: 0.48). The lower number ICC coeficient at the outpatient clinic could be due to the

smaller number of DRPs compared to the inpatient setting (64 versus 203 DRPs); however, this was not further evaluated in the present research.

7.7 Suggestions for future research

The epidemiology data of DRPs presented in this thesis form a foundation for future medication safety research in children with kidney disease.

- The adapted version of the PCNE DRP classification developed in this research can be used to characterise DRPs in future research involving paediatrics and adults. The operational definition of this adapted version could be useful in minimising bias in data interpretation and would enable comparison of data.

- Currently, no validated tools have been introduced for the assessment of DRP severity. Future research in testing the methods for evaluating DRPs would be very beneficial.

- This research has shown medication discrepancies as a contributory factor for DRPs in patients with kidney disease. Very little work has been done in this area and it would be interesting to investigate the effect of medication reconciliation as a strategy to minimise DRPs at all levels of care for children with kidney disease.

- As health technology is becoming more relevant in today's healthcare system, many studies have been done to study the reliability of the eMR in identifying medication safety signals at the primary care level.

Patients with kidney disease are frequently seen at the clinics and frequently admitted due to complications and/or further clinical investigations. It would be interesting to investigate the degree of discrepancies of information in the eMR and the paper-based medical charts in identifying medication safety signals at the tertiary care setting.

- The thesis also revealed that problems of sub-optimal drug effects and drug administration problems identified at the renal outpatient clinics were contributed by patient's poor understanding of treatment and difficulties in getting supply of refill prescriptions at the community level. Further research is required to investigate whether these problems were latent factors resulting in medicine-related visits to the emergency department or hospitalisation. It would also be important to formulate a comprehensive intervention framework to measure the positive effect of a medicine management programme in the community. Experience from this research would highly suggest the need for proper financial and human resources in order to formulate a comprehensive intervention model at the outpatient setting.

- The consumption of financial and human resources as well as the healthcare professionals' time required in identifying and resolving DRPs were not part of this research objective. Future research could include the economic impact of managing DRPs for children with kidney disease.

7.8 Research contributions

What is already known on this topic?

- Drug-related problems may lead to significant drug-related morbidity and mortality
- There is a lack of epidemiology data on DRPs in children with kidney disease at the tertiary care

What this research adds?

- Epidemiology data on the characteristics (incidence, risk factors, severity, types, contributory factors and resolutions rate) of DRPs
- Strategies to identify, prevent and solve DRPs
- Potential tools that could be used for the identification and classification of DRPs in clinicians' practice
- Strategies to improve the conduct of observational and interventional research in pharmacy practice

in children with kidney disease at the inpatient and outpatient setting.

7.9 Conclusion

This research has successfully filled in the gap in the knowledge of DRPs in nephrology paediatric patients. This thesis compiles the epidemiological data on DRPs in children with kidney disease that was investigated using with mixed methodological approaches and a standard definition as well as

classification system for DRPs. This thesis also investigated the impact of CP interventions at the renal outpatient clinic. The DRPs in children with kidney disease are different to those in adults but share similar characteristics with the general paediatric population. DRPs in children with kidney disease at inpatient level differ to those seen in renal outpatient clinics. Therefore, strategic approaches should be tailored to meet requirements of different hospital settings.

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APPENDICES

Appendix 1 Overview of the classification system for drug-related problems from 1990 to 2010

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
Strand classification (Strand et al., 1990)	**Drug-related problem** This is the first DRP classification that became the foundation of new classifications.	Y An event or circumstance involving drug therapy that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care	8	N	N	N	N	Y
American Society of Hospital Pharmacists (ASHP) guideline, 1996	**Medication-related problem** This system was part of a published guideline for a standardised	Y An event or circumstance involving	13	N	I	N	N	Y

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
(ASHP, 1996)	pharmaceutical care. Prior to this, in 1993 ASHP adapted the classification derived by Strand et al., 1990.	medication therapy that actually or potentially interferes with an optimum outcome for a specific patient						
Westerlund classification, 1996 (cited in van Mil et al., 2004)	**Drug-related problem** This system included intervention classification and manual for its use. It was developed as part of a Ph.D thesis and was first used in 1996. This system underwent minor amendments prior to incorporation into nationwide Swedish pharmacy software.	Y A drug-related problem is a circumstance related to patient's use of a drug, that actually or potentially prevents the patient from gaining the intended benefit of the drug	13	N	I	Y	Y	Y

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
Problems-Assessment-Solutions (PAS) System (van Mil and Thromp, 1997)	**No specific term for DRP was introduced** This classification system was originally developed to document patients' questions on their drug therapy, not to classify all DRPs.	N	5	Y	Y	Y	Y	N
Cipolle et al., 1998 (cited in Fernandez-Llimos et al., 2004, pg 3957)	**Drug therapy problem** Drug-related problems in this system did not include potential problems and thus can only be employed when an event has already been experienced by the patient. Used in many community pharmacies in the US to evaluate pharmacists' activities in their daily provision of pharmaceutical care.	Y Any desirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with desired patient outcomes	7	N	N	N	Y	Y

Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	*DRP classification criteria					
			Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
Granada classification 1st consensus 1998 2nd consensus 2002 3rd consensus 2007 (Granada Consensus Committee, 2002; Granada Consensus Committee, 2007)	**Drug therapy problem** and later changed to **Negative health outcome associated with medications**	Y Health problem that are considered as negative clinical outcomes, resulting from pharmacotherapy, that for different reasons, either do not achieve therapeutic objectives, or produce undesirable effect	6	N	I	N	N	Y
PCNE classification, 1999	**Medicine-related problem** and later changed to **Drug-related problem** This system was developed in 1999 by pharmacy practice researchers during a working conference of the Pharmaceutical Care Network Europe	Y A drug related problem is an event or circumstance involving drug therapy that actually or potentially	6	Y	Y	N	Y	Y

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
	(PCNE) in an effort to develop a standardised classification system that is suitable and comparable for international studies. This was the first classification scheme that introduced a hierarchical structured system with a clear definition of DRP. It comprised separate codes for problems, causes and interventions. In the 2nd version, The word 'medicine' was changed to 'drug'. The latest version is 6.2 introduced in 2010.	interferes with desired health outcomes						
The ABC of DRPs, 2000 (Meyboom et al., 2000*)*	**Drug-related problem** Problems were separated from dose-unrelated problems and appropriate use from inappropriate use. This classification system was created for	N	3	N	I	N	N	N

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
	use in the World Health Organisation (WHO) and focuses on side effects and adverse reaction.							
Krska classification, 2001 (Krska, et al., 2001)	**Pharmaceutical care issue** This classification system was developed during a drug-use evaluation research involving 332 patients.	Y Pharmaceutical care issue is an element of a pharmaceutical care need which is addressed by the pharmacist	13	N	N	N	I	Y
Mackie classification, 2002 (cited in van Mil et al., 2004)	**Clinical drug-related problem** Adapted from a classification system introduced by Cipolle *et al.,* (1998). This classification system was generated based on the authors' research on a random sample of 50	Y A clinical drug-related problem is considered to exist when a patient experiences or is likely to experience	13	N	N	N	N	Y

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
	patients with one or more DRP.	either a disease or symptom having an actual or suspected relationship with drug therapy						
Problem-Intervention Documentation (PI-DOC), 2002 (Schaefer, 2002)	**Drug-related problem** Hierarchical system for problem-intervention documentation developed in Germany with emphasis on the user-friendliness in community pharmacy practice. The first study that used PI-Doc classification was published in 1995. Implemented in most German pharmacy-software systems. Also used in a study in Denmark with a slightly modified format. Subcategories indicate the causes of DRP.	N	6	Y	I	N	Y	Y

Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	*DRP classification criteria					
			Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
National Coordinating Council for Medication Error Reporting (NCC-MERP) Taxonomy of Medication Errors, 2003 (NCC-MERP, 2003)	**Drug-related problem** Definition of DRP in this system is process-oriented and focuses on injectable administration of drug in non-ambulatory settings. The error section includes errors (potential DRPs) that do not become relevant for the patient. This is a hierarchal classification that separated the problems from the causes but does not provide clear intervention taxonomy.	Y Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health care professional, patient or consumer	14	N	I	N	Y	Y
Health Base Foundation Subjective Evaluation Plan (SHB-SEP), 2003 (cited in van Mil et al.,	**No specific term for DRP was introduced** Developed by the Health Base Foundation in Netherland for use in pharmacy software. Based upon	N	10	Y	Y	N	Y	N

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
2004)	medical SOEP (Subjective/Objective/Evaluation/Plan). The S and O codes have been combined into one problem description. This system is still in use but each updated version is not sequentially numbered to facilitate differentiation from previous versions.							
Gordon classification, 2005 (Gordon et. al., 2005)	**Medication-related problems** A tool to identify medicine related problems from patients' perspective at the community settings.	Y *Any problem experienced by a patient that may impact on their ability to manage or take their medicines effectively*	9	N	N	Y	N	Y
AbuRuz classification, 2006	**Treatment-related problems**	Y An event or	6	Y	Y	Y	Y	Y

			*DRP classification criteria					
Classification system	Term for drug-related problem (or other similar terms)	Is this classification system based on clear definition for drug-related problem (or other similar terms)?	Number of main categories for problems	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published studies (usable in practice)
(AbuRuz et al., 2006)	This classification system was developed as a tool for use in teaching, practicing and researching pharmaceutical care and to improve identification, resolution and prevention of treatment-related problems in Jordan.	circumstances involving patient treatment that actually or potentially interferes with an optimum outcome for a specific patient						
I = cause integrated in the problem description; Y = yes; N = no *DRP Classification criteria as suggested by van Mil et al., 2004								

Appendix 2 List of search terms and literature search strategy

Search terms for 'Drug related problem'		AND	Search terms for 'Paediatric'		AND	Search terms for 'Chronic kidney disease'	
"adherence"	OR		"adolescent(s)"	OR		"acute kidney disease"	OR
"adverse drug event(s)"	OR		"adolescence"	OR		"acute renal disease"	OR
"adverse drug reaction(s) reporting systems"	OR		"child"	OR		"acute kidney failure"	OR
"compliance"	OR		"children"	OR		"acute renal failure"	OR
"drug toxicity"	OR		"juvenile"	OR		"chronic kidney failure"	OR
"drug eruptions"	OR		"neonatology"	OR		"chronic renal disease"	OR
"non-adherence"	OR		"Pediatric nursing"	OR		"chronic renal failure"	OR
"noncompliance"	OR		"paediatric(s)"	OR		"dialysis"	OR
"non-compliance"	OR		"pediatric(s)"	OR		"end stage kidney disease"	OR
"drug related problem(s)"	OR		"teenager(s)"	OR			
			"preschool"	OR			

Search terms for 'Drug related problem'		AND	Search terms for 'Paediatric'		AND	Search terms for 'Chronic kidney disease'	
"drug-related problem(s)"	OR		"preschool child"	OR		"end-stage kidney disease"	OR
"drug therapy problem(s)"	OR		"preschool children"	OR		"end stage renal failure"	OR
"drug-therapy problem(s)"	OR		"youth(s)"	OR		"end-stage renal failure"	OR
"medication error(s)"	OR					"end stage kidney failure"	OR
"medication therapy management"	OR					"end-stage kidney failure"	OR
"medicine related problem(s)"	OR					"haemodialysis"	OR
"medicine-related problem(s)"	OR					"hemodialysis"	OR
"pharmaceutical care"	OR					"kidney disease"	OR
						"kidney failure, chronic"	OR

Search terms for 'Drug related problem'	AND	Search terms for 'Paediatric'	AND	Search terms for 'Chronic kidney disease'
				"kidney diseases" OR "kidney failure" "nephrology" "renal failure" "renal disease" "peritoneal dialysis"

Appendix 3 Visual analogue scale for DRP severity assessment

Visual analogue scale for assessing the clinical importance of drug-related problems
Adapted from (Dean and Barber 1999)

Case No.	ASSESSING THE CLINICAL IMPORTANCE OF DRUG RELATED PROBLEMS	
1	**Example:** Mother complained of general rash after 2 doses of Amoxicillin syrup.	No effects — Death 0 1 2 3 4 5 6 7 8 9 10
2	**Example:** At day 4 of admission for uncontrolled hypertension, blood pressure remain high (SBP 180, DBP 100 mmHg) on Perindopril 4mg OD.	No effects — Death 0 1 2 3 4 5 6 7 8 9 10
		No effects — Death 0 1 2 3 4 5 6 7 8 9 10
		No effects — Death 0 1 2 3 4 5 6 7 8 9 10
		No effects — Death 0 1 2 3 4 5 6 7 8 9 10
		No effects — Death 0 1 2 3 4 5 6 7 8 9 10
		No effects — Death 0 1 2 3 4 5 6 7 8 9 10

Appendix 6 Descriptions of DRPs identified in feasibility study (I) (n=13)

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
1	Co-Amoxiclav tablet Patient A has acute kidney impairment due to acute tubular necrosis. Upon discharge, kidney function shows improvement. The dosage regimen to take away for Co-amoxiclav not adjusted to the current kidney profile. Pharmacist suggested the BD interval be increased to TDS.	Treatment effectiveness (Potential) Drug effect not optimal	Dose selection Dose too low Dosage regimen not frequent enough	Drug level Changed dosage	Totally solved
2	Hydralazine 25mg tablet Patient B has severe hypertension due to vascular disease and will undergo vascular surgery on day 3 of admission. Blood pressure is stable on 4 types of antihypertensives: Atenolol 50mg OD, Clonidine 25ug OD, Doxazosin 3mg OD (increased from 2mg), Hydrazaline 9.4mg BD and	Treatment effectiveness (Potential) Wrong effect of drug	Drug selection Too many drugs for indication	Drug level Drug stopped	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
	Amlodipine 5mg OD. Pharmacist suggests to review antihypertensives pre-operatively to prevent drug-induced intra-op hypotension. Atenolol 50mg is withheld on the night before surgery.				
3	Atenolol 25mg tablet Patient B has severe hypertension due to vascular disease and will undergo vascular surgery on day 3 of admission. Blood pressure is stable on 4 types of antihypertensives; Atenolol 50mg OD, Clonidine 25ug OD, Doxazosin 3mg OD (increased from 2mg), Hydrazaline 9.4mg BD and Amlodipine 5mg OD. Pharmacist suggests to review antihypertensives pre-operatively to prevent drug-induced intra-op hypotension. Clonidine 25ug is withheld on the night	Treatment effectiveness (Potential) Wrong effect of drug	Drug selection Too many drugs for indication	Drug level Drug stopped	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
	before surgery.				
4	Doxazosin 4mg tablet Patient B has severe hypertension due to vascular disease and will undergo vascular surgery on day 3 of admission. Blood pressure is stable on 4 types of antihypertensives: Atenolol 50mg OD, Clonidine 25ug OD, Doxazosin 3mg OD (increased from 2mg), Hydrazaline 9.4mg BD and Amlodipine 5mg OD. Pharmacist suggests to review antihypertensives pre-operatively to prevent drug-induced intra-op hypotension. Doxazosin 3mg is withheld on the night before surgery.	Treatment effectiveness (Potential) Wrong effect of drug	Drug selection Too many drugs for indication	Drug level Drug stopped	Totally solved
5	Clonidine 25 µg tablet	Treatment	Drug selection	Drug level	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
	Patient B has severe hypertension due to vascular disease and will undergo vascular surgery on day 3 of admission. Blood pressure is stable on 4 types of antihypertensives: Atenolol 50mg OD, Clonidine 25ug OD, Doxazosin 3mg OD (increased from 2mg), Hydrazaline 9.4mg BD and Amlodipine 5mg OD. Pharmacist suggests to review antihypertensives pre-operatively to prevent drug-induced intra-op hypotension. Hydrazaline 9.4mg is withheld on the night before surgery.	effectiveness (Potential) Wrong effect of drug	Too many drugs for indication	Drug stopped	
6	Methylprednisolone sodium succinate 500mg injection Patient C is supposed to be on a three-day course of injections of Methylprednisolone 600mg OD for the treatment of glomerulonephritis. Prescription for injection	Adverse reaction (Potential) Toxic adverse event	Treatment duration Treatment duration too long Drug use process Drug over-	Drug level Changed instruction for use	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
	Methylprednisolone 600mg OD has missing information on treatment duration. Pharmacist notifies prescriber and suggest adding treatment duration to prevent prolonged treatment.		administered Logistics Prescribing error (treatment duration not mentioned)		
7	Sevelemer 2.4mg sachet Patient D is admitted for tenkoff catheter insertion. He is on maintenance dose of Sevalemer 600mg TDS. On admission Sevalemer is ordered as 2.4g three times daily. Pharmacist notifies prescriber of the dosing error and suggests correction as follows: Sevalemer 600mg (Take 1 blue scoop of Sevalemer 2.4g) three times daily.	Adverse reaction (Potential) Toxic adverse event	Dose selection Drug dose too high Logistics Prescribing error (wrong dose)	Drug level Dosage changed Changed instruction for use	Totally solved
8	Darbopoetin alpha injection	Treatment cost	Dose selection	Drug level	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
	Patient D is admitted for tenkoff catheter insertion. He is on maintenance dose of Darbopoetin alpha once a week at every alternate week. Darbopoetin alpha is prescribed for continuation on admission; however, there was no clear information on his exact dose and dosing schedule. The pharmacist checked with carer who keeps a drug diary and confirms the dose of 2000 units to be given every alternate week on Thursdays starting in the coming week instead of the present week.	(Potential) more than necessary	Dosage regimen too frequent Drug use process Drug over-administered Logistics Prescribing error (treatment duration not mentioned)	Dosage changed Patient level Talked to family member (mother) to obtain drug history	
9	Dailyvit tablet Patient E is on Dailyvit tablet OD. During this current admission, Dailyvit is temporarily out of stock. Pharmacist informs prescriber and suggests Ketovite as an alternative.	Treatment effectiveness (Potential) Untreated indication	Drug use process Patient gets drug at wrong time (delayed administration time because prescribed drug	Drug level Dosage changed	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
			(or its alternative) is not available Logistics Prescribed drug not available		
10	Dailyvit tablet Patient F is on Dailyvit tablet OD. During this current admission, Dailyvit is temporarily out of stock. Pharmacist informed prescriber and suggested Ketovite as alternative.	Treatment effectiveness (Potential) Untreated indication	Drug use process Patient gets drug at wrong time (delayed administration time because prescribed drug (or its alternative) is not available Logistics Prescribed drug	Drug level Dosage changed	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
			not available		
11	Total parenteral nutrition Patient G is on total parenteral nutrition (TPN). At almost 12 noon, the new TPN formulation is not yet finalised, pending the latest blood test result (request for TPN must reach the lab before 12 noon for compounding). Pharmacist reminds the prescriber to put up a TPN request, then suggests the most optimal formulation in a short discussion and passes the TPN order form to the lab for compounding.	Treatment effectiveness (Potential) Untreated indication	Logistics Prescribed drug not available	Drug level Formulation changed	Totally solved
12	Total parenteral nutrition Patient H is on total parenteral nutrition (TPN). The clinical team decides to increase calorie content of TPN once G has started haemodialysis. On the actual day, no changes are	Treatment effectiveness (Potential) Untreated indication	Dose selection Drug dose too low	Drug level Changed formulation	Totally solved

Case number	Drug Description of drug-related problem	Problem type Main & sub - categories	Possible causes by sub-categories	Level of actions	Outcome for actions
	made to the formulation. Pharmacist notifies prescriber and suggests new formulation.				
13	Ranitidine syrup is ready to be dispensed. The pharmacist notices that it is not supposed to be prescribed for the patient and prevents it from being dispensed.	Treatment effectiveness (Potential) Untreated indication	Drug selection No indication for drug Logistics Dispensing error	Other level Pharmacy level	Totally solved

OD – Once daily
BD – Twice daily
TDS – Three times daily

Appendix 7 Operational definition for the adapted PCNE DRP classification version 6.2

Main Category: Types of DRPs	Codes	Sub-categories	Operational definition
Drug effect	P1		There is a (potential or manifested) problem with the (lack of) effect of the pharmacotherapy.
	P1.1	No effect of treatment/therapy failure	*There is neither improvement nor worsening of patient's symptoms.*
	P1.2	Sub-optimal drug effect	*There is improvement in patient's symptoms but not to the intended target.*
	P1.3	Wrong effect of drug treatment	NA
	P1.4	Untreated indication	*There is a symptom (or an anticipated symptom) requiring drug therapy that is not treated*
Adverse drug events	P2		Patient suffers, or will suffer, from an adverse drug event
	P2.1	Non-allergic adverse reaction	*An unintended pharmacological effect from an adverse drug event not suspected as allergic reaction (or toxic effect) commonly known to be related to the prescribed drug at doses normally used for the intended indication (e.g. side effects, intolerable intended pharmacological effect, e.g. hypotension from the use of an antihypertensive agent)*

Main Category: Types of DRPs	Codes	Sub-categories	Operational definition
	P2.2	Allergic drug reaction	*An unintended pharmacological effect from an adverse drug event suspected as an allergy reaction or toxicity; commonly known to be related to the prescribed drug at doses normally used for the intended indication (e.g. rash and Penicillin).*
	P2.3	Toxic adverse reaction	*An unintended pharmacological effect related to the drug at doses higher than maximum dose normally used for the intended indication or adverse effect cause by accumulated doses.*
Treatment costs	P3		The drug treatment is more expensive than necessary
	P3.1	Drug treatment more costly than necessary	*There is an alternative drug that is cheaper but not being used*
	P3.2	Unnecessary drug treatment	*The drug that is newly (or previously) prescribed is not required (or no longer required)*
Other	P4		Other causes not specified above
	P4.1	Patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes	*

Main Category: Types of DRPs	Codes	Sub-categories	Operational definition
	P4.2	**Drug administration problems**	*Difficulties in administering the appropriate drug at the correct doses to the intended patient (e.g. Paracetamol suppository 540mg was prescribed but the preparation available at the dispensary is 240mg suppository; incomplete instructions for drug administration; any circumstance that hinders drug administration)*

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
Drug selection	C1		The cause of the DRP is related to the selection of drug
	C1.1	Inappropriate drug (including contra-indication)	*The wrong drug is selected or the selected drug is contraindicated for the patient.* *Wrong drug is, for example, a patient who is supposed to be on antibiotic A, but is administered antibiotic B.* *Contraindicated drug use is, for example, a patient received a drug to which s/he had previously experienced an allergy reaction*
	C1.2	Inappropriate combination of drugs	*The selected drug interacts (or has the potential to interact) with another drug(s), food or device*
	C1.3	Inappropriate duplication of therapeutic group or active ingredient	*More than one drug of the same therapeutic group or active ingredient is used concurrently*
	C1.4	Indication for drug treatment not noticed	*The drug that is indicated to treat a symptom is not used because the existence of the symptom is not noticed*
	C1.5	Too many drugs prescribed for an indication	*More than the necessary drugs are used for treating the same symptom(s)*
	C1.6	More cost-effective drug available	*An alternative drug that is cheaper and as effective (or more effective) is not used*

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
	C1.7	Synergistic/preventive drug required and not given	*A drug that is required to enhance the existing treatment (synergistic effect) or to prevent the development of another symptom is not used*
	C1.8	New indication for drug treatment presented	*The drug has a new indication that requires change of dosing regimen (e.g. steroid maintenance dose in post transplantation and pulse doses in acute rejection)*
Drug form	C2		Inappropriate drug form
	C2.1	Inappropriate drug form	Inappropriate drug form and/or formulation
Dose selection	C3		*The cause of the DRP is related to the selection of the dosage schedule*
	C3.1	Drug dose too low	*Dose is insufficient to achieve the therapeutic outcome*
	C3.2	Drug dose too high	*Dose is more than necessary to achieve the therapeutic outcome*
	C3.3	Dosage regimen not frequent enough	*Dosing frequency is insufficient to achieve the therapeutic outcome*
	C3.4	Dosage regimen too frequent	*Dosing frequency is more than necessary to achieve the therapeutic outcome*
	C3.5	No therapeutic drug monitoring	*Serum level for drug with narrow therapeutic index not monitored*
	C3.6	Pharmacokinetic problem requiring dose adjustment	*Changes in renal function requiring dose adjustment*

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
	C3.7	Deterioration/Improvement of disease state requiring dose adjustment	*Changes to disease state requiring dose adjustment*
	C3.8	**Dose difficult to measure**	*Prescribed dose is difficult to measure*
Treatment duration	C4		The cause of the DRP is related to the duration of therapy
	C4.1	Treatment duration too short	*Treatment duration is shorter than necessary*
	C4.2	Treatment duration too long	*Treatment duration is longer than necessary*
Medication errors	**C5**		**Mishaps or accidents during any stage of drug handling, prescribing, transcribing, dispensing and administering**
	C5.1	Inappropriate timing of administration and/or dosing intervals	*Error in the process of drug administration*
	C5.2	Drug underused/under-administered	*Error in the process of drug administration*
	C5.3	Drug overused/over-administered	*Error in the process of drug administration*
	C5.4	Drug not taken/administered	*Error in the process of drug administration*

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
		at all	
	C5.5	Wrong drug taken/administered	*Error in the process of drug administration*
	C5.6	Drug abused (unregulated overuse)	*
	C5.7	Patient unable to use drug/drug form as directed	Moved to category Patient factor (C7.5)
	C5.8a	**Prescribing error in decision making**	*Error in deciding for treatment*
	C5.8b	Prescribing error in prescription writing	Error in writing prescription
	C5.9	Dispensing error	*Error in dispensing the prescribed drug*
	C5.10	**Dilution error**	*Error in the process of diluting a drug to its prescribed concentration*
Drug supply	C6.1	Prescribed drug not available	Prescribed drug not available for use
Patient factor	C7		The cause of the DRP can be related to the personality or behaviour of the patient.

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
	C7.1	Patient forgot to use/take drug	*
	C7.2	Patient used unnecessary drug	*
	C7.3	Patient took food that interacts with the prescribed drug(s)	*
	C7.4	Patient stored drug inappropriately	*
	C7.5	Patient refused to take the drug	*
	C7.6	Patient unable to use the drug	*
Others	C8		Other causes not specified above
	C8.1	**Poor medication reconciliation**	*Discrepancies between patient's own drugs with the ones prescribed on admission.* *Discrepancies between drugs planned to take home and the ones on Discharge Prescriptions*
	C8.2	**Unwanted side effects**	*Known undesirable effect of a drug other than the intended therapeutic effects*
	C8.3	**Inappropriate drug administration site/route**	*Wrong site and/or route for the prescribed drug*
Main Category: Intervention	Codes	Sub-categories	Operational definition
I0: No intervention	I0	No intervention	No intervention
I1: At prescriber level	I1.1	Prescriber informed only	*Note: In this research, pharmacist encounters with*

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
	I1.2 I1.3 I1.4 I1.5	Prescriber asked for information Intervention proposed, approved by prescriber Intervention proposed, not approved by prescriber Intervention proposed, outcome unknown	*the prescriber were seen as a process that precedes an intervention rather than a type of intervention (see discussion)*
I3: At drug level	I2.1	Drug changed to…	*Changes to the selection of drug*
	I2.2	Dosage changed to…	*Changes to the prescribed dose*
	I2.3	Drug form/formulation changed to…	*Changes to the types of drug formulation*
	I2.4	Instructions for use changed to…	*Changes to the instruction on using the drug (e.g. drug dilution).*
	I2.5	Drug stopped	*The prescribed drug was stopped*
	I2.6	New drug started	*A new drug prescribed*
	I2.7	**Dosing frequency changed to…**	*Changes to the dosing frequency*
	I2.8	Route/site of administration	*Changes to the route or site of administration*

Main Category: Contributory factors for DRPs	Codes	Sub-categories	Operational definition
		changed to…	
	I2.9	Treatment duration changed to…	*Changes to the number of days in the treatment*
	I2.10	Request for serum drug level	*
I3: At patient/carer level	I3.1	Patient (medication) counselling	Counselling on drug treatment
	I3.2	Written information provided only	*
	I3.3	Referred patient to prescriber	*The solution of the DRP requires referral to prescriber for further action*
	I3.4	Family members spoken to	*Discussion with family members/carer to solve problems*
I4: Interventions of other levels	I4.1 I4.2	Other intervention (specify) Side effect reported to authorities	

Main Category: Outcome of the interventions	Codes	Sub-categories	Sub-categories
O0: Not known	O0.0	Outcome intervention not known	Outcome intervention not known
O1: Solved	O1.0	Problem totally solved	Problem is solved not requiring further interventions
O2: Partially solved	O2.0	Problem partially solved	The problem is temporarily solved and requires further intervention
O3: Not solved	O3.1	Problem not solved, lack of cooperation from patient	*
	O3.2	Problem not solved, lack of cooperation from prescriber	*
	O3.3	Problem not solved, intervention not effective	*
	O3.4	No need or possibility to solve problem	*

The new category/sub-category introduced or modified are **in bold**
Operational definition that were not adapted from the original classification are in *italics*
*Self-explanatory
NA – Not applicable because the CPs were not comfortable in using the term
Potential DRPs: Drug problems identified before the problem occurred/patient experienced harm
Manifested DRPs: Drug problems identified after the problem had occurred/patient experienced harm

Appendix 8 Drug-related problem registration form (DRP-Rf)

DRP Registration Form (DRP-RF) ID DRP #

Adapted from PCNE DRP Classification System version 6.2

PATIENT DEMOGRAPHY

Gender	: M F	DOB	:	RRT :	
Age	:	DOA	:	☐ HD	
Ht (cm)	:	DODc	:	☐ PD	
Wt (kg)	:	Type of admission:		☐ Tx	
BSA (m^3)	:	☐ Elective	☐ Transfer	☐ No RRT	
GFR(ml/min)	:	☐ Emergency	☐ Internal ref.	☐ CKD stage: 1 2 3 4	
			☐ External ref.		
No. prescribed items	:				

CLINICAL INFORMATION

Primary cause of kidney disease

- ☐ Dysplastic kidney
- ☐ P/M cystic kidney
- ☐ Renal artery stenosis
- ☐ Glomerulonephritis
- ☐ Kidney stones
- ☐ Unknown
- ☐ Others:
- ☐ Congenital nephrotic

Concurrent diseases:

- ☐ Hypertension
- ☐ Diabetes
- ☐ Others

Notes

Diagnosis & Problem lists

History of allergies:

History of non – adherence documented: ☐ Yes ☐ No

Past medication history ☐ Medication record ☐ Patient

Drug name	Dose	Frequency	Notes

1

DRP Registration Form (DRP-RF) ID DRP #

Adapted from PCNE DRP Classification System version 6.2

A. DESCRIPTION OF DRUG

Drug name & dosage regimen

Main active ingredients (ATC code)

Type of prescription:

- ☐ New
- ☐ Continue DHx

B. DESCRIPTION OF DRP

Problem identified by:

- ☐ Pharmacist
- ☐ Prescriber
- ☐ Nurse
- ☐ Patient/Carer
- ☐ Others

Intervention initiated by:

- ☐ Pharmacist
- ☐ Prescriber
- ☐ Nurse

Date /time DRP identified:
Date /time action taken :
Date/time DRP resolved :
No. of prescribed item when DRP is identified :

Description of problem

Evaluation of outcome

- ☐ Outcome unknown
- ☐ Totally solved
- ☐ Partially solved
- ☐ Problem not solved

C. TYPE OF PROBLEM (tick only 1 problem and indicate if the problem is potential or manifested)

☐ Potential problem ☐ Manifested problem

[P1] Drug Effect

- ☐ No effect of drug treatment
- ☐ Effect of drug treatment not optimal
- ☐ Wrong effect of drug treatment
- ☐ Untreated indication

[P2] Adverse drug event (ADE)

- ☐ Adverse drug reaction (non-allergic)
- ☐ Adverse drug reaction (allergic)
- ☐ Toxic adverse reaction

[P3] Treatment Cost

- ☐ Treatment cost more than necessary
- ☐ Unnecessary drug treatment

[P4] Others

- ☐ Administration problems
- ☐ Patient dissatisfied with therapy
- ☐ Therapy failure (unknown reason)

2

DRP Registration Form (DRP-RF) ID DRP #

Adapted from PCNE DRP Classification System version 6.2

D. CAUSES OF PROBLEM (maximum 3 boxes to be ticked)

[C1] Drug selection

- ☐ Inappropriate drug (including contra-indicated)
- ☐ No indication for drug
- ☐ Inappropriate combination of drugs or food (including drug interaction)
- ☐ Inappropriate duplication of therapeutic groups or active ingredient
- ☐ Too many drugs prescribed for same indication
- ☐ More cost-effective drug available
- ☐ Synergistic/preventive drug required and not given
- ☐ New indication of drug treatment presented
- ☐ Unnoticed indication

[C2] Inappropriate drug form

- ☐ Inappropriate drug form

[C3] Dose selection

- ☐ Drug dose too LOW
- ☐ Drug dose too HIGH
- ☐ Drug concentration too LOW
- ☐ Drug concentration too HIGH
- ☐ Dosage regimen not frequent enough
- ☐ Dosage regimen TOO FREQUENT
- ☐ No therapeutic drug monitoring
- ☐ PK problem requiring dose adjustment
- ☐ Deterioration/improvement of disease state requiring dose adjustment
- ☐ Dose difficult to measure for administration

[C4] Treatment duration

- ☐ Treatment duration too SHORT
- ☐ Treatment duration too LONG

[C5] Medication error

- ☐ Prescribing error (a) in decision making (b) in writing
- ☐ Dispensing error
- ☐ Inappropriate timing of administration and/or dosing intervals
- ☐ Drug administered to the wrong patient
- ☐ Wrong drug administered
- ☐ Drug not administered at all
- ☐ Drug administered at the wrong time
- ☐ Drug under administered
- ☐ Drug over administered
- ☐ Drug abuse (unregulated overuse)

[C6] Drug supply & procurement

- ☐ Prescribed drug not available *(Describe reason)*

[C7] Patient factor

- ☐ Refuse to take the drug
- ☐ Forgets to take the drug
- ☐ Unable to use drug as prescribed
- ☐ Uses unnecessary drug
- ☐ Takes food / 'own drug' that is suspected to interact with the drug

[C8] Other causes

- ☐ Unwanted drug side effect
- ☐ Prescriber unsure of dosage regimen
- ☐ Prescriber unsure of treatment duration
- ☐ Illegible handwriting and/or inappropriate abbreviation
- ☐ Poor documentation of drug history
- ☐ Other unspecified causes:

3

DRP Registration Form (DRP-RF) ID DRP #
Adapted from PCNE DRP Classification System version 6.2

E. INTERVENTION AT PRESCRIBER LEVEL

- ☐ No intervention at Prescriber Level
- ☐ Prescriber informed only
- ☐ Prescriber asked for information
- ☐ Intervention proposed; APPROVED
- ☐ Intervention proposed; NOT approved
- ☐ Intervention proposed; acceptance/approval unknown

F. ACTIONS TAKEN TO SOLVE DRP (maximum 3 boxes to be ticked)

A1 No action taken

A2 Drug Level

- ☐ Drug changed to:
- ☐ Dosage changed to:
- ☐ Frequency changed to:
- ☐ Formulation changed to:
- ☐ Concentration for dilution changed to:
- ☐ Administration route changed to:
- ☐ Treatment duration changed to:
- ☐ Instruction for use changed to:
- ☐ Drug stopped/suspended:
- ☐ New drug started:
- ☐ Suspended drug restarted:
- ☐ Drug level taken:

A3 Patient Level

- ☐ Medication and/or disease counselling
- ☐ Provide written information
- ☐ Refer patient to prescriber
- ☐ Spoken to family member/carer

A4 Other Levels

- ☐ Drug not dispensed
- ☐ Biochemistry checked:
- ☐ Others:

G. OUTCOME OF ACTIONS

- ☐ Outcome unknown
- ☐ Problem solved
- ☐ Problem partially solved; further actions are required to achieve the desired outcome

Problem not solved:

- ☐ Lack of cooperation from patient
- ☐ Lack of cooperation from prescriber
- ☐ No need or possibility to solve problem:
- ☐ Patient passed away
  - ☐ Other reason:
  - ☐ Intervention not effective

4

Appendix 9 Study information leaflet for healthcare providers (Inpatient)

For circulation to healthcare providers

What is a DRP?

A drug-related problem (DRP) is also known as a medicine-related problem or medication-related problem. By definition, a DRP is *"An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*.

What is the aim of the study?

The global challenge in nephrology is to shift the emphasis of treating kidney disease from providing more kidney replacement therapy to early detection and prevention of progressive chronic kidney disease (CKD). Pharmaceutical care has an important role to play in achieving this target. It is crucial to investigate the DRP component to complement the impact of medical intervention. Studies of DRPs in CKD so far have only been performed in adults and little is known of their epidemiology in children. Hence, the aim of this study is to investigate the epidemiology of DRPs in paediatric patients with CKD.

How long is the study period?

This study will be conducted from 1st September 2011 to 30th September 2012.

Why is it important to understand the nature of DRP in children with CKD?

The incidence of CKD in children has steadily increased and it is known to be one of the most common chronic illnesses in childhood. It demands lifelong health care and future solid organ transplantation. The management of drug therapy for patients with kidney disease is specialised and complex puts this group of children at risk of DRPs. Examples of DRPs are adverse drug reactions, inadequate or toxic drug effect, therapy failure, increased cost of healthcare and patients' poor adherent to treatment. Each of these may contribute to the progression CKD.

How will this study affect my daily work?

Your work is unlikely to be affected.

How will it be conducted?

Throughout this study, a pharmacy PhD student will collect information about DRPs by observing ward pharmacists perform their daily ward rounds. The PhD pharmacy student will suggest intervention only in the situation that a DRP with the possibility of harming the patient is not otherwise identified. The presence of the researcher will be as discrete as possible so as not to interfere with the work of the ward pharmacist and other ward staff.

Who do I speak to if I have further enquiries, suggestions or complaints?

For enquiries and suggestions, please contact the researcher, Ms Nor Ibrahim, by phone on 020 7874 1531 or by email on norkasihan.ibrahim@live.pharmacy.ac.uk

If you have any complaints about the way in which this study is being or has been conducted, please discuss them with Ms Nor Ibrahim in the first instance. If the problems are not resolved, or you wish to comment in any other way, you may contact:-

Professor Ian C.K Wong, Director
The Centre for Paediatric Pharmacy Research (CPPR)
The School of Pharmacy, University of London
Tel: 020 7874 1530 extension 1535
Email: ian.wong@pharmacy.ac.uk

Dr Yogini Jani, Chief Investigator
The Centre for Paediatric Pharmacy Research (CPPR)
The School of Pharmacy, University of London
Tel: 084515555 extension 5000/73509
Email: yogini.jani@pharmacy.ac.uk

Patient Advice and Liaison Service (PALS):
1) Great Ormond Street Hospital for Children
Tel: 020 7829 7862
2) St Thomas' Hospital
Tel: 020 7188 7188

Appendix 10 Study invitation: Cover letter

Study material Cover Letter/protocol V2-02112012/12/LO/0709

Guy's and St Thomas' NHS
NHS Foundation Trust

Dear Parents,

Invitation to participate in a study at the renal outpatient clinic

Hello parents, warm greetings from the research team!

We would like to invite you and your child to take part in our study. This study is conducted by University College London School of Pharmacy, and has been approved by the London – Hampstead Research Ethics Committee.

Our study is to answer the question *'What types of problems related to the use of medicines are faced by children with chronic kidney disease (CKD) and does having a medication review (MR) programme by clinical pharmacist at the renal clinic helps in resolving the problems?'* You and your child are invited into this study because your child has been prescribed with medicines to either prevent or slow the progression of CKD and its complications.

Before you decide, we would like you to understand why the study is being done and what it would involve for you and your child. Please find enclosed the Patient Information Sheet for you and your child. We will ring up to ask if you have received this reading material and whether you are happy to take part.

If you and your child agree to take part, please bring along the enclosed sheets with you during your child's next renal clinic appointment. A member of our team would be happy to will go through the information sheet with you at the clinic and answer any questions you have.

If you decide not to take part, this will not affect the standard of care that your child will receive.

Thank you for your kind consideration.

With kind regards,

Chief Investigator

Appendix 11 Study Information Leaflet for parents

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Medicine-related Problems in Children with Chronic Kidney Disease

An Invitation

We would like to invite you and your child to take part in our study.

Before you decide we would like you to understand why the study is being done and what it would involve for you and your child. We would suggest this should take about 5 minutes.

Part 1 tells you the purpose of this study and what will happen if you and your child take part. Part 2 gives you more detailed information about the conduct of the study.

Two weeks after the postage of this study material, we will phone you to see if you have received the postage and whether you are interested in taking part.

Talk to others about the study if you wish. A member of our team will go through the information sheet with you at the clinic and answer any questions you have. You can tell us your decision during your child's next routine clinic appointment. Please ask us if there is anything that is not clear.

PART 1 – This section provides information on the purpose of the study and what will happen to you and your child as study participants.

What is the purpose of our study?

Our study is to answer two questions – (1) 'What types of problems related to the use of medicines are faced by children with chronic kidney disease (CKD) and does having a medication review (MR) programme by clinical pharmacist at the renal clinic helps in resolving the problems?' and (2) 'Does MR programme help in achieving a better blood pressure control in children with chronic kidney disease who have been diagnosed hypertension?'

Similar studies conducted in the adult group have shown that patients in CKD are more likely to have problems with their medications. Efforts to manage these problems have shown positive effects to patient's treatment outcome. Such information is not available for children. Currently, we are assuming children shares similar problems and solutions; this assumption may not be valid.

What does the term 'medicine-related problems' in the title mean?

A medicine-related problem (MRP) is an event or circumstance involving medication therapy that actually or potentially interferes with desired health outcomes. Medicine-related problem includes adverse reactions, allergy, medication error and undesired experience caused by medicines such as side effects, drug-drug or drug-food interaction, unpalatable taste or formulation, administration problem and difficulties in obtaining supplies to name a few.

What does the term 'chronic kidney disease' and 'medication review' mean in the title?

Chronic kidney disease (CKD) is a long-term condition where the kidneys do not work as well as normal. A person with CKD may or may not yet be on dialysis, and this includes those who have undergone kidney transplantation. Medication Review is a holistic review of patient's medication with patient's underlying condition. This activity is focused on identifying actual and potential problems related to the use of medicines that may compromise patient's treatment outcome.

Why have you and your child been invited?

You and your child are invited into this study because your child has been prescribed with medicines for the kidneys. As medicines for children with CKD are sometimes complex, we would like to know if your child is having problems in taking them as prescribed.

Do you and your child have to take part?
It is up to you and your child to decide. We will call you two weeks after posting this study material to ask whether you are interested to participate. If you do, we will go through this information sheet at the clinic when you come for the next renal clinic appointment. When you have decided to participate, we will ask you to sign a consent form. We will also seek agreement (assent) from your child. You and your child are free to withdraw at any time, without giving a reason. This would not affect the standard of care your child receives.

What will happen to me and my child if I take part?
When you have given a signed consent, the researcher will screen through your child's medical notes to identify any medicine-related problems. Participants will then be assigned into two groups – the **pharmaceutical care group** and the **standard care group.** To make sure the groups are the same to start with, each patient is put into a group by chance (randomly). There is a 50% chance for you to be assigned in either of the groups.

If you fall in to the **pharmaceutical care group**, you and your child will receive pharmaceutical care service whilst waiting to see the doctor. This service is a 20-minute session with the clinical pharmacist. During this session, the clinical pharmacist will review the medication and ask questions to determine:

- An accurate list of your child's long term medications
- How your child is getting on with the medications and whether there is any problem in taking them as prescribed.

The pharmacist will then summarise the problems your child may have in regards to medications and provide appropriate recommendations to the doctor on a note that will be placed in the medical file. The doctor will then discuss the matter with you to decide if there is a need for changes to your child's current medications or other possible resolution (when required). Other than meeting the clinical pharmacist, you are not expected to do anything extra apart from the usual routine during your child's normal clinic appointments.

If you fall in to the **standard care group,** you will follow the normal clinic routine. No new intervention will be introduced to the usual routine during your child's renal clinic appointments.

We will measure and compare the types and numbers of medicine-related problems that may have the potential to compromise patient's treatment in both groups. If your child has a diagnosis of hypertension, we will trace the blood pressure level from the medical notes four weeks afterward. Your child is not required to come for any extra visit to the hospital for this purpose.

Please refer to the flow chart at the end of this sheet to gain a better understanding about the process of this research.

How much time will this involve?
The whole process will take place during your child's renal clinic appointment day. The session with the clinical pharmacist is approximately 20 minutes.

What will my child and I need to do?
You are not expected to do anything more than what is required from your normal routine at the renal clinic. If you are assigned to the **pharmaceutical care** group, you may need to facilitate your child to answer questions about his/her medicines during the session with the clinical pharmacist.

What are the possible benefits and risks of taking part?
We do not see any risk involved with taking part in this research. We cannot promise the study will help your child but the information we get from this study will help improve the medicine management of children with chronic kidney disease. We would also like to use the results of this study to improve pharmacy services for renal patients at the outpatient setting. All information will be kept confidential and only those related to medications are recorded.

Will my participation in the study and my child's involvement be kept confidential?
Yes. Patient confidentiality will be maintained in line with the ethical and legal practice. The research team has a contract with the hospital Trust is responsible to follow the Trust policies and procedures for patient confidentiality and information governance. Data will be anonymous and only anonymous data will leave the hospital, and it shall be maintained anonymous during assessment and analysis. Please see part 2 for further details.

If the information in Part 1 has interested you and your child, and both are considering participating in the study, please read the additional information in Part 2 before making any decision.

PART 2 – This section will provide more details about the conduct of the study.

What will happen if I don't want to carry on with the study?
You and your child are free to withdraw at any time, without giving a reason. This would not affect the standard of care your child receives.

What if serious problem(s) is identified?
If this happens, the doctor will be informed for further clinical judgement. We will follow the Trust rules and regulations on medication safety.

Who is organising and funding the research?
This research is organised by the UCL School of Pharmacy in collaboration with the Pharmacy Department of two paediatric hospitals - Evelina Children Hospital and Great Ormond Street Hospital for Children. This study is part of a PhD project and not funded by any organisation.

Who has reviewed the study?
All research in the NHS is reviewed by an independent group of people, called a Research Ethics Committee, to protect your child and your interests. This study has been reviewed and given favourable opinion by London – Hampstead Research Ethics Committee.

If your child and you are happy to participate in the study we will enclose the following: -
- Patient information sheets for parents (Version 2/25072012)
- Patient information sheets for your child (this will be age appropriate), if your child is under five, please read the leaflet and explain this to your child
- Consent form for you to sign
- Assent form for your child to sign or for you to sign on their behalf

Who do I speak to if I have further enquiries, suggestions or complaints?
If you have any enquiries, suggestions or complaints about the way in which this study is being or has been conducted please contact the research team:

Mrs Nor Ibrahim Researcher
E: norkasihan.ibrahim.11@ucl.pharmacy.ac.uk
☎ 020 7874 1531

Dr Yogini Jani Chief Investigator
E: y.jani@ucl.ac.uk
☎ 020 3456 7890 ext 7350

Mr Stephen Tomlin Principal Investigator
stephen.tomlin@gstt.nhs.uk
☎ 020 7188 9202

If you are still not happy and wish to comment in any other way, you may contact:-

Patient Advice and Liaison Service (PALS) St Thomas' Hospital
Tel: 020 7188 8801/03

Research flowchart

Study information materials will be posted 3 weeks before your next clinic appointment

Two weeks later, we will make a phone call to see if you have received the postage and whether you are interested in taking part

When you come to register your child's renal clinic appointment, the research team will ask about your decision to participate in the study. If you decide to take part, you will have to sign the consent form

The researcher will screen through your child's medical notes to identify any medication related problems. You will then be randomly assigned to either the Standard Care or the Pharmaceutical Care group

STANDARD CARE group

PHARMACEUTICAL CARE group

The pharmacist will review your child's current medicines and discuss about problems your child may have in taking them as prescribed (this may take approximately 20 minutes and will take place while you are waiting to see the doctor)

The pharmacist will then summarise relevant information on a note that will be delivered to your doctor. The doctor will discuss the matter with you to decide if there is a need for changes to the medicines or other possible solution

The researcher will evaluate the resolution of the identified problems from documentation in the medical notes

4 weeks later

If your child has been diagnosed high blood pressure, we will trace blood pressure level from the medical notes. Your child does not have to come for any extra visit to the hospital apart from the scheduled renal clinic appointments.

Appendix 12 Study Information Leaflet for children aged 16 to 18 years

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Medicine-related Problems in Children with Chronic Kidney Disease

An Invitation

We would like to invite you to take part in our study.

Before you decide we would like you to understand why the study is being done and what it would involve for you. We would suggest this should take about 5 minutes. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

Two weeks after the postage of this study material, the researcher will phone you to see if you have received the postage and whether you are interested in taking part. Talk to your family, friends, doctor or nurses about the study if you wish. You can tell us your decision during your next renal clinic appointment. Ask us if there is anything that is not clear. A member of our team will go through the information during your next renal clinic appointment.

PART 1 – This section provides information on the purpose of the study and what will happen to you as study participants.

What is the purpose of our study?

Our study is to answer two questions – (1) 'What types of problems related to the use of medicines are faced by children with chronic kidney disease and does having a medication review programme by clinical pharmacist at the renal clinic helps in resolving the problems?' and (2) 'Does MR programme help in achieving a better blood pressure control in children with chronic kidney disease who has been diagnosed hypertension?'

Similar studies conducted in the adult group have shown that patients in CKD are more likely to have problems with their medications. Efforts to manage these problems have shown positive effects to patient's treatment outcome. Such information is not available for children. Currently, we are assuming children shares similar problems and solutions; this assumption may not be valid.

What does the term 'medicine-related problems' in the title mean?

A medicine-related problem (MRP) is an event or circumstance involving medication therapy that interferes with desired health outcomes. Medicine-related problem includes adverse reactions, allergy, medication error and undesired experience caused medicines such as side effects, drug-drug or dug-food interaction, unpalatable taste or formulation, administration problem and difficulties in obtaining supplies to name a few.

What does the term 'chronic kidney disease' and 'medication review' mean in the title?

Chronic kidney disease is a long-term condition where the kidneys do not work as well as normal. A person with CKD may or may not yet be on dialysis, and this includes those who have undergone kidney transplantation. Medication Review is a holistic review of patient's medication with patient's underlying condition. This activity is focused on identifying actual and potential problems related to the use of medicines that may compromise patient's treatment outcome.

Why have you been invited?

You are invited into this study because you are taking medicines for the kidneys. As medicines prescribed for children with CKD are sometimes complex, we would like to know if you are facing any difficulties in taking them as prescribed.

Do you have to take part?
No. It is up to you to decide. We will describe the study and go through this information sheet when you come for your next renal clinic. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?
When you have given a signed consent, the researcher will screen through your medical notes to identify any medicine-related problems. Participants will then be assigned into two groups – the **pharmaceutical care group** and the **standard care group.** To make sure the groups are the same to start with, each patient is put into a group by chance (randomly). There is a 50% chance for you to be assigned in either of the groups.

If you fall in to the **pharmaceutical care group**, you will receive pharmaceutical care service whilst waiting to see the doctor. This service is a 20-minute session with the clinical pharmacist. During this session, the clinical pharmacist will review the medication and ask questions to determine:

- An accurate list of your long term medications
- How you are getting on with the medications and whether there is any problem in taking them as prescribed.

The pharmacist will then summarise the problems you may have in regards to medications and provide appropriate recommendations to the doctor on a note that will be placed in the medical file. The doctor will then discuss the matter with you to decide if there is a need for changes to your current medications or other possible resolution (when required). Other than meeting the clinical pharmacist, you are not expected to do anything extra apart from the usual routine during your renal clinic appointments.

If you fall in to the **standard care group,** you will follow the normal clinic routine. No new intervention will be introduced to the usual routine during your renal clinic appointments.

We will measure and compare the types and numbers of medicine-related problems that may have the potential to compromise patient's treatment in both groups. If you have been diagnosed hypertension, we will trace the blood pressure level from the medical notes four weeks afterward. You are not required to come for any extra visit to the hospital for this purpose.

Please refer to the flow chart at the end of this sheet to gain a better understanding about the process of this research.

How much time will this involve?
The whole process will take place during your renal clinic appointment day. The session with the clinical pharmacist is approximately 20 minutes.

What will I need to do?
You are not expected to do anything more than what is required from your normal routine at the renal clinic. If you are assigned to the intervention group, you will need to answer questions about how you are getting on with your medicines during
the session with the clinical pharmacist.

What are the possible benefits and risks of taking part?
We do not see any risk involved with taking part in this research. We cannot promise the study will help you but the information we get from this study will help improve the medicine management of children with chronic kidney disease. We would also like to use the results of this study to improve pharmacy services for renal patients at the outpatient setting. All information will be kept confidential and only those related to medications are recorded. Please refer to the flow chart at the end of this sheet to gain a better understanding about the process of this research.

Will my participation and involvement in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Please see part 2 for further details.

If the information in Part 1 has interested you, and you are considering participating in the research, please read the additional information in Part 2 before making any decision.

PART 2 – This section will provide more details about the conduct of the study

What will happen if I don't want to carry on with the study?
You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

Will my participation in the research be kept confidential?
Yes. Patient confidentiality will be maintained in line with the ethical and legal practice. The research team has a contract with the hospital Trust is responsible to follow the Trust policies and procedures for patient confidentiality and information governance. Data will be anonymous and only anonymous data will leave the hospital, and it shall be maintained anonymous during assessment and analysis. Please see part 2 for further details.

What if serious problem(s) is identified?
If this happens, the doctor will be informed for further clinical judgement. We will follow the Trust rules and regulations on medication safety.

Who is organising and funding the research?
This research is organised by the UCL School of Pharmacy in collaboration with the Pharmacy Department of two paediatric hospitals - Evelina Children Hospital and Great Ormond Street Hospital for Children. This study is part of a PhD project and not funded by any organisation

Who has reviewed the study?
All research in the NHS is reviewed by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by London – Hampstead Research Ethic Committee.

If you are happy to participate in the study we will enclose the following: -
- Patient information sheets for you (this will be age appropriate)
- Consent form for you to sign

Who do I speak to if I have further enquiries, suggestions or complaints?
If you have any enquiries, suggestions or complaints about the way in which this study is being or has been conducted please contact the research team:

Mrs Nor Ibrahim Researcher
E: norkasihan.ibrahim.11@ucl.pharmacy.ac.uk
☎ 020 7874 1531

Dr Yogini Jani Chief Investigator
E: y.jani@ucl.ac.uk
☎ 020 3456 7890 ext 7350

Mr Stephen Tomlin Principal Investigator
stephen.tomlin@gstt.nhs.uk
☎ 020 7188 9202

If you are still not happy and wish to comment in any other way, you may contact:-

Patient Advice and Liaison Service (PALS) St Thomas' Hospital
Tel: 020 7188 8801/03

Research flowchart

Study information materials will be posted 3 weeks before your next clinic appointment

Two weeks later, we will make a phone call to see if you have received the postage and whether you are interested in taking part

When you come to register your renal clinic appointment, the research team will ask about your decision to participate in the study. If you decide to take part, you will have to sign the consent form

The researcher will screen through your medical notes to identify any medication related problems. You will then be randomly assigned to either the Standard Care or the Pharmaceutical Care group

STANDARD CARE group

PHARMACEUTICAL CARE group

The pharmacist will review your current medicines and discuss about problems you may have in taking them as prescribed (this may take approximately 20 minutes and will take place while you are waiting to see the doctor)

The pharmacist will then summarise relevant information on a note that will be delivered to your doctor. The doctor will discuss the matter with you to decide if there is a need for changes to the medicines or other possible solution

The researcher will evaluate the resolution of the identified problems from documentation in the medical notes

4 weeks later

If you are diagnosed high blood pressure, we will trace your blood pressure level from the medical notes. You do not have to come for any extra visit to the hospital apart from your scheduled renal clinic appointments.

Appendix 13 Study Information Leaflet for children aged 11 to 15 years

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Medicine-related Problems in Children with Chronic Kidney

An Invitation

We are asking if you would take part in a research project to understand what problems children who attend the renal clinic may have with their medicines.

Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. We will phone your mom and dad in two weeks time to see if you have received this reading material and whether you are interested in taking part. So please consider this leaflet carefully.

Talk about it with your family, friends, doctor or nurse if you want to.

PART 1 – This section should help to give you first thoughts about the project.

Why are we doing this research?

When children have health conditions that affect their kidneys, the doctor usually prescribes them medicines. Sometimes children may have problems with these medicines. We would like to know what problem these children have with their medicines and how pharmacists can help with these. If these children have high blood pressure, we would like to know how pharmacists can help to improve blood pressure levels.

What does the research title means?

A medicine-related problem refers to any undesired effect caused by medicines. This includes for example allergic reaction, unwanted side effects and unpalatable taste. Chronic kidney disease is a condition where the kidneys do not work as well as normal.

Why have I been invited to take part?

You are invited into this study because you are taking medicines for your kidneys. There are approximately 1000 children with kidney disease in the UK and this is the earliest study to look into problems these children have in taking the prescribed medicines.

Do I have to take part?

No. It is up to you. We will phone your parent (or carer) to see if you have received this material and whether you are interested in taking part. If you do, we will answer any questions you have about this study in your next renal clinic appointment. If you are still happy to participate, your mom and dad will have to sign the agreement form. You will be given a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive.

What will happen to me if I take part?

First, you will be assigned to one of two groups. Then, the researcher will read your medical notes. If you are in Group A, you will follow the usual routine during your renal clinic appointments.

If your name falls in Group B we will invite you, parent(s) for a 20-minute session to meet a clinical pharmacist; this will be whilst you are waiting to see the doctor. The clinical pharmacist will review your medical notes and ask you several questions to find out if you have any problems with your medicines. The clinical pharmacists will note down the problems you may have with your medicines. Later on, the doctor will discuss with you, mom and dad on the best solution for the problems you have with your medicines. Other than meeting the clinical pharmacist, you are not expected to do anything extra from the usual routine during your renal clinic appointments.

If you have high blood pressure, the researcher will look for your blood pressure level from the medical notes four weeks later. You do not have to come for any extra visit to the hospital apart from your scheduled renal clinic appointments.

How much time will this involve?
The whole process will take place during your appointment at the renal clinic. The session with the clinical pharmacist is approximately 20 minutes.

What will I be asked to do?
You are not expected to do anything more than what is required from your normal routine at the renal clinic. If you are invited to meet the clinical pharmacist, you will be asked questions about how you are getting on with your medications.

What are the risks and the possible benefits of taking part?
We do not see any risk involved with taking part in this research. We cannot promise the study will help you but the information we get might help us find ways to help children with kidney disease manage the problems they have with their medicines.

Will my participation and involvement in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Please see part 2 for further details.

Thank you for reading this far, if you and your parent/carer are considering participating in the study, please read the additional information in Part 2 before making any decision.

PART 2 – Information you need to know if you still want to take part.

What will happen if I don't want to carry on with the study?
You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receives.

Will anyone else know I am doing this?
We will keep your information in confidence. This means we will only tell those who have a need or right to know. Your doctors, nurses and parent will know that you are taking part in this study.

Who is organising and funding the research?
This research is organised by the UCL School of Pharmacy in collaboration with the Pharmacy Department of two paediatric hospitals - Evelina Children Hospital and Great Ormond Street Hospital for Children. This study is not funded by any organisation.

Who has reviewed the study?
Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is fair. Your project has been checked by the London – Hampstead Research Ethics Committee.

Who do I speak to if I have further enquiries, suggestions or complaints?

If you have any enquiries, suggestions or complaints about the way in which this study is being or has been conducted please contact the research team:

Mrs Nor Ibrahim Researcher
E: norkasihan.ibrahim.11@ucl.pharmacy.ac.uk
☎ 020 7874 1531

Dr Yogini Jani Chief Investigator
E: y.jani@ucl.ac.uk
☎ 020 3456 7890 ext 7350

Mr Stephen Tomlin Principal Investigator
stephen.tomlin@gstt.nhs.uk
☎ 020 7188 9202

If you are still not happy and wish to comment in any other way,
you may contact:-

Patient Advice and Liaison Service (PALS) St Thomas' Hospital

Tel: 020 7188 8801/03

Research flowchart

Study information materials will be posted 3 weeks before your next clinic appointment

Two weeks later, we will make a phone call to see if you have received the postage and whether you are interested in taking part

When you come to register your renal clinic appointment, the research team will ask about your decision to participate in the study. If you decide to take part, you will have to sign the consent form

The researcher will screen through your medical notes to identify any medication related problems. You will then be randomly assigned to either the Standard Care or the Pharmaceutical Care group

Group A

Group B

The pharmacist will review your current medicines and discuss about problems you may have in taking them as prescribed (this may take approximately 20 minutes and will take place while you are waiting to see the doctor)

The pharmacist will then summarise relevant information on a note that will be delivered to your doctor. The doctor will discuss the matter with you to decide if there is a need for changes to the medicines or other possible solution

The researcher will evaluate the resolution of the identified problems from documentation in the medical notes

4 weeks later

If you are diagnosed high blood pressure, we will trace your blood pressure level from the medical notes. You do not have to come for any extra visit to the hospital apart from your scheduled renal clinic appointments.

Appendix 14 Study Information Leaflet for children aged 6 to 10 years

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Medicine-related Problems in Children with Chronic Kidney

When you come to the clinic, you see your doctor and nurse. The pharmacist also wants to see you.

Pharmacist takes care of your medicine. The pharmacist would like to talk to your mum and dad about your medicine.

The pharmacist will work with your doctor to help solve the problems that make you unhappy with your medicine.

If you like to take part, your mum and dad will have to give their consent. We will not share this information to anyone except for your doctor, nurse and the research team.

Appendix 15 Study Information Leaflet for children aged 5 and below

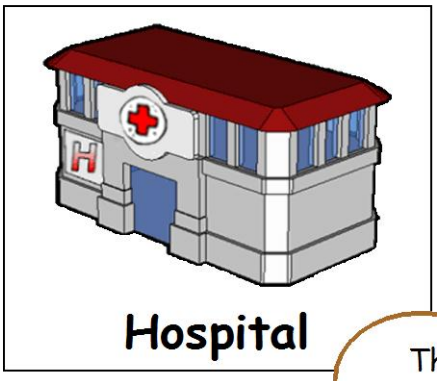
Information about the research – for children aged 5 and below/ Protocol V2-02112012/ 12/LO/0709

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Medicine-related Problems in Children with Chronic Kidney

This leaflet is intended for the parent/carer read to the child aged 5 years and below



Hospital

There are times I dislike my medicines

The pharmacist with Mum and Dad would be able to help me with my medicines

Appendix 16 Informed consent form

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Centre Number:
Study Number:
Patient Identification Number for this study:

CONSENT FORM

Title of Project: MEDICINE-RELATED PROBLEMS IN CHILDREN WITH CHRONIC KIDNEY DISEASE

Name of Researcher: NORKASIHAN IBRAHIM

Please initial in the box

1 I confirm that I have read and understand the information sheet dated..... (Version 2/25072012) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my (and my child's) participation is voluntary and that I am free to withdraw at any time without giving any reason, without my child's medical care or legal rights being affected. ☐

3 I understand that relevant sections of my medical notes and data collected during the study, may be looked at by research team from The Centre for Paediatric Pharmacy Research, (UCL School of Pharmacy, London), from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my child's records. ☐

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

Name of patient	Date	Signature
Name of person taking consent	Date	Signature

When completed, 1 copy for patient; 1 copy for researcher site office; 1 (original copy) to be kept in medical note

Appendix 17 Assent form

Guy's and St Thomas' NHS
NHS Foundation Trust

Centre Number:
Study Number:
Patient Identification Number for this study:

ASSENT FORM

Title of Project: MEDICINE-RELATED PROBLEMS IN CHILDREN WITH CHRONIC KIDNEY DISEASE

Child (or if unable, parent on their behalf) /young person to tick all they agree with:-	YES	NO
Have you read (or had read to you) about this project?		
Has somebody else explained this project to you?		
Do you understand what this project is about?		
Have you asked all the questions you want?		
Have you had your questions answered in a way you understand?		
Do you understand it's OK to stop taking part at any time?		
Are you happy to take part?		

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

Your name _____ Date _____

The pharmacist who explained this project to you needs to sign too:

Pharmacist Name _____ Sign _____ Date ____

When%completed,%1%opy%or%atient;%1%opy%or%esearcher%ite%ffice;%1%original%opy)%o%e%ept%n%medical%ote%%

Appendix 18 Medication review form (Pages 1-3)

Medication Review Form/ DRP in Children with CKD/Protocol V2-02112012/ 12/LO/0709 ID:

Centre Number:	
Study Number:	
Patient Identification Number for this study:	
Birth date	
Gender	Boy / Girl
Day of medication review	Mon / Tue / Wed / Thur / Fri
Date of medication review	
Pharmacist	1 / 2 / 3

1

Medication Review Form/ DRP in Children with CKD/Protocol V2-02112012/ 12/LO/0709 ID:

Instruction on using this form:

1. List down all medicines that the patient is currently taking in column A.
2. Review the clinic notes in the last 3 months to identify DRPs. Describe the problem in column B. Examples of drug problems are listed in Table 1. If a drug has more than 1 problem, the problem should be registered in different rows.
3. In column C, tick (√) **either** M or P. Tick M for manifested DRPs - Active problem associated with the use of prescribed and non-prescribed item that the patient is still on or may have received in the last 6 months. Tick P for potential DRPs - A DRP associated with the use of prescribed and non-prescribed item that the patient is still on or may have received in the last 6 months that can potentially happen if not prevented.
4. Record the causes of the problems in column D. If the possible causes are not listed in Table 1, please describe it in column D. Each drug problem can have more than 1 cause (maximum of 3 causes).
5. Record pharmacist's recommendation to solve the problems in column E.

Table 1 **Types of drug problems**

1	No effect of drug treatment: The DrugDRP has not improve or worsen patient's condition
	Effect of drug not optimal: The DrugDRP does not brings optimal therapeutic outcome
3	Wrong effect of drug: The DrugDRP resulted in unwanted outcome
4	Untreated indication: The drug is supposed to be prescribed/administered for a condition
5	Adverse drug reaction(non-allergic): Drug use within the normal dose for a recommended indication causing adverse event not related to the allergic reaction (including known side effects)
6	Adverse drug reaction(allergic): Drug use within the normal dose for a recommended indication causing adverse event due to an allergic reaction (involving the immune system)
7	Toxic adverse event: Drug use in a dose higher than recommended causing toxic effect
8	Unnecessary drug treatment: The DrugDRP was prescribed without an indication
9	Administration problems: There is a problem in the administration of the prescribed DrugDRP
10	Patient dissatisfied with therapy
11	Therapy failure: The DrugDRP does exert intended therapeutic outcome for an unknown reason
12	Others

Table 2 **Causes of drug problems**

1_1	Inappropriate drug (incl contar-indication)
1_2	No indication for drug
1_3	Inappropriate d-d, d-f combination (incl drug interaction)
1_4	Inappropriate duplication of therap grps/active ingredients
1_5	Too many drug prescribed for same indication
1_6	More cost effective drug available
1_7	Synergistic/preventive drug required and not given
1_8	New indication of drug treatment presented
1_9	Indication unnoticed
2_1	Inappropriate drug form
3_1	Dose too LOW
3_2	Dose too HIGH
3_3	Drug concentration too LOW
3_4	Drug concentration too HIGH
3_5	Dosage regimen not frequent enough
3_6	Dosage regimen TOO FREQUENT
3_7	No therapeutic drug monitoring
3_8	PK problem requiring dosage adjustment
3_9	Deterioration/improvement of disease and/or symptoms req dose adjustment
3_10	Prescribed dose difficult to measure for administration
4_1	Treatment duration TOO SHORT
4_2	Treatment duration TOO LONG
5_1	Prescribing error (a_decision making) (b_prescription writing)
5_2	Dispensing error
5_3	Inapp timing of administration and/or dosing interval
5_4	Drug administered to the WRONG PATIENT
5_5	WRONG DRUG administered
5_6	Prescribed drug NOT ADMINISTERED at all
5_7	Drug administered at the WRONG TIME
5_8	Drug UNDER administered
5_9	Drug OVER administered
5_10	Drug abuse (unregulated overuse)
6_1	Prescribed drug not available (reason to be described)
7_1	Patient refuse to take the prescribed drug
7_2	Patient forgets to take the prescribed drug
7_3	Patient unable to use the drug as prescribed
7_4	Patient uses unnecessary drug
7_5	Patient takes food / 'own drug' that is suspected to interact with the drug *(including OTC or items not prescribed or not known to prescriber)*
8_1	Unwanted side effect
8_2	Prescriber unsure of dosage regimen (dose and/or frequency)
8_3	Prescriber unsure of treatment duration
8_4	Illegible handwritting and/or inappropriate abbreviation
8_5	Poor documentation of drug history
8_6	Other unspecified causes

Medication Review Form/ DRP in Children with CKD/Protocol V2-02112012/ 12/LO/0709 ID:

A. Drug name and regimen	B. Type of drug problem	C.		D. What causes the drug problem? Refer Table 2 for causes of DRPs. If the cause(s) is not listed, describe it here.	E. What is the recommendation to solve this problem? If a solution is not possible/not required, please explain the reasons.
		(M)Manifested	(P)Potential		

Appendix 19 Screening tool for DRP by Gordon et al. (2005) – 4 pages

CONFIDENTIAL

SCREENING INTERVIEW SCHEDULE

IDENTIFICATION NUMBER:.....

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DAY OF INTERVIEW:.....

DATE OF INTERVIEW:.....

START TIME:..... FINISH TIME:..... Before consultation

START TIME:..... FINISH TIME:..... After consultation

ABOUT YOUR MEDICINES

1. Which GP surgery do you go to?	Which GP(s) do you usually consult?

2. Which pharmacy(ies) do you usually take your prescriptions to be dispensed?	Do you take all your regular prescriptions to this pharmacy? (Prompt: all rxs; more than ½ rxs; last 4 rxs)

3. Can you tell me the names of the prescription medicines you take or use. If you are unable to tell me any names, please describe them to me.
(Prompt: under-the-tongue spray, patches, water tablets, inhalers, creams)

1	8
2	9
3	10
4	11
5	12
6	13
7	14
8	15

About each medicine:

How many/much and how often do you take/use each day?	Do you know what you are taking/using this medicine for?	For how long have you been taking/using this medicine?
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		

What other medicines do you take or use? (Prompt: medicines/vitamins bought from the pharmacy, herbal or natural remedies/ teas, garlic, homeopathic remedies)

About each medicine:

What is the name of the medicine	What are you using this medicine for?	How often do you use this medicine? (Prompt: regularly with prescription medicines, how many times a year, last time)
1		
2		
3		

4. Does anyone help you with your medicines? (Prompt: to remember to take them, collect prescriptions from GP surgery or medicines from pharmacy)
Yes ❶1 No ❶2 If yes,

Who is this person?	How does this person help you?

ABOUT YOURSELF

5. May I ask how old you are?.....years (last birthday)

6. Where is your country of birth?

England	❶1
Scotland	❶2
Wales	❶3
Northern Ireland	❶4
Irish Republic	❶5
Other	❶6 (other than UK or Ireland)

For other, please tell me the present name of the country?.....In which year did you come to the UK?.....

Which ethnic group do you consider yourself to belong to?

White	❶1
Black-Caribbean	❶2
Black-African	❶3
Black-Other	❶4 Please describe:.....
Indian	❶5
Pakistani	❶6
Bangladeshi	❶7
Chinese	❶8
Any other ethnic group	❶9Please describe:.....

7. Do you live alone or with others?

Alone ❶1
With others ❷2Please tell me who:.....
Does patient fit inclusion criteria: Yes ❶1 ❷2, if no, why:
Insufficient english? ❶1; under 18 ❷2; first rx ❸3, mentally handicapped ❹4; Go to Q14

ABOUT THE ILLNESSES FOR WHICH YOU TAKE YOUR MEDICINES

8. In the past 5 years, have you:

a	been admitted to hospital?	Yes ❶1	No ❷2
b	attended or been taken to A&E/casualty?	Yes ❶1	No ❷2
c	called a GP as an emergency outside surgery hours (i.e. evenings or weekends)?	Yes ❶1	No ❷2
d	called a GP or made an appointment as an emergency during surgery hours (i.e. daytime)?	Yes ❶1	No ❷2

If yes, please tell me:

	Which year and month?	For what reason?	More about this. (Prompt: any follow up, any medicines changed or started?)
a			
b			
c			
d			

Do you:

e	attend hospital as an outpatient?	Yes ❶1	No ❷2
f	see any other person privately for your health? (Prompt: private doctor, osteopath)	Yes ❶1	No ❷2

If yes, please tell me,

	Who you see?	For what reason?	How often?	The last time you attended?
e				
f				

MORE ABOUT YOUR MEDICINES

9. Some people do not always take their medicines according to the instructions, but adjust the dose according to what they think they need. Do you do this?

Never	Rarely	Sometimes	Often	Very often
❶1	❷2	❸3	❹4	❺5

Tell me more about this? (Prompt: what do you mean, the last time, why)

People sometimes forget to take their medicines.
Do you do this?

Never	Rarely	Sometimes	Often	Very often
❶1	❷2	❸3	❹4	❺5

Tell me more about this. (Prompt: what do you mean, the last time, why)

What problems have you experienced with taking your medicines (Prompt: side effects, problems with 2 medicines taken together)

What would you do if you had a problem with taking your medicines? (Prompt: is problem solved)

ABOUT YOUR GP SURGERY & PHARMACY VISITS

10. How often do you usually consult / see your GP about your illnesses and regular medicines? (Prompt: e.g. blood pressure measurement)

Do you usually consult / see any other person employed at the surgery about your illnesses and regular medicines? (Prompt: nurse, dietician)
Yes ❶1 No ❷2 If yes, please tell me,

Who you see?	For what reason?	How often? (Prompt: last time)

How well does this arrangement at your surgery suit you? (Prompt: what do you mean?)

When was the last time you consulted / saw your GP or anyone else employed at the surgery about your illnesses or regular medicines?

Prompt	Date (month)	Who	Reason for visit
Before today			
Today			
Next time			

11. How do you usually get your prescriptions from your GP surgery?

Prompt: how do you order them	Prompt: how do you collect them

How often do you usually get prescriptions for your regular medicines
Every month ❶1
Every six weeks ❷2
Every two months ❸3
Every three months ❹4
Other ❺5 describe:.....

12. Have you ever delayed taking your prescription to the pharmacy, after your supply of medicines has run out? Yes ❶1
No ❷2

If yes, tell me more about this. (Prompt: the last time, why)

Have you ever talked to your pharmacist/chemist about any matters?
Yes ❶1 No ❷2

If yes, please tell me what matters. (Prompt: information on new medicines)

13. What do you think about the information you are given on your medicines? (Prompt: from who/where, what information)

Do you have enough information or would you like more?
Enough ❶1 More ❷2

If more, what suggestions do you have to improve this?

14. Are there any further comments about your medicines that you would like to add? (Any points we have not discussed)

Do you have any questions that you would like to ask me?

It is important that I see you again, but you are free to drop out of the study, at any stage, if you wish to do so.

I would like to ask you your permission to:
a) look at your medication records in your GP surgery and the pharmacy to check they contain the correct information about your medicines.

Yes ❶1 No ❷2

b) contact you again in about ..... weeks (or arrange a date ...../...../.....) to visit you in your home for another interview and ask you more questions about your medicines (this will include your views on the health service, and views on your illnesses and medicines) in greater detail.
Yes ❶1 No ❷2

If no, may I share this information with your GP/pharmacist?
Yes ❶1 No ❷2

For patients who consent
please may I have your:
Name (In print)
.....
Address
.....
.....
.....
.....
.....
Post code .....

Telephone 01 1 -.....
Patient's signature .....

For patients who do not consent
please may I ask why?:
a
.....
.....
.....
.....
.....
.....
.....
.....
b
.....
.....
.....
.....
.....
.....
.....
.....

THANK YOU VERY MUCH FOR YOUR TIME & YOUR HELP

Remember to insert interview finish time on page 1

nterviewer's comments and notes

Where were the interviews conducted:

IN THE GP SURGERY	IN THE PHARMACY
❶11 Lee Health Centre	❷21 Lords Pharmacy
❶12 Baring Road Medical Centre	❷22 Grove Park Pharmacy
❶13 Clapham Manor Health Centre	❷23 J Green Dispensing Chemist
❶14 Avicenna Health Centre	❷24 Medica Dispensing Chemist
❶15 Pavilion Medical Centre	
❶3 Patient's home	❷3 Patient's home

Is the patient: Male ❶1 Female ❷2

Is there a potential DRP:

Yes	No
❶ Study group - management affected	❷ Control group
❶ Study group - management not affected	

Comments and notes:
.....
.....
.....
.....
.....
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.....
.....
.....
.....
.....
.....

Appendix 20 Pharmacist Note

UCL

Guy's and St Thomas' NHS
NHS Foundation Trust

Pharmacist Note
Project Title: Medicine-related problems in Children with chronic kidney disease
Patient name /(Study ID):
Date :

Dear Doctor,

We have reviewed the medication list and interviewed..... (and parent/carer). Here are our findings and recommendations on the identified drug problems for your consideration. Please tick (√) in the yellow boxes if the recommendations are accepted. Thank you.

Medicine name and regimen	Problem description	Recommendation	Please tick (√) if the recommendation is accepted

Doctor's name & Initial: .....

NOTE:
When completed, 1 copy for researcher site office; 1 (original copy) to be kept in medical note

Appendix 21 Patient interview form (Pages 1-6)

Interview Form/ DRP in Children with CKD/F2-Protocol V2-02112012/ 12/LO/0709 ID:

UCL Guy's and St Thomas' NHS
NHS Foundation Trust

Study ID:	
Name: Birth date:	
Gender	Boy / Girl
Day of medication review	Mon / Tue / Wed / Thur / Fri
Date of medication review	
Pharmacist	1 / 2 / 3

Note for pharmacists:

1. This form consists of two sections. Part 1 is a screening tool to identify drug-related problems (DRPs) during medication review.
2. Part 2 is a screening tool to identify DRPs from patient interview. This part contains 5 questions.
3. All identified DRPs should be recorded in the DRP-Rf

The content of this form was adapted with permission from:

Gordon KJ, Smith FJ, Dhilon S. 2005. The development and validation of a screening tool for the identification of patients experiencing medicine-related problems. IJPP. 13(3): 187-193.

1

Instructions for Part 1:

1. Fill up Table 1. List down all medicines that the patient is currently taking in column A.
2. Review the clinic notes in the last 3 months to identify DRPs and describe them in column B.
3. In column C, tick either M or P. Tick M for manifested DRPs i.e. active problems associated with the medicine that the patient is still taking. Tick P for potential problems i.e. problems that could potentially occur and are associated with the medicines that the patient is taking.
4. Record the contributory factors of the DRPs in column D as listed in the DRP-Rf.
5. Record pharmacist's recommendations to solve the problems in column E.
6. Fill up Table 2 according to patients' input.

Interview Form/ DRP in Children with CKD/F2-Protocol V2-02112012/ 12/LO/0709 ID:

Part 1
Table 1: Refer to instructions on how to fill in this table.

ABOUT YOUR MEDICINES					
A. Drug name and regimen	B. Type of problems*	C.		D. DRP contributory factors*	E. Recommendations
		Manifested (M)	Potential (P)		
1 *Example:* *Lisinopril 10mg OD*	Effect not optimal	√ BP 160/80, proteinuria ++		Not taking medicine Dislike taste	Medication counselling
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
*Refer to the DRP-Rf					

Part 2

Table 2: Refer to instructions on how to fill in this table.

A. Can you tell me the names the medicines you (your child) take or use? If you are unable to tell me any names, please describe them to me. (Prompt: under-the-tongue spray, patches, water tablets, inhalers, creams)	B. How many/much and how often do you take/use each day?	C. Do you know what you are taking/using this medicine for? Y (yes) or N (no)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

Interview Form/ DRP in Children with CKD/F2-Protocol V2-02112012/ 12/LO/0709 ID:

Questions	Tick (√) when answered by parent/carer
1. Does anyone help you with your medicine? □ Yes If yes, who is this person? ..... □ No	
2. Children sometimes forget to take their medicines. Do you do this? Never Rarely Sometimes Often Very often 1 2 3 4 5 Pharmacist's comment:	
3. Some children do not always take their medicines according to the instructions, but adjust the dose according to what they think they need. Do you do this? Never Rarely Sometimes Often Very often 1 2 3 4 5 Tell me more about this? (Prompt: what do you mean, the last time, why)	
4a. (To child) Apart from what you just mentioned, what problems have you experienced with taking your medicines? □ Adverse drug reactions and drug interactions □ Cognitive, physical and sensory problems (ex: forgets, difficulties in taking medicine at school) □ Drug-prescribing problems □ Intentional non-compliance □ Monitoring and review of medicines, nclusding interface between primary and secondary care □ Problems with non-prescription medicines □ Lack of information or opportunity to discuss medicine related issues or concern with healthcare professionals □ Problems in the processes of obtaining repeat prescriptions through the GP or community pharmacy □ Problems with services from GP or community pharmacy □ Other problems:	

5

4b. (To parent): What problems have you experienced with managing medicines for your child? □ Adverse drug reactions and drug interactions □ Cognitive, physical and sensory problems (ex: forgets, difficulties in taking medicine at school) □ Drug-prescribing problems □ Intentional non-compliance □ Monitoring and review of medicines, nclusding interface between primary and secondary care □ Problems with non-prescription medicines □ Lack of information or opportunity to discuss medicine related issues or concern with healthcare professionals □ Problems in the processes of obtaining repeat prescriptions through the GP or community pharmacy □ Problems with services from GP or community pharmacy □ Other problems:	

Appendix 22 Study information leaflet for healthcare providers (Outpatient)

Leaflet for healthcare providers: Proposal V2/25072012

Pharmaceutical Care practice in resolving Drug Related Problems (DRP)

at the renal paediatric clinics

For circulation to healthcare providers
PHARMACY RESEARH PROJECT IN PAEDIATRIC NEPHROLOGY UNITS AT EVELINA CHILDREN'S HOSPITAL and GREAT ORMOND STREET HOSPITAL

Introduction on Pharmaceutical Care (PC) and Drug-related Problems (DRPs)

Pharmaceutical care (PC) is a concept in pharmacy practice that manages the prevention, identification and resolution of DRPs. A drug-related problem (DRP) is also known as a medicine-related problem or medication-related problem. By definition, a DRP is *"An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*. Pharmaceutical care services for renal paediatric patients in the NHS standard care are well accepted at the inpatient setting, but are yet to be established at the out-patient clinics. The global challenge in nephrology is to shift the emphasis of treating kidney disease from providing more kidney replacement therapy to early detection and prevention of progressive chronic kidney disease (CKD). Pharmaceutical care has an important role to play in achieving this target.

What is the aim of the study?

The aim of this study is to identify DRPs to test the study hypothesis that pharmaceutical care has a positive impact in resolving drug problems by at least 30% more than the standard care.

How long is the study period?

This study will be conducted from 1st September 2012 to 30th April 2013.

Why is this study important?

This study is part of one of the first research to identify problems related to the use of medicines among children with CKD by introducing PC services at the paediatric renal out-patient clinic. This study looks to build on significant clinical pharmaceutical skills available within the study sites and enhance the multidisciplinary team working together for patient benefit. The work will enhance the reputation of King's Health Partners and the name of Evelina Children Hospital and Great Ormond Street Hospital for Children by being transferable to practice across the country. Most importantly the research should help ensure that the children attending these clinics get the very best possible care (internally and during transition of care) and may potentially save money by reducing the negative impact of DRPs.

How will this study affect my daily work?

Your work is unlikely to be affected.

How will it be conducted?

This is a randomized control trial on the impact of on pharmaceutical care to identify and resolve drug problems in children seen at the tertiary paediatric nephrology clinics. Participants in the control arm receive the current standard care at the out-patient clinics; pharmacists are not directly involved in the management of patient's drug therapy at the clinic. If a new prescription is written, the pharmacist at the dispensary reviews the prescription as per standard care without. Participants who are allocated to the intervention arm receive pharmaceutical care; the pharmacist conduct medication review and patient interview with access to clinical notes to identify and solve drug problems. Please refer overleaf for the workflow and more information about this study.

Who do I speak to if I have further enquiries, suggestions or complaints?

For enquiries and suggestions, please contact the researcher, Ms Nor Ibrahim, by phone on 020 7874 1531 or by email on norkasihan.ibrahim.11@ucl.ac.uk

If you have any complaints about the way in which this study is being or has been conducted, please discuss them with Ms Nor Ibrahim in the first instance. If the problems are not resolved, or you wish to comment in any other way, you may contact:-

Dr Yogini Jani, Chief Investigator
The Centre for Paediatric Pharmacy Research (CPPR)
The School of Pharmacy, University of London
Tel: 084515555 extension 5000/73509
Email: yogini.jani@pharmacy.ac.uk

Patient Advice and Liaison Service (PALS)
1) Great Ormond Street Hospital for Children
Tel: 020 7829 7862
2) St Thomas' Hospital
Tel: 020 7188 7188

Appendix 23 List of drugs associated with DRPs by the first level of the WHO ATC Classification system (N=203)

WHO – ATC code	Counts
(A) ALIMENTARY TRACT AND METABOLISM (n=52)	
Alfacalcidol	4
Bisacodyl	1
Calcihew D3 Forte	4
Calcium acetate anhydrous	1
Calcium carbonate	5
Calcium lactate	1
Glycopyrronium bromide	1
Lactulose	1
Macrogol, combinations	1
Magnesium glycerophospate	1
Nystatin	16
Omeprazole	4
Ranitidine	11
(B) BLOOD AND BLOOD FORMING ORGANS (n=27)	
Acetylsalicylic acid	7
Darbopoetin alfa	4
Erythropoetin	5
Human albumin	1
Iron and multivitamins	1
Magnesium glycerophosphate	1
Sodium bicarbonate	2
Sodium chloride	2
Sodium feredetate	3
Sodium phosphate	1
Tranexamic acid	1
(C) CARDIOVASCULAR SYSTEM (n=10)	
Clonidine	1
Doxazosin	1
Enalapril	1
Furosemide	2
Midodrine	1
Nifedipine	2
Prazosin	1
Spironolactone	1

WHO – ATC code	Counts
(D) DERMATOLOGICALS (n=4)	
Fusidic acid	1
Gentamicin	1
Mupirocin	1
Zinc product	1
(G) GENITO URINARY SYSTEM AND SEX HORMONES	
Oxybutynin	2
(H) SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS (n=15)	
Hydrocortisone	1
Levothyroxine sodium	1
Methylprednisolone	4
Octreotide	1
Prednisolone	8
(J) ANTIINFECTIVES FOR SYSTEMIC USE (n=49)	
Amikacin	2
Amoxicillin	2
Amoxicillin and enzyme inhibitor	3
Cefotaxime	1
Ceftazidime	4
Ceftriaxone	1
Ciprofloxacin	6
Dapsone	2
Diphtheria-Hemophilus influenzae B-pertussis-poliomyelitis-tetanus vaccine	1
Flucloxacillin	1
Fluconazole	3
Ganciclovir	1
Gentamicin	1
Linezolid	1
Meningococcal polysaccharide groups A, C, Y and W135 vaccine	2
Metronidazole	1
Penicillin V	1
Piperacillin and enzyme inhibitor	3
Sulfamethoxazole and trimethoprim	2
Teicoplanin	1
Trimethoprim	5
Valganciclovir	2

WHO – ATC code	Counts
Vancomycin hydrochloride	2
Varicella vacine (live)	1
(L) ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS (n=11)	
Azathioprine	1
BCG Vaccine	2
Cyclophosphamide	1
Mycophenolic acid	2
Tacrolimus	5
(M) MUSCULO-SKELETAL SYSTEM (n=1)	
Pamidronic acid	1
(N) NERVOUS SYSTEM (n=23)	
Codeine	1
Levetiracetam	1
Morphine	6
Paracetamol	15
(P) ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS (n=1)	
Levamisole	1
(R) RESPIRATORY SYSTEM (n=7)	
Calcium lactate gluconate	1
Cetrizine	1
Chlorpheniramine	1
Cyclizine	2
Fluticasone	2
(S) SENSORY ORGANS (n=1)	
Dexamethasone and antiinfectives	1
(V) VARIOUS	
Polystyrene sulfonate	1

Appendix 24 Description of DRP cases and severity score (Inpatient)

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
1	2Y 2M	11.75	251	Tx	The desired concentration for Tacrolimus in a post renal transplant patient was between 8 and 10mg/L but this increased to 12mg/L possibly caused by its interaction with Fluconazole.	3.3
2	7M 6D	not available	not available	NDT	Sodium chloride 8mmols three times a day was increased to 9mmols three times a day in the past 7 days. However, mother was not aware of the dosage change and continued to administer 8mmols three times a day.	2.1
3	1Y 8M	9.1	401	HD	A Codeine suspension was prescribed 'as and when required' but no maximum dose frequency was stated.	3.7
4	4Y 7M	16.9	35	NDT	A patient developed unexplained fever; possibly caused by Levimasole which was prescribed for the past 6 months for the management of nephrotic syndrome. Influenza-like syndrome are among the common symptoms of prolonged treatment with Levimasole [CRP 5mg/L; WBC 7x10^9/L/L; blood culture showed no growth of any microorganisms]	2.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
5	3Y 3M	13	415	Tx	The patient was regularly taking Omeprazole 10mg once a day but was prescribed twice a day in hospital.	2
6	12Y 8M	53.2	629	PD	Oxybutynin 5mg was prescribed once a day. However, the recommended dosage frequency for the patient's age should have been twice a day.	1.9
7	9M 14D	5.5	321	NDT	The patient was taking Calcium carbonate 1000mg nightly and 250mg four times a day with snacks. However, the hospital had prescribed only 1000mg to be taken once a day. There were no plans to change the dosage regimen. [PO4 2.22mmol/L]	3.5
8	10M 16D	6.35	340	NDT	The patient regularly took SYTRON® 27.5mg twice a day but was prescribed three times a day on the ward. There were no plans to change the dosage regimen. [Hb 11.3g/dL; Transferrin saturation 33.5%]	1.5
9	1Y 2M	7.09	19	NDT	Liquid Sodium bicarbonate was prescribed but the prescription could not be fulfilled because the preparation was not available due to manufacturing problems.	1.7

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
10	44 DAYS	1.8	370	HD	IV Ranitidine 3.75mg (equivalent to 2mg/kg) three times a day was prescribed. The appropriate dose for the patient's age and renal function should have been in the range of 1 to 2mg (which is 0.5-1mg/kg) three times a day.	3.4
11	10M 16D	6.35	340	NDT	The patient's urine culture showed a strain resistant to Trimethoprim and therefore treatment with Trimethoprim should have been stopped.	3.9
12	2Y 2M	11.75	251	Tx	At 14 days post renal transplant, it transpired that the patient did not take Prednisolone for 5 days as it was suspended during IV Methylprednisolone therapy for graft rejection treatment and not restarted.	6
13	2Y 6M	14.7	672	PD	IV Ciprofloxacin 5mg/kg twice a day was prescribed, however the correct dose should have been 10-15mg/kg once a day as per the protocol. [PD fluid culture: Pseudomonas sensitive to Ciprofloxacin]	4.1

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
14	3Y 1M	15	689	Tx	Paracetamol 240mg four times a day was prescribed for post operative pain and febrile. However, the dosing frequency should have been amended to 'when required' because the patient was afebrile and no longer in persistent pain.	1.3
15	1Y 7M	13.4	80	Tx	Poorly dissolved Omeprazole enteric-coated granules may have caused clogging of the nasogastric tube. Treatment should have been changed to Lansoprazole orodispersible tablets, which are more soluble.	4.5
16	14Y 2M	37.7	1187	PD	The patient had a history of being allergic to Penicillin but this was not documented on the patient's medication chart.	6.2
17	9Y 3M	24.35	408	HD	55mg of an oral iron supplement taken once a day should have been changed to administration by injection as the patient's dialysis modality had been changed from PD to HD. The patient is susceptible for iron deficiency anaemia due to parental non-compliant. [Hb 8.2g/dL; Transferrin saturation 26%].	3

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
18	11Y 15D	3.8	185	PD	IV Paracetamol 60mg every (which equates to a dose of 15mg/kg) 6 hours as and when required was prescribed. However, the recommended dosage regimen for the patient's weight was 7.5mg/kg/dose every 4 to 6 hours.	4.6
19	12Y 2M	23.95	98	Tx	The patient was taking 37.5mg of Aspirin twice a week but was prescribed 37.5mg once a day in hospital. However, there were no plans to change the dosing frequency.	2.0
20	2Y 6M	14.7	672	PD	IV Amikacin 150mg once a day was prescribed and patient received 2 doses without drug level monitoring. The Amikacin trough level requested by the pharmacist on the third day before the next dose was 31mg/L.	5.1
21	8Y 9M	21	1124	PD	2500 units of Epoetin beta initially prescribed to be taken twice a week was increased to three times a week. The treatment should have been switched to 10mcg of Darbopoetin alfa once a week as it is more cost-effective for children over 20kg in weight.	1.3

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
22	9Y 3M	45	518	Tx	A patient had constipation possibly caused by IV Morphine which was prescribed for the past 10 days for post-operative pain. The condition did not noticeably improve with a combination of Lactulose and Doccusate Sodium treatment. A third agent (e.g. MOVICOL®) should have been prescribed to promote a synergistic effect.	2.9
23	4Y 7D	16.9	35	NDT	After IV Cyclizine administration, the patient developed a whole body rash and complained of 'heart started to race' and dizziness. The aforementioned symptoms developed immediately after the administration of IV Cyclizine. It was noted that the patient had a history of allergic reactions to Cyclizine in previous hospital admissions but this had not been documented on the patient's medication chart.	7
24	9M 10D	6.42	53	NDT	IV Ranitidine 10mg twice a day was prescribed on the discharge prescription. However, the dosage form should have been stated tablets instead.	1.9
25	10Y 7M	25.25	46	PD	The patient was taking one tablet of Calcichew (calcium carbonate) three times a day but had been prescribed one tablet of Calcihew D3 Forte (calcium carbonate-vitamin D3 combination) three times a day. There were no plans to change the treatment; and the recommended dosage frequency for Calcichew D3 Forte is once a	1.7

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
					day. [Ca 1.71mmol/L; PO4 1.92mmol/L; Alb <20g/dL] [Each Calcichew D3 Forte tablet contains 500mg of Calcium carbonate and 10mcg of vitamin D3] [Each Calcihew tablet contains 500mg of Calcium carbonate].	
26	1Y 11M	11.28	229	PD	The patient's dialysis was temporarily suspended after the removal of the haemodialysis access. The dosage regimen for IV Ceftazidime 120mg every 24 hours, which was previously prescribed while the patient was on dialysis, should have been changed to every 48 hours.	4
27	7Y 4M	19	295	PD	Intraperitoneal Ciprofloxacin was prescribed on the discharge prescription. The treatment duration was stated as '28 days' but should have been '10 days'.	3.6
28	1Y 9M	11.9	53	NDT	Alfacalcidol was suspended during a clinic assessment due to the patient's low level of parathyroid hormone but was continued when the patient was in hospital. There were no recent PTH levels measured and no notes detailing when the treatment should be restarted. [PTH level taken 2 weeks prior to hospital admission was 27ng/L].	3.1

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
29	1Y 10M	12	218	PD	The patient was prescribed Chlorpheniramine 'as and when required' for the management of purpuric rash. However, a regular dose of three times a day should have been prescribed as the patient was constantly itching [Urea 24.6mmol/L].	2.3
30	13	3.6	415	Tx	IV Ceftazidime for the prevention of surgical site infection was not prescribed on the pre-operation prescription.	4.7
31	17Y 10M	38.75	553	HD	Dapsone 75mg once a day was prescribed for the preceding 6 months for PCP prophylaxis post renal transplant but may have resulted in worsening anaemia. The patient also had cardiac and pulmonary disease; two risk factors that are suscpetible to Dapsone induced haemolytic anaemia [Cr 553μmol/L; Hb 6.5g/dL].	5.5
32	2Y 9M	13.9	613	HD	IV Paracetamol 210mg (0.21ml) four times a day was prescribed. The dose should have been rounded to down to 200mg (0.2ml) for ease of administration.	0.7

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
33	9M 10D	6.42	53	NDT	Oral Ranitidine 10mg twice a day was changed to IV Ranitidine 10mg twice a day. However, the appropriate dosage regimen for IV Ranitidine should have been 6mg three times a day. The recommended IV Ranitidine dosage frequency for the patient's age and renal function was 1mg/kg three times a day.	2.1
34	5M 8D	7.3	218	PD	IV Piperacillin/Tazobactam was prescribed for the wrong patient.	4.5
35	12Y 6M	41	232	Tx	Neutropenia was possibly caused by Mycophenolate Mofetil which was prescribed for the last 6 months [WBC 3.2 x10^9/L; MMF level 0.3 mg/L].	3.1
36	8Y 9M	21	1124	HD	The patient completed treatment with broad spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been stopped as per the protocol.	1.2
37	9Y 6M	24	279	Tx	Co-Trimoxazole for the treatment of PCP and urinary tract infection prophylaxis post transplant was not prescribed. The patient was at day 3 post transplant. All patients should have received PCP prophylaxis post transplant as per the protocol.	3.5

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
38	9Y 1M	28	585	Tx	Paracetamol 540mg four times a day was prescribed. However, the dosage should have been determined by taking into account the rounded to nearest measureable dose for ease of administration. Paracetamol tablets are available is in strengths of 500mg and 1000mg.	0.9
39	2Y	23.75	25	NDT	Methylprednisolone for IV Rituximab premedication was prescribed as daily dose but should have been a 'stat' dose and not continued.	4.1
40	2Y 11M	15.1	127	Tx	IV Amikacin 150mg once a day was prescribed but level monitoring was not ordered. The daily drug level should have been monitored for the first three days in order to prevent toxicity.	4.3
41	11Y 15D	3.8	185	PD	Morphine suspension 0.243ml (4.87mg) four times a day was prescribed. However, the dose should have been rounded down to 0.24ml (4.8mg) for ease of administration. The recommended dose for the patient's age was from 5 to 10mg.	0.6

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
42	14Y 2M	37.7	1187	PD	Calcium carbonate 1.5g was prescribed three times a day. However, this did not prove to be a sufficient dose in order to control serum phosphate levels because the patient snacked between main meals. The dosage should have been amended to take into account snacking between main meals. [PO4 2.7 mmol/L; CorCa 1.58mmol/L; PTH 959 ng/L]	3.3
43	9M 10D	6.42	53	NDT	IV Co-Amoxiclav was prescribed for a urinary tract infection but the dose was not stated.	2.6
44	6Y	14.7	218	NDT	Bisacodyl 1.6mg once a day was prescribed. However, the recommended dose based on the patient's body weight and age should have been 3.3mg once a day.	1.8
45	1M 30D	3.8	35	NDT	5mg of IV Furosemide was administered after an albumin infusion. However, within the same hour as the IV Furosemide was administered, the patient had already received 4mg of Furosemide in tablet form. This resulted in the patient having a systolic blood pressure of 60mmHg. The recommended Furosemide dose for the patient's age is 2 to 8mg which equates to 0.5 to 2mg/kg divided into 2 to 3 doses a day.	5.5

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
46	11M 15D	3.8	185	PD	IV Fluconazole was prescribed for a fungal infection. Nystatin which had previously been prescribed for candidiasis prophylaxis while the patient was on broad spectrum antibiotics should have been stopped.	2.5
47	2Y 6M	14.7	672	PD	Ranitidine 1.66ml (25mg) twice a day was prescribed but should have been rounded up to 2.0ml (30mg) in order to simplify administration. The recommended Ranitidine dose for the patient's age and renal function is 1-2mg/kg twice a day.	0.1
48	4M 24D	3.2	47	NDT	A 'stat' dose of 3mg IV Furosemide for administration at 0600hrs was prescribed twice.	3.8
49	12Y 8M	53.2	629	PD	The patient was taking two tablets of Calcichew (calcium carbonate) three times a day but had been prescribed two tablets of Calcihew D3 Forte three times a day (calcium carbonate-vitamin D3 combination). The patient was already taking Alfacalcidol. There were no plans to change the treatment; and the recommended dosage regimen for Calcichew D3 Forte is one tablet once a day. [Ca 2.47mmol/L; PO4 2.0mmol/L] [Each Calcihew D3 Forte tablet contains 1250mg of Calcium carbonate and 10 mcg of vitamin D3] [Each Calcihew tablet contains 500mg of Calcium carbonate]	2.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
50	10M	23.3	633	NDT	Morphine suspension 4.54ml (9.08mg) four times a day was prescribed; however, the dose should have been rounded down to 4.5ml (9.0mg) for ease of administration.	0.4
51	8Y 9M	21	1124	NDT	Calcium polystyrene sulfonate 20g once a day was prescribed for the management of hyperkalaemia. The prescribed dose should have been divided into 3 to 4 doses adjusted against the serum potassium level of 5mmol/L in order to avoid severe potassium depletion.	4.5
52	8Y 9M	21	1124	PD	Intraperitoneal Ciprofloxacin was prescribed for PD peritonitis but the treatment duration was not stated.	2.7
53	11M 15D	3.8	185	PD	Fluconazole 25mg once a day was prescribed for fungal infection prophylaxis. The correct dose based on the patient's age and dialysis modality should have been a 25mg-loading dose and a subsequent dose of 12.5mg once a day.	3.4
54	7Y 5M	27.8	480	Tx	Valganciclovir 500mg once a day was prescribed for the treatment of cytomegalovirus prophylaxis. The correct dose based on the patient's body surface area and renal function should have been 90mg once a day.	6.4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
55	6Y 7M	23.2	53	NDT	Doxazosin 2mg once a day was prescribed for the past 7 days but did not prove effective in improving systolic blood pressure. The dose should have been increased. [The patient's SBP was in the range of 130-140mmHg; the target range was 111-123mmHg].	2.7
56	8M 19D	3.2	540	NDT	Ranitidine 0.5ml (7.5mg) three times a day was prescribed but the patient was administered 5ml (75mg) three times a day. The recommended dose for the patient is in the range of 3.2 to 6.4mg (equivalent to 1-2mg/kg) three times a day.	5.7
57	11M 15D	3.8	185	PD	Oxybutynin 12.5mg twice a day was prescribed. However, the correct dosage regimen should have been 0.5mg once a day. [The recommended Oxybutynin dose for children less than 2 years old is 0.1-0.2mg/kg/day; the maximum dose is 1.25mg three times a day].	6.1
58	9Y 3M	24.35	408	HD	IV Ciprofloxacin 5mg/kg twice a day was prescribed. However, the correct dose should have been 10 to 15mg/kg once a day as per the protocol. [PD fluid culture: E. coli sensitive to Ciprofloxacin].	4.4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
59	9Y 1M	28	585	Tx	Morphine suspension 6.46mg (0.32ml) 'as and when required' was prescribed. However, the dose should have been rounded down to 6mg (0.3ml) for ease of administration. The recommended dose for the patient's age was from 5 to 10mg.	0.4
60	1Y 3M	7.7	229	PD	Mupirocin 2% ointment was prescribed for topical application around the gastrostomy site. The correct preparation should have been Mupirocin intransal ointment because Mupirocin 2% ointment contains polyethylene glycol (macrogol) which is not compatible with plastic tubing.	3.2
61	11M 15D	3.8	185	PD	Fluconazole was not prescribed post nephrostomy tube insertion but should have been prescribed for candidiasis prophylaxis as per the protocol.	3.6
62	11M 15D	3.8	185	PD	Trimethoprim 8mg was prescribed to be taken nightly. However, the aforementioned was a duplicate prescription as the patient was already taking 8mg of Trimethoprim twice a day.	1.9

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
63	8Y 9M	21	1124	NDT	Live attenuated vaccines were administered in the same week as the Tuberculin test takes place. The Tuberculin test should have taken place four weeks later as it suppresses the effect of vaccination.	3.5
64	44 DAYS	1.8	370	HD	IV Linezolid 20mg (equivalent to 11mg/kg) three times a day was prescribed. The recommended dose for the patient's age was 18mg (equivalent to 10mg/kg) three times a day. [Cr 370µmol/L; TBil <2µmol/L; ALP 106 IU/L; ALT 13 IU/L].	1.5
65	3Y 1M	15	689	Tx	Co-Trimoxazole (a combination of Trimethoprim and sulphamethoxazole) was prescribed for post renal transplant prophylactic treatment of PCP. Trimethoprim that was already prescribed for prophylactic treatment of recurrent urinary tract infection should have been stopped.	1.9
66	6Y 10M	27.15	64	Tx	The patient was 6 months post transplant. Nystatin for candidiasis prophylaxis should have been stopped as per the protocol.	0.8

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
67	11Y 8M	63.5	53	NDT	The patient received Prednisolone 60mg once a day for the management of nephrotic syndrome but steroid-induced gastritis prophylaxis treatment was not prescribed for.	3.1
68	45.7	10.08	184	NDT	Liquid Ciprofloxacin was prescribed on the discharge prescription but the patient would have preferred 'tablet' form.	1.9
69	15Y 7M	20	933	HD	The patient's weight was 20kg but was misread as 30kg. This error resulted in 600mg of Paracetamol being prescribed four times a day. The correct dose should have been 400mg four times a day.	5.7
70	12Y 10M	116.2	174	NDT	Hydrocortisone 100mg premedication for IV Rituximab infusion was prescribed in tablet form. The prescription should have been prescribed for an injection form. Patient was never exposed to Rituximab. [Rituximab infusion-related side effects are frequently reported primarily during the first infusion].	3.1

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
71	3Y 2M	15.2	25	Tx	The patient was taking Aspirin 15mg once a day but was prescribed 7.5mg once a day in the hospital. However, there was no documentation to suggest a change in dose.	1.8
72	1Y 10M	12	218	PD	The patient was prescribed Paracetamol 'as and when required' for pain due to purpuric rash. However, regular doses of Paracetamol should have been prescribed as the patient was in constant pain.	3.2
73	1M 30D	3.8	35	NDT	Spironolactone prescribed for the previous 4 days for the management of congenital nephrotic syndrome may have been the cause of hypernatremia. At this point, Spironolactone should have been suspended. [Na baseline was 137mmol/L, Na four days after Spironolactone was 132mmol/L].	3.7
74	8Y 6M	22.5	500	HD	The patient was taking 1.5g of calcium carbonate three times a day but the hospital prescribed 1.5g to be taken three times a week. No plans to change the dosing frequency were documented. [Ca 1.34mmol/L; PO4 1.8mmol/L; Alb 42g/L].	3.9

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
75	9Y 3M	28.5	56	Tx	A patient at 5 weeks post transplant missed 1 day of steroid treatment because Prednisolone was not restarted after IV Methylprednisolone pulse doses for the treatment of graft rejection.	2.7
76	9Y 1M	28	585	Tx	Methylprednisolone 45mg twice a day was prescribed on day 1 post renal transplant. However the dose should have been 22mg twice a day as per the protocol. The recommended Prednisolone dose day 1 to day 3 post-op is 60mg/m2/day in two separate doses [BSA 0.75m2].	3.3
77	4Y 11M	20.35	169	NDT	A PAMIDRONATE® infusion of 15mg every 24 hours for the treatment of hypocalcaemia was prescribed but the termination date was not stated. The recommended dosage regimen should have been for infusions over 2 to 4 days based on the daily serum calcium level in order to avoid severe hypocalcaemia. [Ca 2.3mmol/L]	4.4
78	6Y 7M	23.2	53	NDT	IV Clonidine that was prescribed for the past 5 weeks for the management of resistant hypertension was stopped abruptly. Clonidine should have been withdrawn gradually in order to avoid hypertensive crisis.	5.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
79	2Y 3M	9.6	169	Tx	Post-op Prednisolone 52.2mg was prescribed after a renal transplant. The total daily dose of Prednisolone 7 days post-op should have been adjusted from 52.2mg to 50mg as per the protocol.	0.7
80	9M 10D	6.42	53	NDT	Sodium chloride 1mmol twice a day was prescribed on the discharge prescription. However, the correct dose should be 11mmol twice a day.	4.5
81	3Y 1M	15	689	Tx	IV Fluconazole was prescribed for a fungal infection. Nystatin which was previously prescribed for candidiasis prophylaxis while the patient was taking broad spectrum antibiotics should have been stopped.	0.5
82	1Y 8M	9.1	194	PD	Paracetamol 5.62ml (135mg) four times a day was prescribed. However, the dose should have been rounded down to 5.7ml (134.4mg) for ease of administration. The recommended dose for the patient's age was 120 to 240mg every 4 to 6 hours as and when necessary.	0.6
83	1Y 8M	9.1	194	PD	135mg of Paracetamol was prescribed 'as and when required' but the maximum dosage frequency was not stated.	3.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
84	15Y 6M	40.9	871	PD	The patient was reluctant to comply to taking MOVICOL®, Doccusate Sodium and Lactulose which had been prescribed in the past 8 days for the management of impacted faecal matter. However, when the patient did take the treatment this resulted in positive bowel movement and output and therefore the ongoing treatment should have been simplified as per the protocol.	2.8
85	7Y 5M	27.8	41	Tx	Valganciclovir 400mg once a day was prescribed for the treatment of cytomegalovirus prophylaxis. The dose should have been optimised to 500mg as the patient's renal function had improved. [Previous Cr 120μmol/L; Current Cr 41μmol/L].	3.6
86	1Y 10M	12	218	PD	IV Ceftriaxone 960mg once a day was prescribed. However, the recommended dosage regimen for the patient's age and renal function should have been approximately 500mg once a day.	4.3

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
87	14Y 8M	35.3	63	Tx	Ranitidine 140mg twice a day was prescribed. However, the recommended dose for the patient's age and renal function should have been 150mg twice a day.	0.4
88	14Y 9M	53.7	661	NDT	The patient was taking two tablets of Calcichew (calcium carbonate) three times a day but had been prescribed two tablets of Calcihew D3 Forte (calcium carbonate-vitamin D3 combination) three times a day. The patient was already taking Alfacalcidol. There were no plans to change the treatment; and the recommended dosage regimen for Calcichew D3 Forte is one tablet once a day. [Ca 2.54mmol/L; PO4 2.14mmol/L] [Each Calcihew D3 Forte tablet contains 1250mg of Calcium carbonate and 10 mcg of vitamin D3] [Each Calcihew tablet contains 500mg of Calcium carbonate].	3.4
89	6Y 7M	23.2	53	NDT	Glycopyrronium 1mg once a day did not effectively improve hypersalivation; the dosage regimen should have been optimised to 1 to 2mg three to four times a day.	2.8

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
90	3Y 1M	15	689	Tx	Tacrolimus induction therapy was prescribed 30 minutes prior to the living donor renal transplantation the day of the operation. However, Tacrolimus should have been administered one hour prior to the operation as per the protocol.	0.9
91	17Y 4M	45.2	445	Tx	During a clinic visit, Darbopoetin alfa was increased from 40 to 80mcg to be taken once a week. One week later, the dose was again increased from 80mcg to 100mg to be taken once a week in hospital. However, the patient did not receive the previously prescribed doses (40mcg and 80 mcg once a week). [Hb 7.9 g/dL].	2.9
92	5M 5D	2.23	23	NDT	Sudocream was prescribed as 'Pseudocream'.	0.2
93	12Y	32	393	Tx	At day 7 post transplant the patient was prescribed Prednisolone of which 35mg was to be taken in the morning and 25mg at night. However, the correct doses for weaning the patient off medication should have been 30mg in the morning and 25mg at night.	1.8
94	9Y 1M	28	585	Tx	Flucloxacillin empirical therapy for PD exit site infection that was prescribed before the patient's renal transplant should have been stopped, as the patient was 5 days post transplant and the PD catheter had been removed.	1.5

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
95	2Y 2M	11.75	251	Tx	IV Fluconazole was prescribed for a fungal infection. Nystatin which was previously prescribed for candidiasis prophylaxis while the patient was taking broad spectrum antibiotics should have been stopped.	0.3
96	6Y 7M	23.2	53	NDT	IV Octreotide prescribed for the past 14 days for the management of gastrointestinal bleeding was abruptly stopped. It should have been withdrawn gradually by halving the infusion rate every 6 to 12 hours.	3.6
97	9M	9.3	252	PD	Intraperitoneal Vancomycin was prescribed on the discharge prescription. The treatment duration was stated '28 days' but should be '11 days'.	4.2
98	12Y 2M	23.95	98	Tx	Tacrolimus was prescribed a post transplant patient but the brand name was not stated. The dispensary kept 3 different brands of Tacrolimus. The patient was on regular doses of Tacrolimus (PROGRAF®).	3.1

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
99	6Y 7M	23.2	53	NDT	Ranitidine 3.33ml (50mg) twice a day was prescribed and rounded down to 3.0ml (45mg) in order to simplify administration. The recommended Ranitidine dose for the patient's age and renal function is in the range of 46 to 93mg (equivalent to 2-4mg/kg) twice a day.	0.4
100	7	22.4	96	Tx	Alfacalcidol 0.25mcg once a day was prescribed '0.25mo' once a day in hospital.	2.8
101	9Y 3M	3.12	518	Tx	A post renal transplant patient was prescribed 30mg of Prednisolone to be taken in the morning and 30mg at night. The night dose was abruptly reduced from 30mg to 15mg within 24 hours when it should have been reduced by 5mg per day for 3 days in accordance with the protocol.	1.7
102	13	3.6	415	Tx	Nifedipine MR tablets were prescribed but patient could not swallow tablets or capsules. The prescription should have been changed to liquid Nifedipine.	2.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
103	17Y 10M	38.75	553	HD	A patient experienced suicidal thoughts possibly caused by Levetiracetam 1250mg twice a day, which was prescribed for the previous 3 months. The maximum recommended dose for patient's age, weight and renal function is approximately 400mg twice a day. [Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents including Levetiracetam].	7
104	9Y 6M	24	279	Tx	1000mg of Tranexamic acid was required to be applied to the haemodialysis exit site in order to prevent local haemorrhaging during dialysis. However an IV route of administration was prescribed.	4.6
105	11M 15D	8.9	415	PD	A second dose of Meningococcal vaccine that should have been scheduled to be administered three weeks after the first dose as per the trial protocol was not referred to in the treatment plan.	3.3
106	17Y 10M	38.75	553	HD	Dapsone treatment for PCP prophylaxis continued 7 months post transplant but should have been stopped at 6 months post transplant as per the protocol.	1.5

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
107	9M	9.3	252	PD	Nystatin was prescribed on the discharge prescription. The treatment duration was stated as '28 days' but should have been '11 days'.	0.9
108	9Y 10M	23.3	633	NDT	The patient was taking 6 tablets of Calcichew (calcium carbonate) three times a day; but had been prescribed 6 tablets of Calcihew D3 Forte three times a day in hospital. There were no plans to change the treatment; and the recommended dosage regimen for Calcichew D3 Forte is one tablet once a day. [Ca 2.36mmo/l, PTH 62.3ng/L] [Each Calcihew D3 Forte tablet contains 1250mg of Calcium carbonate and 10 mcg of vitamin D3] [Each Calcihew tablet contains 500mg of Calcium carbonate]	4.7
109	8Y 9M	21	1124	NDT	Calcium carbonate 2000mg four times a day was prescribed for the past 7 days but did not effectively control serum phosphate levels despite diet restrictions. The treatment should have been switched to Calcium acetate [Ca 1.29mmol/L; PO4 3.13mmol/L; PTH 168ng/L].	2.4
110	15Y 7M	20	933	HD	A loading dose of 6mg IV Morphine was prescribed when a dose of 4mg (the correct dose) should have been prescribed. [The recommended loading dose for the patient's age was 0.1-0.2mg/kg].	3.7

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
111	1Y 7M	13.4	80	Tx	The patient had PTH level at the higher end of normal range and hypocalcaemia and should have been treated with vitamin D supplements [PTH 58ng/L; Ca 2.02; Alb 24 g/dL; CorCa 2.44mmol/l]	2.7
112	15Y 7M	20	933	HD	The patient's weight was 20kg but was misread as 30kg. This error resulted in 30mg of Cyclizine being prescribed three times a day. The correct dose should have been in the range of 10 to 20mg three times a day.	4.1
113	1M 27D	3.6	65	NDT	Co-Amoxiclav was prescribed on the patient's discharge prescription. The dosing frequency was stated as 'three times a day' but should have been 'once a day' based on the patient's age.	3.6
114	12Y 5M	91	641	HD	The patient was taking 37.5mg of Aspirin on dialysis days but was prescribed three times a day in hospital. However, there were no plans to change the dosing frequency.	4.4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
115	10.9	6.12	19	NDT	The patient had a history of being allergic to Penicillin but this was not documented on the patient's medication chart.	5.5
116	15Y 10M	61.95	762	NDT	IV Gentamicin was prescribed for the management of septicaemia but serum drug level was not monitored. This resulted in acute kidney injury. The patient had also received iodine radiocontrast which may worsen kidney injury. [Cr baseline not available; Cr on presentation 762μmol/L].	7.4
117	13	3.6	415	Tx	The patient's Omeprazole dose was increased from 10mg once a day to 20mg once a day while the patient was on high dose steroid treatment. The dose should have been changed back to 10mg once a day after the steroid treatment had been completed.	2.2
118	12Y 2M	23.95	105	Tx	Epoetin beta 2500units once a day was prescribed. However, the recommended dosage frequency is twice a week. [Hb 9.0 g/dL]	4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
119	9M 10D	6.42	53	NDT	IV Co-Amoxiclav was prescribed for a urinary tract infection but duplicated treatment as the patient was already taking oral Amoxicillin. The oral antibiotic treatment should have been stopped before the IV antibiotic commenced.	1.9
120	6M 3D	29.8	42	Tx	IV Cefotaxime was prescribed but the treatment duration was not stated.	2
121	5M 19D	8	279	NDT	IV Piperacillin/Tazobactam 570mg (equivalent to 71mg/kg) twice a day was prescribed. However, the correct dose based on the patient's renal function should have been 730mg (equivalent to 90mg/kg) twice a day.	2.9
122	7Y 5M	27.8	283	Tx	Prednisolone was prescribed at Day 0 post renal transplant but the dose was not stated.	3.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
123	14Y 9M	49.7	320	Tx	Nifedipine capsule 10mg twice a day was prescribed. However, the dosing frequency should have been three times a day. [The manufacturer' s dosing frequency for Nifedipine preparations are as follows: three times a day for capsules, twice a day for modified release tablets and once a day for slow release tablets].	2.2
124	7Y 4M	19	295	PD	A 50mcg in 5ml preparation of Levothyroxine was prescribed on the discharge prescription. However, the appropriate preparation should have been 25mcg in 5ml because there was problem in obtaining supply for the 50mcg in 5ml preparation during that period.	1.3
125	3Y 1M	15	689	Tx	Aspirin was prescribed on the discharge prescription. The instruction for GP to continue the prescription after the patient has completed 14 days treatment was stated as 'yes' but should have been 'no'.	3.7
126	2Y 9M	13.9	613	HD	Ranitidine 75mg (equivalent to 5.4mg/kg) twice a day was prescribed. The appropriate dose for the patient's age and renal function should have been in the range of 14 to 28mg (equivalent to 0.5-1mg/kg) twice a day.	4.6

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
127	5M 19D	8	239	NDT	Paracetamol 120mg 'as and when required' was prescribed but the maximum dose frequency was not stated.	3.6
128	2Y 3M	9.6	169	Tx	Aspirin 10mg once a day was prescribed on the discharge prescription but the dispensary produced a label stating that 25mg was to be taken once a day.	4.4
129	3Y 1M	12	220	PD	Paracetamol 180mg four times a day was previously prescribed for pyrexia but should have been stopped because the patient was no longer presenting with pyrexia.	2.8
130	1Y 2M	7.09	19	NDT	The patient was prescribed a phosphate supplement on the discharge prescription. The dose stated was '2.8mmols three times a day' but should have been '4mmols three times a day'.	3
131	7Y 5M	27.8	283	Tx	The patient was prescribed IV Ceftazidime 1.4g twice a day but the correct dosage frequency based on the patient's renal function should have been once a day.	4.4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
132	12Y 5M	91	641	HD	Repeated serum magnesium level was below the normal range. Magnesium supplements should therefore have been prescribed. [Mg 0.59mmol/L]	2.0
133	32D	4.1	21	NDT	A 50mcg stat dose of Prazosin was prescribed but 500mcg was administered. The recommended dose for children is 10-15mcg/kg/dose.	5.5
134	8Y 9M	21	1124	NDT	The Varicella vaccination for a renal transplant candidate was not scheduled as part of the pre-transplant treatment plan.	3.4
135	2Y 2M	2.88	36	NDT	Maxitrol eye ointment preparation that was intended for topical application at the gastrotomy site was prescribed for administration on both eyes.	3.7
136	3Y 1M	15	689	Tx	Methylprednisolone induction therapy was prescribed 30 minutes prior to the living donor renal transplantation on the day of the operation. However, Methylprednisolone should have been administered one hour prior to the operation as per the protocol.	1.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
137	7Y 4M	19	295	PD	Intraperitoneal Vancomycin was prescribed on the discharge prescription. The treatment duration was stated as '28 days' but should have been '10 days'.	3.6
138	3Y 1M	15	689	Tx	Paracetamol was prescribed on the discharge prescription. The treatment duration was stated as '28 days' but should have been '11 days'; and the instruction for GP to continue prescribing was stated as 'yes' but should have been 'no'.	2.6
139	9Y 1M	28	585	Tx	Fusidic acid cream empirical treatment for PD exit site infection should have been stopped as the patient was no longer on dialysis.	1.9
140	9Y 9M	26.4	1027	Tx	Azathioprine was administered 8 hours pre-transplant but should have been administered post transplant as per the transplant protocol.	1.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
141	1M 30D	3.8	35	NDT	20% Human albumin was mixed with IV Furosemide. However, the manufacturer's compatibility report does not recommend Human albumin to be mixed with other medicinal products except the recommended diluent (e.g. 5% glucose or 0.9% sodium chloride).	2.8
142	1M 30D	3.8	35	NDT	Enalapril that is indicated for the management of congenital nephrotic syndrome was prescribed without a test dose. A test dose with a short acting ACE-inhibitor (e.g. Captopril 50mcg/kg) is recommended to prevent severe hypotension in neonates.	3.8
143	11Y 8M	63.5	53	NDT	Penicillin 250mg four times a day was prescribed for the treatment of prophylaxis against gram positive infection in glomerulonephritis. However, the correct frequency for prophylactic treatment should have been twice a day.	2.9
144	16Y 11M	62	178	Tx	IV Piperacillin/Tazobactam was changed to Co-Amoxiclav tablets but both antibiotics were prescribed on the discharge prescription.	2.9

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
145	14Y 2M	37.7	1187	PD	The patient was prescribed Calcium (SANDOCAL®) but the dose not stated. This resulted in the patient receiving 1000mg tablets instead of the usual prescription of 400mg tablets three times a day.	4.3
146	1M 30D	3.8	35	NDT	The patient has been hospitalised on a long-term basis for congenital nephrotic syndrome. A Diphtheria vaccination is a requirement at 2 months of age but appears to have been overlooked as it was not in the treatment plan.	3.4
147	16Y 11M	62	178	Tx	Injections of Metronidazole were prescribed on the discharge prescription but oral Metronidazole should have been prescribed instead.	2.4
148	11M 15D	3.8	185	PD	The haemoglobin concentration achieved was 13g/dL as a result of the patient receiving Epoetin beta treatment. The Epoetin dose at the time was not reviewed.	2.9

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
149	4Y 1M	16.8	893	PD	Teicoplanin 160mg twice a day was prescribed. However, the correct dosing regimen based on the patient's renal function should have been 55mg once a day hours for 3 days and subsequently 30mg once a day maintenance dose.	3.8
150	8Y 7M	21	1124	PD	The BCG vaccination for a renal transplant candidate was not scheduled as part of the pre-transplant treatment plan.	4
151	15Y 1M	51.8	280	NDT	IV Cyclophosphamide 750mg once a month was prescribed for the management of systemic lupus erythematous. However, only half of the total dose was administered because the patient developed acute chronic renal failure. The remaining dose, which was supposed to be given in 2 weeks, was not documented in the treatment plan. [Cr 280μmol/L; BSA: 1.5m2].	3.6
152	15Y 7M	20.7	933	HD	The patient was taking SERETIDE® accuhaler (combination of Fluticasone and Salmeterol) but was prescribed FLIXOTIDE® accuhaler (Fluticasone monotherapy) in hospital. There were, however, no plans to change the combination treatment.	3.6

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
153	1Y 8M	9.1	401	HD	Midrodrine 1.25g once a day was prescribed but did not effectively prevent intradialysis hypotension. The dose should have been optimised to 2.5mg as per the protocol.	4.2
154	2Y 11M	14.7	114	Tx	Prednisolone pulse doses for the management of graft rejection were prescribed 'stat' without an accompanying continuation schedule. The Prednisolone pulse doses should have been prescribed for at least 3 days as per the protocol.	4.2
155	11Y 15D	33.15	67	Tx	Ganciclovir 80mg twice a day was prescribed but this dose should have been increased to 160mg twice a day based on the renal status of the patient at the time. [Previous GFR 30ml/min/1.7m3; Current GFR 80ml/min/1.7m3].	5
156	9Y 9M	26.4	1027	Tx	Methylprednisolone, which was supposed to be administered post renal transplant, was not prescribed. It should have been prescribed as per the protocol.	3.3

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
157	8Y 9M	21	1124	HD	The patient was on treatment with broad spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per the protocol.	3.6
158	3Y 4M	15	38	NDT	Paracetamol 250mg 'as and when required' was prescribed but the maximum dose frequency was not stated.	3.6
159	11Y 9M	9.48	264	Tx	Darbopoetin alfa treatment was increased from 20mcg to 40 mcg once a week. The correct dose based on the patient's weight should have been 30mcg once a week. [Hb 10.9g/dL] [The recommended Darbopoetin alfa dose is 1mcg/kg]	1.8
160	11M 15D	3.8	185	PD	Trimethoprim 14mg twice a day was prescribed. However, the recommended dose for the patient's age, weight and renal function should have been approximately 8mg twice a day.	2.8
161	12Y 6M	41	232	Tx	A post renal transplant patient experienced diarrhoea possibly caused by combination of high Tacrolimus level. The patient was also prescribed Mycophenolate mofetil 750mg twice a day. [Patient's Tacrolimus level was 20mg/L].	3.7

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
162	8Y 9M	21	1124	PD	SYTRON® 5ml (27.5mg iron) once a day prescribed in the past 14 days did not effectively improve haemoglobin levels. The dose should have been optimised to approximately 15ml (80mg) divided into 2 to 3 doses as recommended for the patient's age. [Hb 7.1g/dL; Transferrin saturation 20%] [Other relevant medicine was Epoetin beta 2000 units twice a week].	3.4
163	17Y 10M	38.75	553	HD	Epoetin beta was prescribed as a daily dose but should have been prescribed three times a week for a patient on haemodialysis.	4
164	1Y 11M	11.28	229	HD	IV Ceftazidime 230mg three times a day was prescribed. However, the recommended dose based on the patient's renal function was approximately 120mg once a day.	5
165	4Y 2M	16.6	55	NDT	Calcium carbonate, which was prescribed for hyperphosphatemia during the oliguric phase of acute kidney injury, was no longer required and should have been stopped. [Levels during kidney injury was PO4 level 2.5mmol/L; Cr 297μmol/L] [Levels after AKI episode was PO4 1.7mmol/L; Cr 55μmol/L].	2.9

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
166	14Y 8M	35.3	63	PD	Co-trimoxazole 425mg was prescribed once a day for the treatment of urinary tract infection prophylaxis but was rounded up to 480mg for ease of administration (one tablet is 480mg). However, the recommended dose for the patient's weight was 420mg (equivalent to 12mg/kg) once a day.	1
167	8Y 9M	21	1124	PD	Patient's serum phosphate levels gradually increased from 1.12mmol/L to 1.68mmol/L within 3 days. However, phosphate binder treatment that was previously suspended not restarted.	2.6
168	11M 15D	3.8	185	PD	Trimethoprim 8mg twice a day was prescribed for prophylactic treatment of post micturating cystourethrogram (MCUG). However, the correct frequency for prophylactic treatment should have been once a day.	1.3
169	5M 5D	2.23	23	NDT	Omeprazole 6mg was prescribed once a day for administration via a nasogastric tube. However, the dose should have been 5mg for ease of administration. [Tablet Omeprazole is available in 10mg and 20mg strengths].	0.5

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
170	3Y 1M	15	689	Tx	Prednisolone 32mg once a day was prescribed post-op renal transplant. The total dose should have been divided into two separate doses of 16mg twice a day as per the protocol.	1.7
171	9M 14D	5.5	321	NDT	The patient was taking '1000 units' of Epoetin beta once a week but the hospital had prescribed '2 units' once a week.	4
172	1Y 8M	9.2	394	PD	Gentamicin cream for the treatment of PD exit site infection prophylaxis was prescribed for the previous 6 weeks. However, the treatment should have been stopped after 4 weeks as per the protocol. [PD fluid culture was negative]	2.3
173	11Y 15D	3.8	185	PD	Paracetamol suppository 540mg was prescribed as and when required. However, the preparation available at the dispensary is 240mg suppository.	2.3

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
174	12Y 9M	65.2	96	Tx	Mother forgot to serve two doses of Tacrolimus. Patient was at 1.5 months post transplant. [Cr baseline is approximately 70-80μmol/L; Cr on presentation 96μmol/L; Tacrolimus level on presentation 5mg/L; Tacrolimus target range 8-10mg/L]	4.5
175	7Y 5M	27.8	283	Tx	Omeprazole 10mg once a day was prescribed for the prevention of gastritis during treatment with high a dose steroid. However, the correct dose should have been 20mg once a day.	2
176	3Y 3M	13	415	Tx	The patient was prescribed Ranitidine for steroid induced gastritis prophylaxis but was already taking Omeprazole.	1.6
177	8Y 9M	21	1124	PD	IV Morphine 2.1mg three times a day was prescribed. The dose should have been rounded down to 2.0mg for ease of preparation.	0.4
178	15Y 6M	40.9	871	PD	The patient was diagnosed with eosinophilic peritonitis and therefore should have been prescribed an antihistamine.	1.4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
179	1Y 8M	9.2	394	PD	Tablet Ciprofloxacin 90mg once a day was prescribed for the previous 6 weeks for urinary tract infection prophylaxis but should have been stopped as the urine culture test was giving negative results.	1.9
180	14Y 9M	53.7	658	PD	Darbopoetin alfa for renal anaemia was prescribed as a 'stat' dose. However, the recommended dose frequency is once a week.	2.4
181	15Y 6M	42	40	NDT	The patient was regularly taking 500mg of Mycophenolate Mofetil twice a day for the treatment of lupus nephritis. However, the patient was prescribed 500mg of Mycophenolate Mofetil once a day in the hospital. There was no plan to change the dosage regimen.	5.4
182	8Y 9M	21	1124	PD	Darbopoetin alfa for administration on dialysis days was not prescribed on the discharge prescription.	2.5
183	13Y 10M	60.9	715	HD	A Furosemide infusion of 20mg/hour was prescribed. However, the patient was already receiving a regular dose of 100mg Furosemide tablets twice a day. The oral Furosemide should have been suspended and only restarted depending on the patient's response to the infusion.	4.1
184	16Y 11M	62	178	Tx	The patient was regularly taking Alfacalcidol 1mcg once a day but was prescribed 0.1mcg in hospital.	3.4

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
185	14Y 9M	49.7	320	Tx	Tacrolimus was prescribed a post transplant patient but the brand name was not stated. The dispensary kept 3 different brands of Tacrolimus. The patient was on regular doses of Tacrolimus (PROGRAF®).	3.3
186	12Y 9M	65.2	96	Tx	Paracetamol 1000mg as and when required was prescribed but the maximum dose frequency was not stated.	3.7
187	1M 44D	1.95	233	NDT	Acute renal failure was possibly caused by IV Amikacin prescribed for 5 days in total for the management of septicaemia at the local hospital. However, the drug level was not monitored.	6.6
188	3Y 1M	15	689	Tx	Fluconazole was prescribed on the discharge prescription. The instruction for GP to continue after the treatment completed was stated as 'yes' but should have been 'no'.	3.5
189	12Y 8M	53.2	629	PD	IV Paracetamol 1000mg as and when required was prescribed for post catheter insertion pain. However, the maximum dosage frequency was not stated. The patient was also taking 1000mg tablets of Paracetamol every 6 hours.	5.1

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
190	2Y 9M	9.7	499	PD	Patient was taking DIALYVITE® one tablet a day but had not been prescribed in hospital. There was no documentation to suggest that DIALYVITE® had been intentionally omitted.	1.3
191	15Y 7M	20.7	933	HD	Ranitidine 1.33ml (20mg) twice a day was prescribed but should have been rounded up to 1.4ml (21mg) in order to simplify administration. The recommended Ranitidine dose for the patient's age and renal function is 1-2mg/kg twice a day.	0.2
192	9M 14D	9.3	252	PD	Paracetamol was prescribed on the discharge prescription. The treatment duration was stated as '28 days' but should have been '11 days'.	2.8
193	2Y 10M	9.6		Tx	The patient completed treatment with broad spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been stopped as per the protocol.	2.4
194	8Y 7M	22.5		HD	The patient completed treatment with broad spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been stopped as per the protocol.	2.3
195	4M 13D	7.3		PD	The patient completed treatment with broad spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been stopped as per the protocol.	1.2

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (μmol/L)	RRT		
196	1Y8M	9.2		PD	Aspirin was prescribed on the discharge prescription. The instruction for GP to continue the prescription after the patient has completed 14 days treatment was stated as 'yes' but should have been 'no'.	1.2
197	2D			NDT	The patient was taking SERETIDE® accuhaler (combination of Fluticasone and Salmeterol) but was prescribed FLIXOTIDE® accuhaler (Fluticasone monotherapy) in hospital. There were, however, no plans to change the combination treatment.	1.2
198	1D	1.8		HD	The patient was being treated with broad-spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per protocol.	1.9
199	5Y11M	13.8		NDT	The patient was being treated with broad-spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per protocol.	1.9
200	17Y4M	45.2		Tx	The patient was being treated with broad-spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per protocol.	1.9

DRP No	Patient's details				Drug-related problems	Severity Score[£]
	Age	Weight (kg)	Cr (µmol/L)	RRT		
201	4Y1M	16.8		PD	The patient was being treated with broad-spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per protocol.	1.9
202	5M	8.0		NDT	The patient was being treated with broad-spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per protocol.	1.9
203	2Y2M	11.8	Tx		The patient was being treated with broad-spectrum antibiotics; Nystatin for candidiasis prophylaxis should have been prescribed as per protocol.	1.9

[§] Severity score: Minor (0-<3), Moderate (3-<7), Severe (7-10)
(HD) Haemodialysis, (PD) Peritoneal dialysis, (Tx) Post transplant, (NDT) Not on HD, PD or Tx

Appendix 25 Description of DRP cases and severity score (Outpatient)

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
1	14Y 5M	53.8	171.9	SAH	Doxazosin 1mg daily is prescribed in combination with Atenolol 50mg daily for hypertension; but patient stopped taking Doxazosin for the previous 6 months because of feeling dizzy and tired when taking in combination with Atenolol [BP 138/52mmHg]	4.8
2	19Y 6M	70.6	181.7	SSNS	Mycophenolate Mofetil is prescribed but patient is unsatisfied with treatment because of inadequate information on its side effects.	3.9
3	3Y 2M	14.5	96.3	STG5	One Alpha Calcidol 0.25mcg a day is prescribed for the prevention of hyperparathyroidism, but patient has problems in obtaining supply from the community. [PTH 566 (previous level 93 ng/l); CorCa 2.41mmol/l)]	3.9
4	4Y			STG3A	Magnesium Glycerophosphate is prescribed but patient is dissatisfied because the tablets are too big, chalky and taste awful.	3.6
5	10Y 6M	48.4	142.4	HSPN	Patient complains of acne; this could be caused by long-term treatment with Prednisolone 60mg daily, prescribed for Henoch Schönlein purpura nephritis.	3.2
6	13Y	61.4	146.7	SRNS	Mycophenolic acid is prescribed for steroid-resistant nephrotic syndrome but patient has problems in taking the medicines as GP surgery refuses to supply.	4.9

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
7	7Y 5M	22	116	STG4	Patient struggles to take Sytron at home because dislikes the taste [Ferritin 65ug/L, Hb 11.5g/dl]	2.1
8	17Y 6M	36.4	142.3	STG5	Patient is on a transplant workout requiring Pneumococcal vaccine; but an updated vaccination record requested from the GP surgery has not been obtained for over 5 months.	2.9
9	14Y 5M			1Y PTx	A patient at 6 months post transplant has Tacrolimus toxicity as shown from a renal biopsy [Tacrolimus level 8ng/l (target level is 6-7ng/L), Serum creatinine 121umol/L (baseline 87umol/L)]	4.5
10	8Y 8M			9Y PTx	A patient who has been hyponatremic for the last 6 months refuses to have sodium supplement dose increased [Na 130mmol/l, Sodium Chloride dose 1200mg three times a day (12 tablets/day)]	4.8
11	2Y	9.9	80.7	NC	One Alpha Calcidol has been prescribed for the past 8 months, but patient has been supplied with vitamin D3 from the community.	3.9
12	14Y 9M			MCNS	Myfortic 540mg twice a day is prescribed, but patient is unable to obtain refill as the community pharmacy is unable to get supply.	4.7
13	3Y 2M	13.5		STG 5	Sodium Bicarbonate 10mmol three times daily is prescribed, but patient has problems in obtaining supply from the community [HCO^3 21mmol/l].	3.5

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
14	11Y	39.5	143	SSNS	The family wants the patient to take alternative medicines to complement the prescribed treatment; but patient is dissatisfied with having to take alternative medicine together with prescribed medicines.	2.4
15	7Y 5M	23	120	STG4	Patient struggles to get sufficient supply of Ferrous Sulphate from the community whenever going away on extended periods of holiday.	2.3
16	7Y 4M			9Y PTx	Neutropenia was possibly caused by Azathioprine 75mg daily which was prescribed for the last 6 months [Neutrophil 0.8 x10^9].	4.9
17	11Y 2M	35.8	140	CRF	Melatonin liquid is prescribed but patient has problem in obtaining extra supply of Melatonin from the community whenever going away on extended periods of holiday.	2.8
18	3Y 6M			1Y PTx	Mycophenolate Mofetil liquid 0.85mg twice a day is prescribed but patient has problem in obtaining extra supply from the community.	5
19	7Y 5M	23	120	STG4	Patient struggles to get sufficient supply of Sodium Bicarbonate from the community whenever going away on extended periods of holiday.	3.7

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
20	11Y	39.5	143	SSNS	Patient complains of gastrointestinal upset; which is possibly caused by combination of Prednisolone and Mycophenolic Mofetil. Ranitidine for the prevention of steroid-induced gastritis is prescribed at alternate day dosing instead of twice daily as per family request in order to take alternative medicines. [The recommended dosing frequency for oral Ranitidine is twice a day].	4.3
21	8Y 5M	65.3	138.4	STG3B	Metformin for weight loss is prescribed at full dose at community; the dose should have been reduced by 25% of normal dose based on patient's renal function to prevent lactic acidosis [GFR 40, BMI 36.6].	5.2
22	7Y 5M	23	120	STG4	Sodium Bicarbonate 3 tablets three times a day is prescribed but patient sometimes forgets to take the lunchtime dose if out and about.	3.4
23	7Y 5M	23	120	STG4	Patient finds it difficult to swallow Ferrous Sulphate because of the large tablet size.	3
24	9Y 9M	18.1	114	STG 3B	Lisinopril liquid is prescribed at 2.5mg daily; but patient has problems obtaining sufficient supply from the community.	3.5
25	3Y 6M	17.3	96.9	1Y PTx	Patient has difficulty in taking Mycophenonate Mofetil because of problems with nasogastric tube reinsertion which is relied on for medication.	5.3

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
26	10Y 8M	41	136	SDNS	Prednisolone is prescribed at 35mg daily for 6 days and to be continued with 10mg alternate days during nephrotic relapse; but patient misunderstood and took 4 days of 35mg and continued with 10mg alternate days. [Albumin 39g/l, Scr 66 (baseline 45-50umol/l)]	4.7
27	6Y			SDNS	Prednisolone 10mg alternate days is prescribed and patient is instructed to increase the dose to 60mg daily during relapses of nephrotic syndrome. However, patient has difficulties in obtaining adequate supply from the community during relapse.	5.2
28	6Y 7M	21	106	PGN	Patient developed facial stigmata due to chronic use of steroid.	4.6
29	15Y 9M	169	51	STG4	Forceval is prescribed at a dose of 1 tablet daily, but patient does not comply with treatment.	2.2
30	3Y 2M	13.3	93.2	STG5	One Alpha Calcidol liquid dose prescribed from the hospital is 0.25ml (0.5mcg) once a day, but patient receives 0.25mcg capsules from the GP.	3.7
31	7Y 5M	23	120	STG4	Patient struggles to get sufficient supply of Folic Acid from the community whenever going away on extended periods of holiday.	2.2
32	3Y 6M			1Y PTx	One Alpha Calcidol is prescribed but patient has problems in ordering and obtaining adequate supply from the community.	3.1

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
33	11Y 5M			9Y PTx	Tacrolimus is prescribed for post kidney transplant but the prescription is not repeated by GP surgery.	5.4
34	17Y 6M	36.4	142.3	STG5	Patient is on a transplant workout requiring vaccination for Meningitis; but an updated vaccination record requested from the GP surgery has not been obtained for over 5 months.	3.1
35	3Y 5M	17.3	96.9	1Y PTx	Patient has difficulty in taking Prednisolone because of problems with nasogastric tube reinsertion which is relied on for medication.	4.9
36	15Y 9M	169	51	STG4	Sodium Bicarbonate 1g twice a day but patient is not compliant with treatment.	4.3
37	11Y 11M			SDNS	Patient is prescribed Cyclosporine for focal segmental glomerulosclerosis; but had not been attending clinic since the dose was adjusted 8 months ago.	5.3
38	3Y 6M	17.3	96.9	1Y PTx	Patient has difficulty in taking One Alpha Calcidol because of problems with nasogastric tube reinsertion which is relied on for medication.	3.8
39	16Y 8M	48.5	156.3	5Y PTx	Tacrolimus 1.5mg twice daily is prescribed but patient takes 2.5mg twice daily.	5.7
40	3Y 2M			SSNS	Prednisolone 40mg daily is prescribed for 4 weeks in a weaning schedule following nephrotic relapse; but patient stops taking Prednisolone after 2 weeks.	4.7

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
41	11Y 2M	43.4	128.8	7Y PTx	The 12 hours' trough Tacrolimus level taken in clinic is 1ng/l. The patient is unsure of current medications. [Target level is 4ng/l, Scr stable 79umol/l]	5.3
42	5Y 8M	15.6	93.6	STG4	Patient has problems in taking Sodium Bicarbonate consistently at home because of inadequate supply from the community.	3.6
43	5Y 11M	16.6	103.3	STG5	Sodium Bicarbonate 15mmol three times a day is prescribed but patient has problem in obtaining supply from the community.	3.4
44	2Y 11M	11	78	STG4	Calcium Carbonate liquid 360mg three times daily is prescribed but patient has problem in obtaining supply from the community.	3.5
45	16Y 8M	48.5	156.3	5Y PTx	One Alpha Calcidol was increased from 0.25 to 0.3mcg four weeks ago, but patient still takes 0.25mcg because preparation is only available in 0.25mcg, 0.5mcg and 1mcg capsules.	3
46	3Y	13.5		STG 5	Sodium Chloride 15mmol daily is prescribed, but patient has problems in obtaining supply from the community. [Chloride 102mmol/l]	3.6
47	7Y 11M	23	120	STG4	Cephalexin liquid is prescribed for urinary tract infection prophylaxis. Patient struggles to get sufficient supply of Cephalexin liquid from the community whenever going away on extended periods of holiday.	3.4

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
48	5Y 7M	16.6	103.3	STG5	Dialyvite Multivitamin is prescribed but patient has problem in obtaining supply from the community.	2.7
49	19Y 6M	70.6	181.7	SSNS	Patient is unsatisfied with steroid treatment because of inadequate information on its side effects.	3.2
50	15Y 10M	49.4	159	3Y PTx	Patient complains of diarrhoea when started taking Ferrous Fumarate in the past 1 week.	3
51	15Y 9M	169	51	STG4	Bisacodyl 1 tablet daily is prescribed but patient is not compliant with treatment	2.6
52	3Y 9M	12.9	94	9Y PTx	Sodium Bicarbonate 4mmol three times a day is prescribed, but patient has difficulty in obtaining extra supply from the community whenever going away on extended periods of holiday.	2.7
53	18Y 9M	136	175.3	SAH	Increased level of alanine transaminase, possibly induced by long-term use of Fluoxetine.	4.5
54	4Y 6M			1Y PTx	Prednisolone 5mg every other day is prescribed but patient has a problem in obtaining supply from the community.	4.8
55	16Y 7M			GFR40	Patient refuses to take Magnesium Glycerophosphate because dislikes the taste.	4.1

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
56	14Y 6M			MCNS	Adcal D3 caplets are prescribed 2 daily; but patient is not compliant in taking them because tablets too large to swallow and dislikes the taste. [Adcal D3 is a calcium and vitamin D supplement]	3.9
57	17Y	44.2		SRNS	A nephrotic patient is responsive to Cyclosporine and alternate day Prednisolone therapy but non-compliant with dosing schedule. This could possibly contribute to the ongoing proteinuria [Urine protein 3+, Alb 36g/L, Cyclosporine trough 66ug/L].	4.9
58	17Y 6M	36.4	142.3	STG5	Patient is on a transplant workout requiring vaccination for Hepatitis B; but an updated vaccination record requested from the GP surgery has not been obtained for over 5 months.	4.2
59	15Y 2M	51.5	162	3Y PTx	Patient buys Spatone iron supplement over the counter, which is quite expensive; other cheaper alternatives could be obtained on prescription.	1
60	9Y 2M	25.7	127.6	PKD	Patient experienced mood swing and sleep disturbance possibly due to side effects of Prednisolone.	3
61	11Y			1Y PTx	Risperidone is prescribed for the management of aggressive behaviour but patient refuses to take it.	3.6
62	3Y 9M	12.4	90	STG3A	Antibiotic prophylaxis for urinary tract infection is prescribed but patient refuses to take it.	3.5

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
63	4Y 6M			1Y PTx	Tacrolimus is prescribed in post renal transplant but patient has problems in obtaining correct prescriptions and adequate supply from the community.	5
64	16Y 10M	81	176	STG4	Vitamin D3 is prescribed for the management of hyperparathyroidism, but patient is not compliant with treatment [PTH 97 (previous level 63ng/l)].	4.2
65	4Y 6M	17.3	96.9	1Y PTx	Patient has difficulty in taking Sodium Bicarbonate because of problems with nasogastric tube reinsertion which is relied on for medication.	3.7
66	10Y 8M	28	127	1Y PTx	Tricitrate 30ml four times a day is increased to 31ml for hypokalemic symptoms; but patient does not receive the new dose from the community and still experiences symptoms.	3.7
67	15Y 9M	169	51	STG4	Enalapril is prescribed at 2.5mg daily but patient is unsure of medications and not complying with treatment.	4.2
68	16Y 5M	65.9	158.7	SRNS	Patient complains of feeling tired and weak all the time; could possibly be caused by long-term side effect of Cyclosporine; the patient is also taking Prednisolone alternate days.	4
69	15Y 9M	169	51	STG4	Trimethoprim 50mg daily is prescribed for recurrent urinary tract infection; but patient is unsure of medications and not complying with treatment.	3.1

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
70	5Y 11M	16		STG5	Sodium Bicarbonate tablet 1g three times a day is prescribed in combination with Sodium Bicarbonate liquid 15mmol three times a day; but patient only takes the liquid formulation because having problems in obtaining supply of the tablets from the community [HCO3 18mmol/l].	3.1
71	4Y 6M			1Y PTx	Sodium Bicarbonate is prescribed but patient has a problem in obtaining supply from the community.	3.5
72	16Y 5M	44.2		SRNS	A nephrotic patient is responsive to Cyclosporin and alternate day Prednisolone therapy but non-compliant with dosing schedule. This could possibly contribute to the ongoing proteinuria [Urine protein 3+, Alb 36g/L, Cyclosporin trough 66ug/L].	5.8
73	15Y 7M	45	163	STG3B	Forceval capsule is prescribed but patient has difficulty in obtaining supply from the community due to national supply problem.	2.4
74	16Y 5M	36.4	142.3	STG5	Patient is on a transplant workout requiring Varicella vaccination; but an updated vaccination record requested from the GP surgery has not been obtained for over 5 months.	3.4
75	11Y 5M			9Y PTx	Mycophenolate mofetil is prescribed for post kidney transplant but prescription not repeated by GP surgery.	5.9
76	11Y 9M			9Y PTx	Itraconazole is prescribed for a post kidney transplant patient but prescription not repeated by GP surgery.	5.4

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
77	13Y 5M	104.8		4Y PTx	Patient complains of acne; this could be caused by long-term treatment with Prednisolone.	3.6
78	5Y 7M	17.8	103.5	STG 3B	Patient is dependent on nasogastric tube and experienced difficulty in taking Sodium Chloride 5mmol (1ml) three time a day orally.	2.9
79	4Y 6M	17.3	96.9	1Y PTx	Patient has difficulty in taking Tacrolimus because of problems with nasogastric tube reinsertion which is relied on for medication.	5.1
80	10Y 1M	35.4	134.8	SDNS	Unable to take post-12 hours Tacrolimus level because patient missed previous night's dose.	4.5
81	5Y 9M	18	99	2Y PTx	Tacrolimus is prescribed but patient had problems in ordering and obtaining adequate supply from the community.	5.5
82	11Y 5M			9Y PTx	Prednisolone 7.5mg alternate days is prescribed for post kidney transplant but prescription not repeated from the community.	5.7
83	9Y 9M	18.1	114	STG 3B	Sodium Bicarbonate 5mmol three times a day is prescribed but patient takes it twice a day as the midday dose is missed.	3.3
84	5Y 7M	17.8	103.5	STG 3B	Patient is dependent on nasogastric tube and experienced difficulty in taking Sodium Bicarbonate 20mmol twice a day orally.	3.7

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
85	13Y	61.4	146.7	SRNS	Patient complains of being forgetful, feeling tired and sometimes 'grumpy', possibly due to side effects of Prednisolone.	3.7
86	1Y 5M	11	78	NS PKD	Sodium Bicarbonate 6mmol three times a day is prescribed but patient has a problem in obtaining supply from the community.	4.1
87	4Y 6M	13.5		STG 5	Calcium carbonate 300mg three times daily is prescribed for the prevention of hyperphosphatemia, but patient has problems in obtaining supply from GP and local chemist. [PO4 1.3mmol/l]	3.5
88	9Y 9M	18.1	114	STG 3B	Patient complains of constipation after taking Sytron and thus stopped taking it at home.	3
89	3Y 6M	17.3	96.9	1Y PTx	Treatment for Attention Deficiency Hyperactivity Disorder (ADHD) should have been started 3 months ago; but this is delayed as the Community Paediatrician is unsure of potential interaction between the newly prescribed medication for ADHD and immunosuppressants that patient is currently taking.	3.6
90	5Y 7M	17.8	103.5	STG 3B	Patient is dependent on nasogastric tube and experienced difficulty in taking Sytron 10mls once a day orally.	2.1
91	15Y 9M	169	51	STG4	One Alpha Calcidol is prescribed at 0.75mcg a day, but patient is not compliant. This could possibly contribute to elevated parathyroid hormone [PTH level 163ng/l (previous level 103 ng/l)].	4.7

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
92	8Y 8M			SDNS	A patient missed two doses of Tacrolimus prior to clinic appointment. Tacrolimus was switched from Mycophenolic acid 2 months ago due to frequent nephrotic relapse.	4.1
93	13Y 6M	35.8	147.3	STG3	Lisinopril 5mg daily is prescribed but patient is not compliant with treatment.	4.1
94	13Y 9M	35.8	147.3	STG3	Nitrofurantoin 50mg daily is prescribed but patient is not compliant with treatment.	3.1
95	17Y 6M	37	142.3	STG5	Patient ran out of medication supply and missed 7 days of Sodium Bicarbonate 1.5g three times daily [HCO 19mmol/l].	5.3
96	2Y 1M	9.6	78	STG4	Sodium Chloride 2.5mmol four times a day is prescribed; but patient takes half the dose for two days due to difficulties in obtaining supply from the community.	4.6
97	18Y	136	175.3	SAH	Increased alanine transaminase, possibly caused by long-term use of Fluoxetine.	5.3
98	17Y 6M	36.4	142.3	STG5	Patient is on a transplant workout requiring HIB vaccination; but an updated vaccination record requested from the GP surgery has not been obtained for over 5 months.	3.5
99	8Y 8M			SDNS	Patient is Cushingnoid; this could possibly caused by prolonged high dose steroid.	4.4

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
100	3Y 2M			SSNS	Levamisole is restarted as steroid sparing agent following nephrotic relapse for 4 weeks; but patient takes the medicine only for the first 2 weeks [Urine protein 2+].	4.9
101	7Y 3M	19		STG4	Patient developed widespread erythemateous uticaria rash over whole body which started a few days after taking Amoxicillin for upper respiratory tract infection.	5.4
102	18Y	70.6	181.7	SSNS	Clonidine is prescribed for the management of hypertension; but patient is unsatisfied with treatment because of inadequate information on its side effects.	4.3
103	17Y 8M	65.9	158.7	SRNS	Patient complains of feeling tired and weak all the time; this could possibly caused by long-term side effect of Prednisolone. The patient is also taking Cyclosporin.	4.4
104	15Y 9M	169	51	STG4	Unsure of medications and not complying with taking Calcium Carbonate during meal times.	4.6
105	15Y 9M	169	51	STG4	Ferrous Fumarate 400mg once a day is prescribed but patient is not compliant.	3.3
106	5Y 7M	18	105	CRF	Itraconazole is prescribed for gene therapy, but patient is unable to finish the treatment because could not tolerate the side effects - vomiting and diarrhoea.	4.7

DRP No	Patient's details*				Drug-related problems	Average Score *
	Age**	Weight (kg)	Height (cm)	Kidney disease***		
107	7Y 3M	27.7	122.7	SDNS	Patient experiences abdominal pain possibly caused by the combination of Prednisolone 15mg alternate days and Mycophenolate Mofetil 750mg twice a day; but prophylaxis for steriod-induced gastritis is not prescribed.	5.3
108	11Y	39.5	143	SSNS	Acne on face possibly related to Prednisolone.	3.7
109	13Y 2M	59.3	158.2	SLE	Mycophenolate Mofetil is prescribed but patient has problem in obtaining regular supply from the community due to different pack sizes, which are available in either 50 or 100 tablets per pack.	3.4
110	5Y 8M	15.6	93.6	STG4	Patient is taking Losartan liquid 10mg daily but received prescription for Losartan tablets from the community.	2.7

*Average Score in severity: Minor (0 - <3), Moderate (3 - <7), Severe (7-10)
(HSP) Henoch Schönlein Purpura, (SAH) Systemic arterial hypertension, (SDNS) Steriod dependant nephrotic syndrome, (SLE) Systemic lupus erythematous, (SRNS) Steroid resistant nephrotic syndrome, (SSNS) Steroid sensitive nephrotic syndrome, (STG) CKD Stage, (PTx) Post transplant

Appendix 26 List of drugs associated with baseline DRPs by the first level (N=64)

WHO – ATC code	Counts n (%)
(A) ALIMENTARY TRACT AND METABOLISM	**12 (18.8)**
Alfacalcidol	5
Bisacodyl	1
Calcium carbonate	3
Forceval (Multivitamins)	1
Metformin	1
Trictrate	1
(B) BLOOD AND BLOOD FORMING ORGANS	**15 (23.4)**
Ferrous fumarate	1
Ferrous sulphate	1
Magnesium glycerophosphate	1
Sodium bicarbonate	6
Sodium chloride	4
Sodium feredetate	2
(C) CARDIOVASCULAR SYSTEM	**2 (3.1)**
Enalapril	1
Lisinopril	1
(H) SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	**10 (15.6)**
Prednisolone	10
(J) ANTIINFECTIVES FOR SYSTEMIC USE	**11 (17.2)**
Amoxicillin	2
Haemophilus influenzae type B vaccine	1
Hepatitis B vaccines	1
Itraconazole	1
Meningococcal polysaccharide groups A, C, Y and W135 vaccine	1
Nitrofurantoin	1
Pneumococcal vaccine	2
Trimethoprim	1
Varicella vacine	1
(L) ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	**10 (15.6)**
Azathioprine	1

WHO – ATC code	Counts n (%)
Ciclosporin	2
Mycophenolic acid	2
Tacrolimus	5
(N) NERVOUS SYSTEM	**3 (4.7)**
Dexamefetamine	1
Fluoxetine	1
Risperidone	1
(P) ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	**1 (1.6)**
Levamisole	1

*Data are count or percentage (%)

Appendix 27 Comparison of DRP data in children with kidney diease to other other populations

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
Setting and study design	Observational study in the paediatric renal wards of two children's teaching hospitals	RCT at the paediatric renal clinic of a children's teaching hospital	Observational study in the general medical wards, NICU and PICU of two children's teaching hospitals	Review of articles from 1990-2010	Observational study in a renal unit of a teaching hospital
Country	UK	UK	UK and Saudi Arabia	US	India
Sample size	127 unique patients (from a total of 166 admissions)	100 patients	333 unique patients (from a total of 732 patients)	48 articles	308 patients
Number of DRPs identified & method of identification	203 DRPs from prescription chart review by pharmacists	64 DRPs from eMR (active problems n=31)	478 DRPs from prescription chart review by pharmacists	NA	327 from pharmacists' documentation
Study duration	10 months	8 months	3 months	NA	9 months
DRP definition	Adapted from the PCNE	Adapted from the PCNE	Adapted from the PCNE	Adapted Hepler and Strand (1990)	Adapted Hepler and Strand (1990)
DRP classification	Adapted from the PCNE classification version 6.2	Adapted from the PCNE classification	Adapted from the PCNE classification version 5.0	Adapted from the Hepler and Strand classification	Adapted from the Hepler and Strand classification

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
		version 6.2		(1990)	(1990)
Incidence of DRPs (95% CI)	51.9% (43.2-60.6) of patients	18% (11.3-26.7) of patients with newly identified DRPs	UK and Ssaudi Arabia data: 45.2% (41.5-48.8) UK data: 39.4% (34.4-44.6)	All studies reported that all patients have at least one DRP	All patients
Predominant types of DRPs	• Sub-optimal drug effect (21.7%) • Toxic adverse reaction (19.2%) • Unnecessary drug treatment (20.2%)	*eMR review:* • Sub-optimal drug effect (39.1%) • Drug administration problems (29.7%) • Non-allergic drug reaction (17.2%) *Patient interview:* • Drug administration problems	• Dose too low or dosing interval too long (31.6%) • Dose too high or dosing interval too short (19.2%) • Non-allergic drug reaction (10.7%)	• Indication without therapy • Inappropriate laboratory monitoring	• Overdose (19.3%) • Adverse drug reactions (19.0%) • Improper dosing schedule (14.4)

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
		(65.2%) • Non-allergic drug reaction (10.9%) • Patient dissatisfied because of inadequate drug information (10.9%)			
Predominant contributory factors	• Prescribing errors • Doses too high • Required synergistic/preventive drug not prescribed	*eMR review:* • Poor understanding of treatment plan and medications • Dependent of enteral feeding tube for drug administration *Patient interview:* • Difficulty in obtaining repeat	• Inappropriate dose selection • Drug side effects • Drug underuse/under-administered	Not reported	Not reported

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
		prescriptions from the community • Drug side effects			
Severity of DRPs	Dean and Barber scale (1999) [1] Severe 1% Moderate 57% Mild 41%	Dean and Barber scale (1999) [1] *eMR review:* Severe 0% Moderate 91% Minor 9% *Patient interview:* Severe 0% Moderate 80% Minor 20%	Dean and Barber scale (1999) [1] Severe 1% Moderate 27% Minor 72%	Not reported	Alderman severity criteria [2] Major 10% Moderate 16% Minor 74%
Significant risk factors	Number of medicines prescribed per child	None of the risk factors were found to be significant	• Number of medicines prescribed per child • Transferred from	Several reports suggested the following factors but none of the articles reported statistical	Risk factors not studied

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
			another ward or hospital	significance: • ≥3 comorbidities, • medications regimen changed ≥4 time per year • On ≥5 medications • History of non-adherence • Treatment with medicines with narrow therapeutic index • On dialysis	
DRP resolution	94% of DRPs resolved during hospitalisation (99% acceptance rate by the clinical team)	No difference in the resolution of DRPs	Not reported	Not reported	Not reported
Acceptance rate by the clinical team towards pharmacist's	99%	83%	Not reported	Not reported	97.2%

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
recommendations					
Drugs associated with DRPs (by first level of the WHO-ATC code)	(J) Antiinfectives for Systemic Use (A) Alimentary Tract and Metabolism (B) Blood and Blood Forming Organs	(B) Blood and Blood Forming Organs (L) Antineoplastic and Immunomodulating Agents (A) Alimentary Tract and Metabolism	(J) Antiinfectives for Systemic Use (A) Alimentary Tract and Metabolism (N) Nervous System	(C) Cardiovascular System (J) Antiinfectives for Systemic Use (A) Alimentary Tract and Metabolism	(C) Cardiovascular System (J) Antiinfectives for Systemic Use (A) Alimentary Tract and Metabolism

Notes:
Abbreviations: DRPs (drug-related problems), eMR (Electronic Medical Record), NA (Not applicable), PCNE (Pharmaceutical Care Network Europe)
[1] Dean and Barber (1999) severity assessment scale:
Severe: Likely to cause death or lasting impairment, *Moderate:* Likely to cause adverse effects or interfere with therapeutic goals, Mild: Unlikely to have any adverse effects
[2] Alderman severity criteria
Major: Interventions expected to prevent or address very serious drug-related problems, with a minimum estimated effect of reducing hospital stay by no less than 24 hours, *Moderate:* Adjustments expected to enhance effectiveness of drug therapy,

Study characteristics	Research reported in this thesis		Children without kidney disease (Rashed et al., 2012b)	Adult dialysis patients (Cardone et al., 2010)	Adult pre-dialysis patients (Castelino et al., 2011)
	DRP study at the inpatient setting	DRP study at the outpatient setting			
producing minor reductions in patient morbidity or treatment costs, *Minor:* Small adjustments and optimisations to therapy, not expected to significantly alter hospital stay, resource utilisation or clinical outcome					

Appendix 28 Email correspondence 1

RE: Information on drug related problem classification (V6.2)

14 January 2014
13:54

Subject	**RE: Information on drug related problem classification (V6.2)**
From	Foppe van Mil
To	norkasihan.ibrahim
Sent	26 February 2012 06:21

I would appreciate to receive a copy of the article that has been published to distribute amongst the e members of the PCNE-DRP group.
You may adapt the classification for your own use, but please bear in mind that you are not supposed to take out items; you may add items but then must refer to the system as ' the adapted PCNE Classification V.....' .

Best regards,

Foppe

****
J.W.Foppe van Mil - van Mil Consultancy
Margrietlaan 1, 9471 CT Zuidlaren, Netherlands
51 grand Rue, 67220 Maisonsgoutte, France
****

From: norkasihan.ibrahim [mailto:norkasihan.ibrahim@live.pharmacy.ac.uk]
Sent: Sat 25-2-2012 8:45
To: Foppe van Mil
Subject: Re: Information on drug related problem classification (V6.2)

Dear Sir,

Thank you for your explanation. I am planning for my next project, and is interested to develop drp classification scheme for children with kidney disease using pcne. If this is approved by my supervisors, I would be happy to share them for others to use.

PCNE previous permission granted for my systematic review was taken care with responsible - it has been accepted to be published in by Pediatric Nephrology ;)

Can I please have permission from PCNE to work on their scheme and modify accordingly for my subjects?

Looking forward to hearing from you.
Many thanks,
//Nor

Appendix 29 Email correspondence 2

Re: Permission to reference and adapt medication-related problems screening tool

20 March 2014
10:28

Subject	Re: Permission to reference and adapt medication-related problems screening tool
From	karen gordon
To	Ibrahim, Norkasihan
Sent	09 July 2012 22:23

Hi Nor.
Thats fine as long as the tool is acknowledged as modified from our referenced tool.
Send me your modified version, so I can see what you've done.
All the best,
Karen

From: "Ibrahim, Norkasihan" <norkasihan.ibrahim.11@ucl.ac.uk>
To: karen gordon <karenjgordon@yahoo.co.uk>
Sent: Monday, 9 July 2012, 9:00
Subject: Permission to reference and adapt medication-related problems screening tool

Dear Karen,
Many thanks for the documents.

May I please ask permission to reference the published paper and adapt the tool for interviewing children (and their parent) at the paediatric renal out-patient clinic settings?

Best wishes,
//Nor

Norkasihan Ibrahim
Research Pharmacist
The Centre for Paediatric Pharmacy Research
University College London School of Pharmacy
Faculty of Life Sciences
British Medical Association (BMA) / Tavistock House
Entrance A, 1st Floor
Tavistock Square
London, WC1H 9JP
Tel: 020 7874 1531
Fax: 020 7387 5693
Email - norkasihan.ibrahim.11@ucl.ac.uk

From: karen gordon [mailto:karenjgordon@yahoo.co.uk]
Sent: 08 July 2012 15:44
To: Ibrahim, Norkasihan
Subject: Re: Request for medication-related problems screening tool

Attached.

Best wishes,

Karen Gordon

From: "Ibrahim, Norkasihan" <norkasihan.ibrahim.11@ucl.ac.uk>
To: "karenjgordon@yahoo.co.uk" <karenjgordon@yahoo.co.uk>
Cc: "Yogini Jani_UCL (yogini.jani@pharmacy.ac.uk)" <yogini.jani@pharmacy.ac.uk>
Sent: Sunday, 8 July 2012, 12:41
Subject: Request for medication-related problems screening tool