

**Off-label and Unlicensed Medicines' Related Problems in Paediatric In-patients**

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## PLAGIARISM STATEMENT

I, WIJDAN ELHIJAZI, certify that this thesis is my original work and that any materials from work of others are clearly acknowledged.

Signature

A handwritten signature in black ink, appearing to read 'Wijdan Elhijazi', written over a faint horizontal line.

Date: 19/10/18

**DEDICATION**

**To my late dad**

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## **Abstract**

**Background:** Current legislations such as paediatric investigation plan (PIP) require pharmaceutical companies seeking marketing authorisation for a new medicine to provide evidence of studies in paediatrics to justify the use of such medicine in this population. In spite of these legislations, there are still challenges with conduct of clinical trials in paediatrics; thus, there is lack of commercially available dosage forms appropriate for use in this population. Consequently, a good proportion of medicines used in treating paediatric patients are used in the unlicensed (UL) or off-label (OL) manner. Use of UL or OL medicines has been associated with higher safety incidents such as, adverse drug reactions (ADRs) than licensed medicines. ADRs are only a subset of medicine related problems (MRPs) associated with the use of medicines. Currently, no studies have explored all aspects of problems associated with the use of OL and UL medicines in paediatrics.

**Aim:** To investigate the prevalence of the use of OL and UL medicines and problems associated with their use in paediatrics patients admitted to intensive care units of a Children's Hospital.

**Method:** A systematic literature review was carried out to identify problems that are associated with the use of OL and UL medicines. A retrospective review of case notes (n=194) of patients who were admitted to Paediatric Intensive Care Unit (PICU) was carried out at medical records units of the hospital. This was followed by a prospective review of case notes (n=147) of patients admitted to PICU. The last study involved a prospective review of case notes (n=87) admitted to Neonatal Intensive Care Unit (NICU); NICU had migrated to electronic prescribing at the time the study was carried out.

Licensing status of medicines was determined using Summary of Product Characteristics of medicines. Definition and categories of MRPs were based on the Pharmaceutical Care Network Europe classification system version 6.2. Naranjo causality scale was used to identify the medicines that was associated with MRPs. Severity and preventability of identified MRPs were assessed using the National Patient Safety Agency categorisation for level of harm and Schumock and Thornton scale respectively. Data was analysed using computer programmes including Excel, Statistical Package for the Social Sciences and STATA.

**Results:** In the retrospective study, 53% of the total number of patients developed at least one MRP and 8% (n=165/2000) of the total number of medicines were associated with MRPs. From the total number of MRPs, 43% were associated with licensed medicines, while 57% were associated with OL and/or UL medicines. Identified MRPs were mostly ADRs and treatment effectiveness problems (84% vs.16%).

In the prospective PICU study, 66% of the total number of patients developed at least one MRP and 11% (n=178/1578) of prescribed medicines were associated with MRPs. From the total number of MRPs, 40.4% were associated with licensed medicines, while 59.6% were associated with OL and/or UL medicines. Among the identified MRPs, 83% were ADRs and 17% were treatment effectiveness problems. In the NICU study, 90% of the patients developed MRPs and 9% (n= 186/1978) of the total number of medicines were associated with MRPs. From the total number of MRPs, 55% were associated with licensed medicines, while 45% were associated with OL and/or UL medicines. All the identified MRPs were ADRs.

**Conclusion:** This research is the first to investigate MRPs associated with the use of OL and UL medicines in paediatric in-patients. MRPs associated with the use of OL and UL medicines were higher than with the use of licensed medicines. Inclusion of paediatrics in clinical trials of new medicines is fundamental to reducing the use of OL and UL medicines and the problems associated with their use.

## **Thesis summary**

Chapter 1 of this thesis provided a background on patient safety, medicines optimisation, and research and development in paediatric population. It also introduced MRPs and the different systems that have been used in classifying MRPs.

In Chapter 2, results from a systematic literature review regarding the use of OL and/or UL medicines in paediatric patients are presented. Research justification, aim, and objectives are also discussed.

Chapter 3 describes research philosophies; the link between these philosophies and the different research methodologies are described. The tools employed in this research are also presented as well as the different study phases.

In chapter 4, findings of a retrospective review conducted in medical records department are presented. MRPs were higher with OL and/or UL medicines than licensed medicines (57% vs 43%) and were ADRs and treatment effective problems.

In Chapter 5, findings of a prospective review of case notes of patients admitted to PICU are described. Findings were consistent with those of the retrospective study.

Chapter 6 of this thesis describes the prospective study conducted in NICU where electronic prescribing had been implemented. Findings were consistent with those of Chapters 4 and 5 in terms of prevalence of use of OL and UL medicines and MRPs occurrence. However, MRPs identified were only ADRs; there were no treatment effectiveness problems.

In Chapter 7, overall discussion of this thesis, research contribution to knowledge, implication for practice, and recommendations are presented.



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## **List of Abbreviations**

A&E	Accidents & Emergency
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AHRQ	Agency for Healthcare Research and Quality
ASHP	American Society of Hospital Pharmacists
BNF-C	British National Formulary for Children
DF	Dosage Form
DIH	Drug Information Handbook
DRP	Drug-Related Problem
EC	European Commission
EMA	European Medicines Agency
EPARs	European Public Assessment Reports
EU	European Union
EXTEMPS	Extemporaneous Products
E-prescribing	Electronic Prescribing
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICD	International Classification of Diseases
ICH	International Conference of Harmonisation
IDCRs	Integrated Digital Care Records
IV	Intravenous
KSA	Kingdom of Saudi Arabia
L	Licensed

LOS	Length of Stay
MA	Marketing Authorisation
MAI	Medication Appropriateness Index
ME	Medication Error
MHRA	Medicines & Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MRP	Medicine Related Problem
MTP	Medicines-Treatment Problem
NHS	National Health Services
NI	Northern Ireland
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPPG	Neonatal and Paediatric Pharmacists Group
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning System
OL	Off-label
PCNE	Pharmaceutical Care Network Europe
PHDU	Paediatric High Dependency Unit
PI	Product Information
PICU	Paediatric Intensive Care Unit
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PIS	Participants Information Sheet
PV	Pharmacovigilance
R&D	Research & Development



RCPCH	Royal College of Paediatrics and Child Health
REC	Research Ethics Committee
RPS	Royal Pharmaceutical Society
SPC	Summary of Product Characteristics
SPSS	Statistical Package for Social Sciences
SSI	Site Specific Information
UH	University of Hertfordshire
UK	United Kingdom
UL	Unlicensed
USA	United States of America
V 6.2	Version 6.2
WHO	World Health Organisation

## **Chapter 1: Introduction**

Medicines have always contributed to improving quality of life and an increase in life expectancy in humans. The fundamental aims of using medicines are to prevent illnesses, manage chronic conditions and/or cure diseases (Royal Pharmaceutical Society, 2013). Although medicines have contributed to an increase in life span, especially in developed countries, use of medicines has been associated with a number of problems and safety incidents. For example, a report commissioned by the Department of Health to explore the costs of unsafe care in the NHS from documented reports of adverse events and harm, found that 5 to 8% of unplanned hospital admissions are due to medicines-related incidents (Frontier Economics, 2014). Medication-related safety incidents in paediatrics have been reported as the most common medical errors; these included dispensing errors, prescribing errors and administration errors (Rees et al., 2017). Reporting, analysis, reduction and prevention of these safety incidents are crucial elements of patients' safety (Aspden, Corrigan, Wolcott et al., 2004). The following section will explore patient safety in the context of medicines use.

### **1.1 Patient safety and key organisational reports**

Patient safety is defined as the prevention of errors and adverse effects to patients associated with healthcare (Aspden, Corrigan, Wolcott et al., 2004; World Health Organisation, WHO 2017). According to the WHO, medical errors and health-care related adverse events occur in 8% to 12% of hospitalisations (WHO, 2017). Patient safety awareness has increased following the Institute of Medicine (IOM) launch of the report "To Err Is Human" in 1999. In the United Kingdom (UK), a Department of Health report titled: "An organisation with a Memory" estimated that about 850 000 adverse events occurs a year, and highlighted the importance of incidents reporting to improve the healthcare quality (Department of Health, 2000). Patient safety is therefore a healthcare discipline that emphasises minimisation of harm in healthcare

through the prevention, reduction, reporting, and analysis of medical error that often leads to adverse effects (Emmanuel et al., 2008). To integrate patient safety into health care, national and international agencies have been established. In England for example, following the publication of “An organisation with a memory” report, “*Building A Safer NHS For Patients*” was published which set out the Government’s plans to promote patient safety. One of the plans included establishment of a system (the National Reporting and Learning System, NRLS) to report and learn from adverse events resulting from medical and other errors occurring in the delivery of care and treatment to NHS patients. It also included introduction of the National Patient Safety Agency (NPSA), whose main function was to unite the functions, skills and experience needed to implement and operate the system (Department of Health, 2001). The NPSA defines a patient safety incident as ‘any unintended or unexpected incident which could have or did lead to harm for one or more patients’ (NPSA, 2007). When the harm results from use of medicines, this is referred to as medication incidents. The NPSA classify harm resulting from medications as non-preventable, preventable and near-miss depending on whether an error occurred or not. Where harm occurs and no error took place in the medication process, this is judged non-preventable; harm that occurs due to an error is judged preventable. Medication incidents that do not cause harm but have the potential to cause harm are called ‘near misses’. In a review of 526, 186 medication incidents reported to the National Reporting and Learning System (NRLS) in England in Wales between 2005 and 2010, 16% reported actual harm to patients, of which 0.9% resulted in death or severe harm. Serious incidents (death or severe harm) are often caused by errors in medicine administration and prescribing (NPSA, 2007). In the NRLS report, the most common incidents were those related to medicine administration 50%, prescribing 18%, omitted and delayed medicine 16%, and wrong dose 15%. (Cousins, Gerrette & Warner, 2012). In a more recent report of medication incidents between October 2014 and March 2015, 71.2% of the total number of incidents were reported

as causing no harm, 23.9% were low harm, 4.3% were moderate harm, less than 1% of all incidents reported severe harm or death (NHS, 2015).

In the NRLS, age is not a mandatory field. Consequently, a significant proportion of the data (39 percent) do not contain information on the patient's age. Although the NRLS reports do not contain information on the patient's age as data presented are combined, incidents reported between October 2007 and September 2008 showed that 2.1% (n= 19,307/910,089) occurred in children treated in acute settings (NPSA, 2009). The NRLS reports do not provide information on the category of incidents involving children whether they were serious incidents, critical incidents or near miss; however, the majority of incidents involving children are reported to have resulted in no harm or low harm (NPSA, 2009). The safety of patients in relation to medicines has led to the concept of medicine optimisation (Royal Pharmaceutical Society, 2013). Medicines optimisation and patient safety, therefore, aim to achieve the same goals in healthcare settings. Medicines optimisation will be discussed in the following section.

## **1.2 Medicines' optimisation principles**

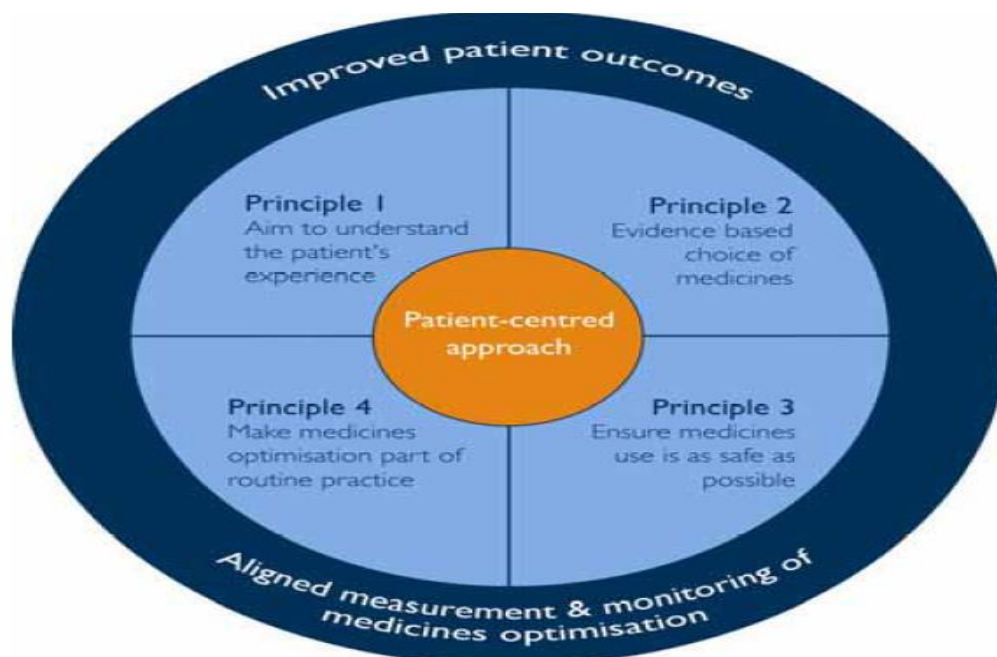
Medicines optimisation refers to the practice of making sure patients get the best out of their medicines (NHS England, 2016). To implement medicines optimisation initiatives in healthcare settings, the National Institute for Health and Care Excellence (NICE) recommends a multidisciplinary team (comprising physicians, pharmacists, nurses) who must work together to individualise care, monitor outcomes, review medicines frequently and support patients. The key priorities for implementing medicines optimisation include (NICE, 2015):

- i. having systems for identifying, reporting and learning from medicines-related patient safety incidents. Organisations are required to use multiple methods to identify medicines-related patient safety incidents, including health record review, patient surveys and direct observation of medicines administration.

- ii. having medicines-related communication systems when patients move from one care setting to another. The guideline recommends health and social care practitioners should share relevant information about patients and their medicines when they move from one care setting to another.
- iii. ensuring medicines reconciliation is carried out by a trained and competent health professional (a pharmacist, pharmacy technician, nurse or doctor) with the necessary knowledge, skills, and expertise.

Other guidelines that have been suggested for effective implementation of medicines optimisation are medication review, self-management plans, patient decision aids, and clinical decision support software (NHS England, 2016).

The components of optimal practice in medicines optimisation have been described by the Royal Pharmaceutical Society. These are summarised in the figure below:



**Figure 1:1: Summary of the four principles of medicines optimisation (Source: Royal Pharmaceutical Society, 2013)**

Each of the guiding principles seeks to achieve specific outcomes (Royal Pharmaceutical Society, 2013). The outcome of implementing principle 1 (aim to understand the patient's experience) includes:

- Patients are more engaged, understand more about their medicines and are able to make choices, including choices about prevention and healthy living.
- Patients' beliefs and preferences about medicines are understood to enable a shared decision about treatment.
- Patients are able to take/use their medicines as agreed.
- Patients feel confident enough to share openly their experiences of taking or not taking medicines, their views about what medicines mean to them, and how medicines impact on their daily life.

The expected outcome of implementing principle 2 (evidence based choice of medicines) includes:

- Optimal patient outcomes are obtained from choosing a medicine using best evidence (for example, following NICE guidance, local formularies etc) and these outcomes are measured.
- Treatments of limited clinical value are not used and medicines no longer required are stopped.
- Decisions about access to medicines are transparent and in accordance with the NHS Constitution.

The outcome of implementing principle 3 (ensuring medicines use is as safe as possible) includes:

- reduction of incidents of avoidable harm from medicines
- making sure patients have more confidence in taking their medicines

- ensuring patients feel able to ask healthcare professionals when they have a query or a difficulty with their medicines
- ensuring patients remain well and there is a reduction in admissions and readmissions to hospitals related to medicines usage.

Implementing principle 4 in the healthcare setting will achieve the following outcomes:

- Patients feel able to discuss and review their medicines with anyone involved in their care.
- Patients receive consistent messages about medicines because the healthcare team liaise effectively.
- It becomes routine practice to signpost patients to further help with their medicines and to local patient support groups.
- Inter-professional and inter-agency communication about patients' medicines is improved.
- Medicines wastage is reduced.
- The NHS achieves greater value for money invested in medicines.
- The impact of medicines optimisation is routinely measured

Although the four guiding principles are interrelated, this thesis is more closely related to the third guiding principle. This implies that safety and efficacy of medicines must be considered when prescribed as off-label (OL) and/or unlicensed (UL).

Harm from medicines occur both in adult and paediatric patient populations, the goal of medicines optimisation is therefore to improve patient outcomes and minimise harm from medicines in all patient groups. However, medicine-related incidents are more prevalent in paediatric patients than in adults (Wong, Wong & Cranswick, 2009). Children are thus more vulnerable to healthcare harm than adults for a number of reasons, including weight-based

dosing; use of medicines in an OL and UL manner, and dependency on caregivers to advocate for them (Rees et al., 2017; WHO, 2007). The following sections provide an overview of classification of paediatric population and medicines use in this population.

### **1.3 Classification of paediatric population**

Children and young adults constitute one of the vulnerable groups in any population (Shivayogi, 2013). Monitoring the use of medicine in this population is of paramount importance as they represent a spectrum of different physiologies and must not be treated as miniature adults (WHO, 2007). The paediatric population range from the very small preterm newborn infant to the adolescent. The paediatric age range is defined in terms of completed days, months, or years as follows (European Medicines Agency, 2001; WHO, 2007).

- preterm newborn infants
- term newborn infants (0 to 27 days)
- infants and toddlers (28 days to 23 months)
- children (2 to 11 years)
- adolescents (12 to 16-18 years (dependent on region))

A number of pharmacokinetic changes occur as children develop into adulthood. Some of these changes include a decrease in the proportion of body water, immaturity of gastro-intestinal and hepatic medicine-metabolising enzymes and transporters, and immature renal functions (WHO, 2007). Neonates, for example, eliminate medicines slowly due to underdeveloped enzymes and renal functions. The following section describes the pharmacokinetics in children.



## **1.4 Pharmacokinetics in paediatrics**

The pharmacokinetics of many medicines varies with age (Kearns, 1998). Some medicines that are completely safe for adults may produce toxic effects in children and adverse events to medicines that have been tolerated by adults have been observed in children when the medicines have not been adequately studied before their use in the paediatric population. For instance, because of the rapid changes in size, body composition, and organ function that occur during the first year of life, clinicians as well as pharmacokineticists and toxicologists are presented with challenges in prescribing safe and effective doses of therapeutic agents (Milsap and Jusko, 1994). Anatomical, physiological and biochemical changes that occur from birth affect pharmacokinetics and pharmacodynamics of medicines. (Fernandez et al., 2011). Pharmacokinetic parameters are age-related and that affects medicine's dose and frequency needed to maintain optimal therapeutic concentration (Fernandez et al., 2011). These parameters include absorption, distribution, metabolism and elimination.

### **1.4.1 Absorption**

Changes in the gastrointestinal tract that occur during growth and development of children affect the absorption rate and bioavailability of medicines after oral administration (Strolin & Baltes., 2003). In percutaneous administration of medicines, absorption is determined by the thickness of the epidermal stratum corneum and the state of skin hydration, this in turn affects the dose required to reach therapeutic concentration (Koren, 1997). In intramuscular administration of medicines, the absorption rate is affected by the perfusion in the injection area and the penetration of the medicine through the endothelium capillary, this affects the choice of the correct dose (Strolin et al., 2005). When patients are unable to tolerate the oral and intravenous routes of administration, the rectal route serves as a useful alternative. This route is less modified by changes during growth and development, for example, the local pH

of the rectum is close to neutral in adults, but alkaline in most children. When the rectal route is used, the dose, frequency and duration of medicine must be optimised to reach the required plasma level. Although intrapulmonary administration is increasingly used in children, developmental changes in the lungs affect the absorption of medicines (Fernandez et al., 2011).

### **1.4.2 Distribution**

Many distribution processes of medicines are different in children when compared to adults. For example, the plasma protein binding is continuously fluctuating throughout the first years of life, which affects the distribution of medicines (Strolin et al., 2005). Also, the blood-brain barrier (BBB) is not fully mature and medicines with low penetration capacity might enter the central nervous system with higher concentrations which might cause toxicity (Cohen-Wolkowicz et al., 2009). The total body water is high in young infants (80-90% of the body weight). This decreases to 55-60% by adulthood. Consequently, there is higher volume of distribution of water-soluble medicines in paediatric patients than in adult patients (McLeod et al., 1992).

### **1.4.3 Metabolism**

Metabolism of medicines depends on many factors including, blood flow, hepatic enzyme activities, transport systems and plasma protein binding (Anderson & Lynn., 2009). Blood flow and drug-metabolising enzymes are reduced in children when compared to adults and some medicines produce metabolites in children that are not normally present in adults such as caffeine production in neonates receiving theophylline (Benedetti & Whomsley., 2007).

### **1.4.4 Excretion**

Changes that occur during growth and maturation of the renal function have implications for medicines that are primarily excreted by the kidney. Factors that affect medicines excretion via

the renal system include glomerular filtration (GFR), tubular secretion and reabsorption. They are dependent on renal blood and plasma flow and increase with age as a result of increase in cardiac output and a reduction in peripheral vascular resistance (Alcorn et al., 2002). Excretion of many medicines in urine in unchanged form is restricted by the immaturity of glomerular filtration and renal tubular secretion observed in neonates, the unchanged form of the medicine therefore remains longer in the blood and may reach toxic levels (Fernandez et al., 2011).

The changing pharmacokinetic profiles in children affect medicines efficacy, toxicity and dosing regimens and therefore optimisation of medicines for this population is crucial. Dosing of medicines in paediatric patients is based on the modification of adult doses and formulations (Batchelor & Marriott, 2015; Standing & Tuleu, 2005; Richey et al., 2013) which might not give good estimates of suitable dosages in some cases (Kimland & Odland, 2012). To ensure optimal use of medicines and availability of age-appropriate medicines in this population, a number of legislations have been introduced. The following section summarises key legislations in paediatric medicines use.

### **1.5 Legislation of medicinal products for paediatric use**

Following the thalidomide disaster (that is, phocomelia or malformation of the limbs in infants whose mothers were treated with thalidomide for nausea during pregnancy) (Kelsey, 1967; Kelsey, 1988; Lenz, 1988; Smithells & Newman, 1992; Vargesson, 2013), pharmaceutical companies are required to provide information on the safety, efficacy and quality of medicines to national medicines regulatory agencies. When the medicine is approved, a marketing authorisation or license is issued with a Summary of Product Characteristics (SPC) (Silva, Ansotegui & Morais-Almeida, 2014). The medicine marketing authorisation or license usually states which indication the medicine can be used for, what doses can be used, how the medicine should be given (e.g. by mouth, by injection), and which group of patients it can be used for (Royal College of Paediatrics and Child Health (RCPCH), Neonatal and Paediatric Pharmacists

Group (NPPG) & WellChild, 2013). The aim of licensing is to control the manufacture, promotion and supply of medicines. To this aim, different regulatory agencies have been set up to ensure safety, efficacy and quality of medicines. These agencies include the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK), European Medicines Agency (EMA), responsible for licensing of medicines in the European Commission (EC); and the Food and Drug Administration (FDA) in United States of America (USA).

A mutual recognition agreement between the European Union (EU) and the United States (US) to recognise inspections of manufacturing sites for human medicines came into force in November 2017 and allows for recognition of each other's inspection outcomes. This agreement helps to strengthen use of each other's medicine inspection expertise and resources, avoids duplication of inspection, and directs resources towards inspection of manufacturing facilities of medicines that have a global public health risks. The FDA now confirms the capability of eight EU Member States including United Kingdom, which is a giant step to benefit from the available resources to safeguard quality and safety of medicines.

## **1.6 History of medicines legislations**

In the UK, the first primary licensing legislation came into existence through the Medicines Act of 1968 (UK Act of Parliament, 1968). The act prohibited all companies to manufacture, promote, sell, or supply any kind of medicine without a prior license from the UK licensing authority (comprising UK Ministers of Health) which is advised by MHRA. The Act was gradually introduced into European Union (EU) legislation, and it is now known as Marketing Authorisation (MA). In order for any product to obtain a MA in the UK, the company is required to offer sufficient evidence to the MHRA to show that the medicine meet all satisfactory standards of efficacy, safety, and quality, when used for its specified indications. The MHRA requires companies seeking a MA to provide information on the medicine for the

prescribers (SPC) as well as for the patients via patients information leaflets (PIL). The information provided become part of the MA and states the indication(s), the dosage, and other important information, including the formulation of the product, the constituents, side effects, and interactions with other substances, warnings, and contraindications (Collier, 1999).

The EMEA was established in 1995 with the mandate to implement a new European medicine registration system. The aim of this new system was to give patients quick access to innovatory new medicines, to facilitate the free movement of medicines within the European Union, and to provide rigorous scientific evaluation of new products (Herxheimer, 1996).

The system used two licensing procedures, namely the centralised procedure through the EMEA (applies to companies that seek license for biotechnology products), and a decentralised procedure which applies to conventional products (Herxheimer, 1996; Impicciatore & Choonara, 1999). Products approved under these procedures are issued the European Public Assessment Reports (EPARs), which provide reasons for approval, summary of product characteristics, and information to be included in patient information leaflet (PIL). A review to evaluate the activity of EMEA regarding paediatric medicines four years after its establishment showed that of 45 substances licensed as of January 1995, 29 (64%) were of possible use in children but only 10 were licensed for paediatric use (Impicciatore & Choonara, 1999). This means that the majority of medicines are licensed for adults but sometimes are used in paediatric patients in an unlicensed/off-label manner.

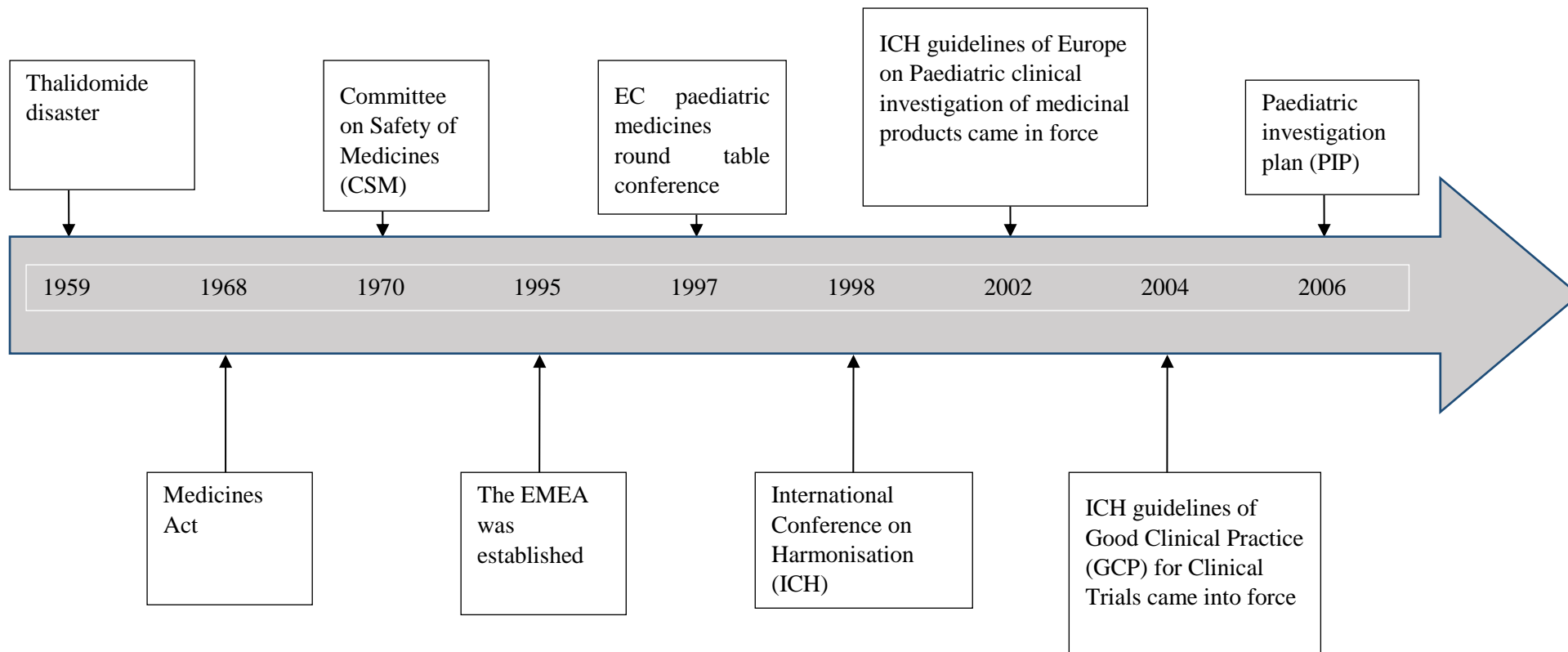
Similarly, in 1997, the European Commission (EC) organised a round table discussion involving experts to discuss paediatric medicines. In 1998, the Commission supported the need for international discussion on the performance of clinical trials in children in the context of the International Conference on Harmonisation (ICH). ICH is an organisation for the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and the USA. The goal of ICH is to encourage and facilitate timely paediatric medicinal product

development, provide an outline of critical issues in paediatric drug development, and promote safe, efficient and ethical studies of medicinal products (European Medicines Agency, 2007). As a result, the guidelines provided by the ICH became the standard guidelines of Europe on clinical investigation of medicinal products in the paediatric population and has been in force since July 2002 (European Medicines Agency, 2007). The adoption of ICH guidelines by the EU was shortly followed by the introduction of Good Clinical Practice (GCP) for Clinical Trials in 2001, which came into force in 2004. The GCP directive, in particular lay down criteria for the conduct of clinical trials in children and protection of children in these clinical trials (European Medicines Agency, 2007).

In 2006, a European parliament and the council of the EU regulation required companies intending to apply for a marketing authorisation to draw up a paediatric investigation plan (PIP) (European Parliament & EU Council, 2006). PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. All applications for marketing authorisation for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver (European Medicines Agency, 2007). The PIP includes the following (European Parliament & EU Council, 2006; European Medicines Agency, 2007):

- a description of the measures to be carried out in children with the medicine;
- description of the measures to adapt the medicine's formulation to make its use more acceptable in children, such as use of a liquid formulation rather than large tablets;
- coverage for all age groups of children, from birth to adolescence;
- definition of the timing of measures in children compared to adults.

Figure 1.2 below shows the timeline of legislations of medicinal products:



**Figure 1:2: Timeline of legislations of medicinal products**

In spite of these legislations, there are still challenges with conduct of clinical trials in children. The following section describes the challenges associated with carrying out trials in the paediatric population.

## **1.7 Research and development of medicines for paediatrics**

The limited number of clinical trials involving children has presented practical obstacles and difficulties for healthcare providers (Fontan, 2004). In their review, Rieder and Hawcutt, 2016 outlined a number of factors that make conduct of early clinical studies difficult in children. These include ethics, acceptability, rarity, standardisation, end points and safety, dosing and feasibility.

### **1.7.1 Ethics and informed consent**

There has been an ongoing discussion on the inclusion of children in clinical trials following the establishment of the value of ethics and informed consent in research (Rieder & Hawcutt, 2016). For a research study to be ethical, consent of participants must be sought and obtained prior to commencement of such research, and respect for research participants must be maintained throughout the research. Respect for persons includes respect for autonomous decision-making which requires attention to all the elements of informed consent, namely adequate information, voluntariness and capacity to understand the information (Canadian Paediatric Society, 2008). While adults have capacity to understand information, and provide informed consent based on their understanding of information provided, the same is not the case with children who are unable to provide full consent themselves. Responsibility for consent to participate in medicine research by children therefore rests on parents or guardians who may be unwilling to consent to enrolment of their children for fear of risk that may be associated with unproven treatment. While there are currently ethical situations that permit or encourage involvement of children in drug research,



especially if such treatment will be beneficial to children with the disorder, current discourse requires that such involvement must pose minimal risk to children. Even in this scenario, children are not ethically eligible to be enrolled in phase 1 trials (testing of new medicines in healthy volunteers to determine the highest dose that can be given safely without serious side effects). However, children are ethically eligible for Phase II (first stages of drug testing for efficacy and safety in patients) and Phase III (comparison of the effectiveness of the drug with a ‘gold standard’) studies. There is also an increasing call that ethical approval should require not only consent from parents but also assent from the children, particularly for adolescents. Thus securing consent for drug research in adolescents remains a problem (Rieder & Hawcutt, 2016).

Recently, the EU General Data Protection Regulation (GDPR) has published a guideline that will ensure the protection of personal data, including paediatric data. This guideline, which came into effect May 2018, highlighted the age at which data subjects can lawfully give consent and introduced changes for the language used in consent requests for children. The age at which a person is no longer considered a child is 16 according to the EU GDPR, however member states are allowed to adjust that limit to anywhere between 13 and 16. Thus the age of consent in particular member states must be taken into account by data controllers and should be obtained from a person holding a “parental responsibility”. As well as consent, data controllers must make sure that privacy notices are written in clear and plain language that a child will understand when services are offered directly to a child. The reason for these rules is to protect safety of children because they may be less aware of the risks, consequences and safeguards of handing of their personal details.

This new regulations have potential benefits and drawbacks. The main drawback of the new regulations is that it might affect the number of paediatric patients that can participate in clinical

trials and research of new medicinal products, because of the complexity of obtaining consent. Also, limited number of trial participants might lead to failure because of the drop-off of participants and the difficulty in obtaining post marketing data. This will in turn lead to decrease the number of paediatric clinical trials and new medicines. On the other hand, the benefits might be that pharmaceutical companies are unable to share or obtain information from third parties; therefore, the recruitment procedure of participants will be with less bias. In addition, children who are able to provide an assent form will be able to understand the form because of the intended simplicity of the form's language.

### **1.7.2 Acceptability**

Acceptability concerns the extent to which families and physicians are willing to enroll children in drug research. Not only are parents reluctant to enroll their children in clinical trial; findings of a study have also shown that paediatricians with limited training in ethics are very reluctant to enroll children in clinical trials (Sammons et al., 2007). Thus, the degree of comfort of study personnel in working with paediatricians and families is a key factor in the success or failure of drug studies in children (Rieder & Hawcutt, 2016).

### **1.7.3 Rarity**

Rarity concerns absence of some paediatric disorders in some institutions, but relatively common in other institutions. As a result, clinical trials of new drugs in a single centre are difficult as sample size is usually small. To ensure multi-centre trials, national and regional networks have been formed, especially in the fields of paediatric haematology and oncology to assess drug therapy and develop evidence-based treatment protocols that have resulted in survival of pre-term babies and high rate of cure of many childhood cancers (Rieder & Hawcutt, 2016).

#### **1.7.4 Standardisation, end points and safety**

A key decision in clinical trials is selection of suitable end points. This is particularly an issue that complicates clinical trials in children as many of the end points used in adults have not been validated in children. There is also the problem of design of clinical trials in children. Clinical trials conducted in children are reported to be associated with high risk of bias, especially with allocation and concealment (Hartling et al., 2012). In relation to safety concerns, the medicine approval process is designed to detect serious and common risks associated with medicinal therapy. Initial clinical trials are conducted to detect these risks; however, serious adverse effects do occur at early phase trials. This makes conducting clinical trials in children difficult.

#### **1.7.5 Dosing and feasibility**

One of the problems with involving children in clinical trials is dose selection of the trial product. This is because children's doses are usually extrapolated from adult doses. A review of failed paediatric medicines' development trials reported that, in up to a quarter of trials that fail to establish efficacy or safety, the selection of the correct dose was a factor in the failure (Momper, Mulugeta & Burckart, 2015).

As a result of the difficulties in conducting clinical trials in children, and lack of commercially available dosage forms appropriate, experts involved in treatment of this population have been left with no other choice than use of medicines in the OL or UL manner (Kimland et al., 2012; Magalhães et al., 2015; RCPCH, 2013; Turner, Nunn, Fielding & Choonara, 1999). The following sections describe OL and UL medicines' use in paediatrics.

## **1.8 Off-label and unlicensed medicine use in paediatric patients**

The definition of off-label (OL) and unlicensed (UL) use of medicines varies between authors, and are sometimes used interchangeably. Turner, Longworth, Nunn, & Choonaran (1998) have described different categories of OL and UL use of medicines. According to these authors, unlicensed use of medicines includes the following:

- modifications to licensed medicines (such as, dispensing a medicine in a different form, for example, crushing tablets to prepare a suspension)
- Extemporaneous medicines that are licensed but the particular formulation is manufactured under a special license (such as, when an adult preparation is not suitable for use in children and a smaller dose must be formulated)
- new medicines available under a special manufacturing license (such as, caffeine injections for apnea of prematurity)
- use of raw chemicals materials as medicines and medicines used before a license has been granted.
- imported medicines which are licensed in other countries but do not have a license in the UK.

Off-label use of medicines includes use in situations not covered by the product license such as:

- administration of a greater dose or more often
- administration for indications not described in the license
- administration to children outside the age range for which the product is licensed
- the use of alternative routes of administration
- use when the product is contraindicated

In an effort to define OL and UL use of medicines in children, Neubert et al. (2008) in a Delphi survey defined “off-label use” as ‘all uses of a marketed medicine not detailed in the SPC including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration’. “Unlicensed use” was defined as ‘all uses of a medicine which has never received a European Marketing Authorisation as medicinal for human use in either adults or children’.

The Neonatal and Paediatric Pharmacists Group (NPPG), Royal College of Paediatrics and Child Health (RCPCH) & WellChild, have used a number of terms to describe unlicensed medicines. According to these bodies, off-label use of medicines is using a medicine in a different way to its license. While UL use of medicines includes:

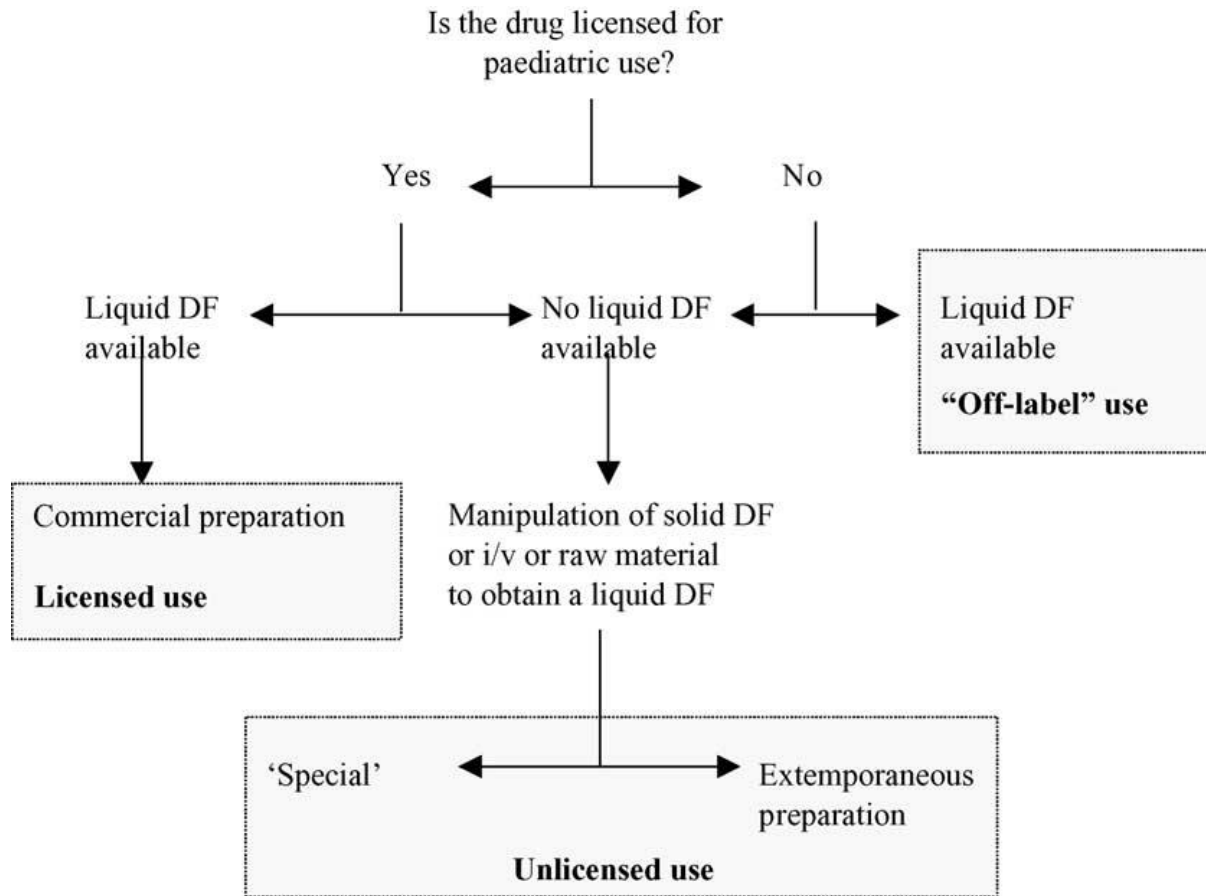
- ‘specials’- medicines made under a special license by a manufacturer
- imports- products with a license, usually in another country, which are imported into the UK
- extemporaneous products (‘extemps’)- formulations for an individual patient and an individual purpose made by a pharmacist combining ingredients
- manipulated products—medicines in which the formulation has been altered (e.g. by crushing tablets or opening capsules)

When there are no suitable medicines for paediatric practice, Medicines Act and Regulations (RCPCH, 2013) provide exemptions which enable prescribers to:

- prescribe UL medicines;
- use clinical trials medicines which are not yet authorised to be marketed.

- use or advise on the use of licensed medicines for indications, or in doses, or by routes of administration, outside the recommendations of the license;
- override the warnings and the precautions given in the license.

The figure below provides a summary of UL or OL use of medicines in paediatric patients:



**Figure 1:3: Unlicensed and off-label medicine paediatric use, DF- dosage form; iv- intravenous**

The term 'special' refers to an extemporaneous non-sterile liquid preparation produced under good manufacturing practice (GMP) conditions by a specials manufacturer, which includes suitably licensed hospitals units. Companies are allowed to supply unlicensed medicinal products

formulated in accordance with the requirement of a doctor ('named patient supply') if they hold a manufacturer's (specials) license issued by the Medicine and Healthcare Products Regulatory Agency (MHRA). Extemporaneous preparations, on the other hand are non-sterile liquid oral preparations are prepared mainly from manipulated solid dosage forms; either by the carers or hospital or community pharmacies. They are also prepared by dilution of an existing liquid dosage form (e.g. injection) or cytotoxic reconstitutions (Standing & Tuleu, 2005). For the purpose of this thesis, Turner et al (1998) definition of OL and UL use of medicines was adopted.

The use of OL and UL medicines is common in paediatric healthcare settings. However, a systematic review assessing OL/UL prescription in paediatrics found higher rates in neonatal versus pediatric wards, and in hospital versus community and primary care settings (Pandolfini & Bonati, 2005). In hospital settings, 90% of patients who were admitted to neonatal intensive care unit (NICU) and 67% of patients who were admitted to paediatric intensive care unit (PICU) were prescribed OL and/or UL medicine (Conroy, McIntyre & Choonara, 1999; Conroy et al., 2000). While UL and OL use of medicines is prevalent in paediatric population (Batchelor & Marriott, 2015; Kimland et al., 2012; Magalhães et al., 2015; RCPCH, 2013; Richey et al., 2013; Turner, Nunn, Fielding & Choonara, 1999), it has been associated with higher incidence of medicine-related problems (Rees et al., 2017; Turner et al., 1999; WHO, 2007). The following section describes medicine related problems.

### **1.9 Medicines related problems (MRPs)**

Problems associated with the use of medicines occur at various stages of the medication use process (prescribing, dispensing, administration and monitoring) (Al Hamid et al, 2016). Medicine-related problems (MRPs) are therefore an important patient safety issue. MRPs have been associated with hospital admissions, emergency department admissions and primary care

visits with increased risk of morbidity and mortality (Johnson & Bootman, 1995). MRP represents a wide array of concepts, consisting of adverse drug reactions (ADRs), adverse drug events (ADEs), and medication errors (MEs).

### **1.9.1 ADRs**

The WHO defines an ADR as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function” (WHO, 1975). ADRs are classified into different subtypes, namely: type A reactions: are dose-dependent, predictable and are augmentations of known pharmacologic effects of the drug. Type B reactions are independent of administered dose; are uncommon and unpredictable, and often occur in a small population of patients. Host/patient factors therefore play role in their occurrence. Type C reactions: are chronic reaction, are uncommon and relate to the cumulative dose of medicine over time. Type D reactions are delayed reactions that appear sometime after the medicines have been administered; they are uncommon and dose-related. Type E reactions are withdrawal effects following discontinuation or end of use of medicines. Type F reactions are unexpected treatment failure due to interactions with other medicines, food or diseases and are dose-related (Edwards & Aronson, 2000). Most ADRs in hospital settings or causing admissions are type A reactions and are avoidable and predictable (Pirmohamed 1998).

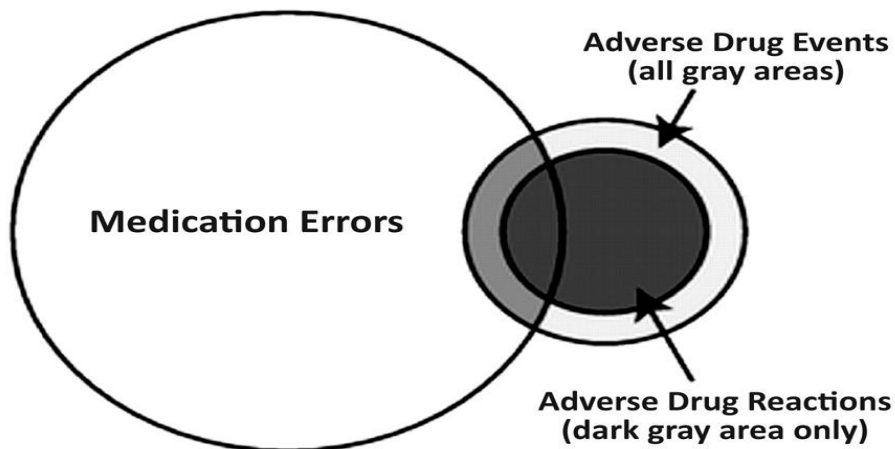
The paediatric population is especially prone to ADRs due to changes in the pharmacodynamics and pharmacokinetics as they develop into adulthood. The high prevalence of off-label and unlicensed prescribing, due to the limited availability of paediatric medicinal products also increases the risk of ADRs (Neubert 2004; Turner 1999). Up to 4.4 to 16.8% of hospitalised



children develop at least one ADR, especially paediatric patients admitted to intensive care units (Du et al., 2013).

### 1.9.2 ADEs

ADRs are sometimes mistaken for adverse drug events. According to the WHO, an ADE is “any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment” (WHO 2005). ADE is defined as “an injury or harm resulting from medical intervention related to a drug” (Bates et al., 1995). ADR differs from ADE in that it is directly attributable to pharmacology and would occur whether prescribing and dosing are appropriate or not. ADE on the other hand may result from inappropriate use of medicine or medication error, but not necessarily due to the pharmacology of the medicine; ADR is therefore a type of ADE (Schatz & Weber, 2015). The relationship between ADR, ADE and ME is shown in Figure 1.4 below:



**Figure 1:4: Relationship between adverse drug reaction; ADE, adverse drug event and medication error**

### 1.9.3 MEs

There is no consensus on the definition of medication errors (MEs) between different authors in the literature. The European Medicines Agency however defines MEs as “unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer” (European Medicines Agency, 2012). The United States National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use” (US National Coordinating Council for Medication Error Reporting and Prevention, 2015). MEs are reported to cause as many as 7000 deaths per year in the US. In the UK, prescribing errors have been reported in 1.5% of prescriptions (Dean et al, 2002), and administration errors occurred in 3-8% of non-intravenous medicines’ doses (Dean, 1999). Majority of ME studies are reportedly conducted among adults patient population (Ghaleb et al., 2006); however a comparative study which assessed the rate of MEs between adult and paediatric patients found that MEs are three times higher in paediatric inpatients than adult inpatients (Kaushal et al., 2001). The actual rate of MEs in paediatric patient population is still unknown due to the fact that ME reporting is voluntary and inconsistent. However, dosing errors have been found to be the most common type of paediatric MEs accounting for approximately one-fifth of all errors because of the high level of off-label and unlicensed prescribing in paediatric practice (Sutcliffe et al., 2014).

#### **1.9.4 Medicines related problems classification systems**

MRPs are sometimes referred to as drug-related problems (DRPs), and are used interchangeably. For the purpose of this thesis, the term MRP was used. This is because in the UK the term 'medicine' is preferred to the term 'drug' (Fernandez -Llimos et al., 2005). Moreover, the term 'drug' may refer to recreational drugs. MRPs have been defined and/or classified variously by different authors. Strand et al. (1990) first defined MRP as “an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes”. The Strand classification of MRPs was developed as means refocusing the role of the pharmacist on patient need and outcome rather than medicines. The authors classified MRPs into eight different types, which included untreated indication, improper drug selection, sub-therapeutic dosage, over-dosage, adverse drug reaction (ADR), drug interactions, failure to receive medication, medication used without indication. The definition developed by Strand et al. (1990) has been a reference point for other authors, including: American Society of Hospital Pharmacists (ASHP), Cipolle et al, Granada Consensus II, Mackie, Westerlund, Hanlon, and Pharmaceutical Care Network Europe (PCNE).

##### **1.9.4.1 American Society of Hospital Pharmacists' classification of medicines related problems**

The ASHP classification of DRP was first proposed in 1993 and later standardised in 1996 and referred to as “medication-therapy problems”. ASHP defined MRP as “an event or circumstance involving medication therapy that actually or potentially interferes with an optimum outcome for a specific patient” (ASHP, 1996). The ASHP classification was developed as part of the standards of pharmaceutical care to enable pharmacists determine the presence of medication-therapy problems and include the following categories:

- medications with no medical indication
- medical conditions for which there is no medication prescribed
- medications prescribed inappropriately for a particular medical condition
- inappropriate medication dose, dosage form, schedule, route of administration, or method of administration Therapeutic duplication
- prescribing of medications to which the patient is allergic
- actual and potential adverse drug events
- actual and potential clinically significant drug–drug, drug–disease, drug–nutrient, and drug–laboratory test interactions
- interference with medical therapy by social or recreational drug use
- failure to receive the full benefit of prescribed medication therapy
- problems arising from the financial impact of medication therapy on the patient
- lack of understanding of the medication therapy by the patient
- failure of the patient to adhere to the medication regimen

#### **1.9.4.2 Cipolle et al. classification**

Cipolle and colleagues used the term drug therapy problem and defined it as “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”. This classification was developed to enhance pharmaceutical care in order to improve patients’ outcomes. The classification is used by US community pharmacists to assess pharmaceutical care services. In this classification system, drug therapy problems include: the need for additional therapy, unnecessary therapy, wrong drug, dosage is too low, dose too high, ADRs and adherence problems (Cipolle et al., 1998).

### 1.9.4.3 Granada consensus II

The Granada consensus was first produced in 1998 by Spanish experts. According to these experts, a drug therapy related problem is “a health problem, related to pharmacotherapy that interferes or may interfere with the expected patient health outcomes” and they grouped drug therapy related problems into:

- indication (the patient does not use the medicines that he needs or the patient uses medicines that he does not need).
- effectiveness (the patient uses an erroneously chosen medicine or the patient uses a dose, interval or duration inferior to the one needed).
- safety (the patient uses a dose, interval or duration superior to the one needed or the patient uses a medicine that causes an adverse drug reaction).

In 2002, a second version of Granada consensus provided further clarification to the definition and classification, in which potential problem was excluded. DRP was therefore defined as “health problems that are considered as negative clinical outcomes, resulting from pharmacotherapy that for different reasons, either do not achieve therapeutic objectives, or produce undesirable effect”. This updated version focused on negative clinical outcomes rather than on health problems of the patient (Granada Consensus, 2002). The last version was produced in 2007 which defined DRP as “situations in which the process of use of medicines cause or may cause the appearance of a negative outcome associated with medication” (Granada Consensus, 2007). In this version, DRPs are classified as:

- Wrongly administered drug
- Personal characteristics

- Unsuitable storage
- Contraindication
- Inappropriate dose, dosage schedule and/or duration
- Duplicity
- Dispensing errors
- Prescription errors
- Non-compliance
- Interactions
- Other health problems that affect the treatment
- Probability of adverse effects
- Health problem insufficiently treated
- Others

#### **1.9.4.4 Mackie classification**

Mackie’s classification was adapted from Cipolle et al. (1998) classification following review of 50 patients for presence of drug therapy problem as part of doctoral research. According to Mackie “a clinical drug-related problem is considered to exist when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy”. This classification system includes the following categories (Mackie, 2002):

- unnecessary therapy
- no indication apparent
- untreated indication
- safety
- adverse reaction

- clinically significant drug interaction
- contraindication
- effectiveness
- ineffective therapy
- inappropriate choice of therapy
- inappropriate formulation/delivery
- inappropriate dose/dosing schedule
- admitted non-adherence

#### **1.9.4.5 Westerlund classification**

This classification system was developed by the author as part of PhD research, and was initially used in 1996 before its incorporation into the Swedish community pharmacy software in 2001. The definition proposed was “A drug-related problem is a circumstance related to the patient’s use of a drug that actually or potentially prevents the patient from gaining the intended benefit of the drug”. This classification system was adapted partly from Strand et al. (1990) classification system of drug related problems and the author’s professional experience. It has been used in community pharmacies in Sweden to estimate the frequency of different types of drug-related problems, to determine relationships between the types and number of the identified problems and gender, age and number of prescribed medicines, and to document interventions made by pharmacists. The system includes the following categories (Westerlund, 2002):

- Uncertainty about aim of the drug
- Drug duplication
- Drug–drug interaction

- Contraindication
- Therapy failure
- Adverse effect
- Underuse of drug
- Overuse of the drug
- Other dosage problem
- Difficulty swallowing tablet/capsule
- Difficulty opening drug container
- Other problem

#### **1.9.4.6 Hanlon classification**

The problem of inappropriate prescribing, especially among the elderly who are often prescribed many medicines due to different comorbid conditions led to the development of Medication Appropriateness Index (MAI), a quality measure for assessing appropriateness of prescribing. The aim of MAI was to improve prescribing quality based on clinical pharmacists' intervention. It consists of 10 questions with three rating choices: "A" being appropriate, "B" being marginally appropriate and "C" being inappropriate. The MAI contains instructions for use, and specific definitions of each criterion, instructions on how to answer each question. The MAI questions are shown in Table 1.1 (Hanlon & Schmader, 2013).



**Table 1:1: Medication appropriateness index**

<b>1</b>	<b>Is there an indication for the drug?</b>
<b>2</b>	Is the medication effective for the condition?
<b>3</b>	Is the dosage correct?
<b>4</b>	Are the directions correct?
<b>5</b>	Are the directions practical?
<b>6</b>	Are there clinically significant drug-drug interactions?
<b>7</b>	Are there clinically significant drug-disease/condition interactions?
<b>8</b>	Is there unnecessary duplication with other drug(s)?
<b>9</b>	Is the duration of therapy acceptable?
<b>10</b>	Is this drug the least expensive alternative compared to others of equal utility?

Although the MAI is a tool for identifying inappropriate prescribing which results in MRPs, a classification of MRPs have been drawn from the 10 questions, which include (Adusumilli & Adepu, 2014):

- Indication
- Effectiveness
- Dosage
- Correct direction
- Practical directions
- Drug–drug interaction
- Drug–disease interaction
- Duplication
- Duration
- Expense

#### 1.9.4.7 Pharmaceutical Care Network Europe classification

The first version of the Pharmaceutical Care Network Europe (PCNE) classification system was developed in 1999 to provide a standardised classification system that is globally comparable. The PCNE classification system used the term drug related problems (DRPs), however; in this thesis the term medicines related problems (MRPs) was used. It categorised MRP into problems, causes, and interventions and is hierarchically structured. For the purpose of this thesis, the PCNE definition and classification system for MRPs version 6.2 (appendix 1), was adopted which defines MRP as: “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” (PCNE, 2010). The PCNE classifies MRP into 4 primary domains for problems, 8 primary domains for causes and 5 primary domains for interventions. The primary domains for problems include:

- treatment effectiveness: which means there is a (potential) problem with the (lack of) effect of the pharmacotherapy and includes i) no effect of drug treatment/ therapy failure, ii) effect of drug treatment not optimal, iii) wrong effect of drug treatment, and iv) untreated indication
- adverse reactions: means patient suffers, or will possibly suffer from an adverse drug event. This includes i) adverse drug event (non-allergic), ii) adverse drug event (allergic), and iii) toxic adverse drug-event
- treatment costs: means the drug treatment is more expensive than necessary and includes i) drug treatment more costly than necessary, ii) unnecessary drug-treatment
- others include i) patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes, and ii) unclear problem/complaint.

According to PCNE classification systems, MRPs result from errors, such as prescribing errors, medicine-use or administration errors. Therefore, MRPs is a broad term that include all types of medication errors that can lead to treatment effectiveness' problems as well as toxic, allergic and non-allergic adverse drug reactions (PCNE, 2010; van den Bemt, Egberts, de Jong-van den Berg, Brouwers, 2000).

Although there are many classification systems of MRPs in the literature, they have similarities between each other in their definitions and categories, with the PCNE classification of MRPs being the only system that has separated the causes from the problems. This has an advantage over the other classification systems because it facilitates the analysis of the root causes of MRPs.

MRPs in paediatrics have been investigated in a very limited number of studies (Rashed et al., 2012; Ibrahim et al., 2013; Easton et al., 2003; Easton et al., 2004). A comparative study to determine the frequency of MRPs in paediatric patients in the UK and Kingdom of Saudi Arabia reported an overall incidence of 45.2% (Rashed et al, 2012). The study found that the incidents of MRPs were higher in PICU than in general paediatric medical ward (Rashed et al., 2012). A related study found that 4.3% of paediatric admissions and 3.3% of Accidents & Emergency (A&E) visits were related to MRPs (Easton et al., 2004).

With respect to research on the use of OL and UL medicines in paediatric patients, the focus has been on ADRs only. In one study, the authors reported that ADRs were more frequent in paediatric in-patients with the use of OL and UL medicines, than with the use of licensed medicines representing 6% and 3.9% respectively (Turner et al., 1999). A related study concluded that OL and UL use of medicines are most likely to be implicated in ADRs than authorised medicines (Bellis et al., 2013). Incidences of ADRs associated with the use of OL and UL medicines in paediatric patients have been reported by other authors (dos Santos, 2012; Theisen, 2013). These

studies have only focused on ADRs, which is only one aspect of MRPs; therefore, there is a need for a holistic evaluation of MRPs associated with the use of OL and UL medicines in paediatric in-patient.

### **1.10 Chapter summary**

This chapter provided an overview of medicines' use in paediatrics population and the challenges encountered in treatment of paediatric illnesses.

- Patient safety is concerned with reducing adverse events associated with medicines use
- The paediatric population is particularly prone to medicine-related adverse events as a result of changes in pharmacokinetic profile as they into adulthood as well as high use of medicines in off-label or unlicensed manner due to underrepresentation of this group in clinical trials
- Dosing in the paediatric population are often extrapolated from adults data with further exposes children to medication incidents
- To promote inclusion of the children in clinical trials, a number of legislation have been published, the latest among them being the paediatric investigation plan
- In spite of these legislations, there is still lack of age-appropriate medicines. Consequently, off-label and unlicensed medicines use is still prevalent among the paediatric population, especially neonates.
- This research sought to investigate the problems that are associated with the use of off-label and unlicensed medicines in paediatric patients.

In the next chapter, the extent of OL and UL medicines use in the paediatric population and the safety concerns are explored.

## **Chapter 2: Systematic literature review of the prevalence of off-label and unlicensed medicines use and associated problems in paediatric in-patients**

### **2.1 Introduction**

In Chapter 1, an overview of medicines' use in paediatrics was provided. It was found that, as a result of difficulties encountered in conducting clinical trials in paediatric population, many of the medicines prescribed in this population are used in the off-label (OL) and/or unlicensed (UL) manner (Chapter 1, section 1.8). Previous reviews have assessed the extent of OL and UL medicines' use in paediatric patients (Kimland & Odling, 2012; Magalhães et al., 2015; Pandolfini & Bonati, 2005; Silva, Ansotegui & Morais-Almeida, 2014). A systematic review assessing OL prescription in children found it to be common in all settings, but higher rates were seen for neonatal versus paediatric wards and for hospital versus community settings. OL medicines use is also reported to be higher in hospital settings when compared to primary care settings (Pandolfini & Bonati, 2005). In their review, Kimland & Odling, (2012) reported that the proportion of OL use varied between 10 and 65% in hospital settings, and between 11 and 31% in primary care. Another systematic review of 34 studies on the use of OL and UL medicines in hospitalised paediatric patients reported that OL medicines' use ranged between 12.2%- 70.6 %; and UL medicines' use ranged between 0.2%- 47.9 % with newborns being the most exposed to these medicines (42.0 to 100 %) (Magalhães et al., 2015).

Use of medicines is associated with problems such as ADRs, ADEs and MEs. The rate of ADRs and MEs in paediatric patient population has previously been investigated. A systematic review and meta-analysis of the incidence of ADRs among in- and out-patients reported an overall incidence of 9.53% and 1.46% among in- and out-patients respectively (Impicciatore et al., 2001).

ADRs associated with the use OL and UL use of medicines was found to be higher when compared with licensed medicines (Turner et al, 1999).

With regard to MEs, different subsets of MEs including prescribing, administration and dispensing errors have been studied. Miller et al. (2007) reported that 5–27% of all medication orders for paediatric patients includes an error within the spectrum of the entire delivery process. Particularly, dosing errors have been reported as the most common types of medication errors among paediatric patients (Ghaleb et al., 2006). In a systematic review to determine extent and nature of the MEs in the UK, Sutcliffe et al. (2014) reported the high prevalence of OL prescribing in primary care resulted in dosing errors in this setting. In paediatric and neonatal acute care settings, the authors also reported that dosing errors were the most common type of ME, accounting for approximately one-fifth of all errors (Sutcliffe et al., 2014). At the time of literature review of this thesis, no published study on MEs associated with the use of OL and UL medicines in paediatric patients in hospital settings was identified.

Building on the reviews described in the preceding paragraphs, the literature review of this thesis sought to provide an update on studies that investigated the prevalence of OL and/or UL medicines in paediatric patients as well as identify studies that investigated problems that are associated with their use. The objectives of this review were therefore:

- i. To determine the prevalence of use of OL and UL medicines in paediatric population.
- ii. To determine problems associated with the use of OL and UL medicines in paediatric population.

## **2.2 Method**

A literature search for articles published between January 1997 and February 2016 was undertaken. The search was carried out in 9 databases namely Scopus, PubMed, British Nursing Index, Pharm-line, Web of Science, British Library Catalogue, CINHALL, Cochrane Library and Google Scholar. A combination of search terms was used including: (“medicine related problems” OR “medicine-related problems” OR “medication errors” OR “medication problems” OR “drug problems” OR “drug-induced death” OR “Adverse drug reactions” OR “adverse reactions” OR “adverse events” OR “adverse drug events” OR “medicine mishap” OR “medication mistake” OR “inappropriate medicines” OR “ADRs” OR “ADEs” OR “drug-death”); (“off-label medicines” OR “off-label prescribing” OR “off-label drugs” OR “off-label medication” OR “unlicensed medicines” OR “unlicensed drugs” OR “unlicensed medications” OR “unlicensed prescribing”); and (paediatrics OR paediatric OR pediatrics OR pediatric OR paed OR ped OR children OR child OR infants OR infant OR newborn OR newborns OR neonate OR neonates). The search terms were derived from previous literature reviews and studies in paediatric population. All synonyms were agreed on by the researcher and supervision team.

### **2.2.1 Inclusion and exclusion criteria**

The following were the inclusion criteria:

- Primary studies investigating prevalence, incidence and problems associated with use of OL and UL medicines in paediatrics (0-18years)
- Studies carried out in in-patient care settings
- Studies published in English

The exclusion criteria were:

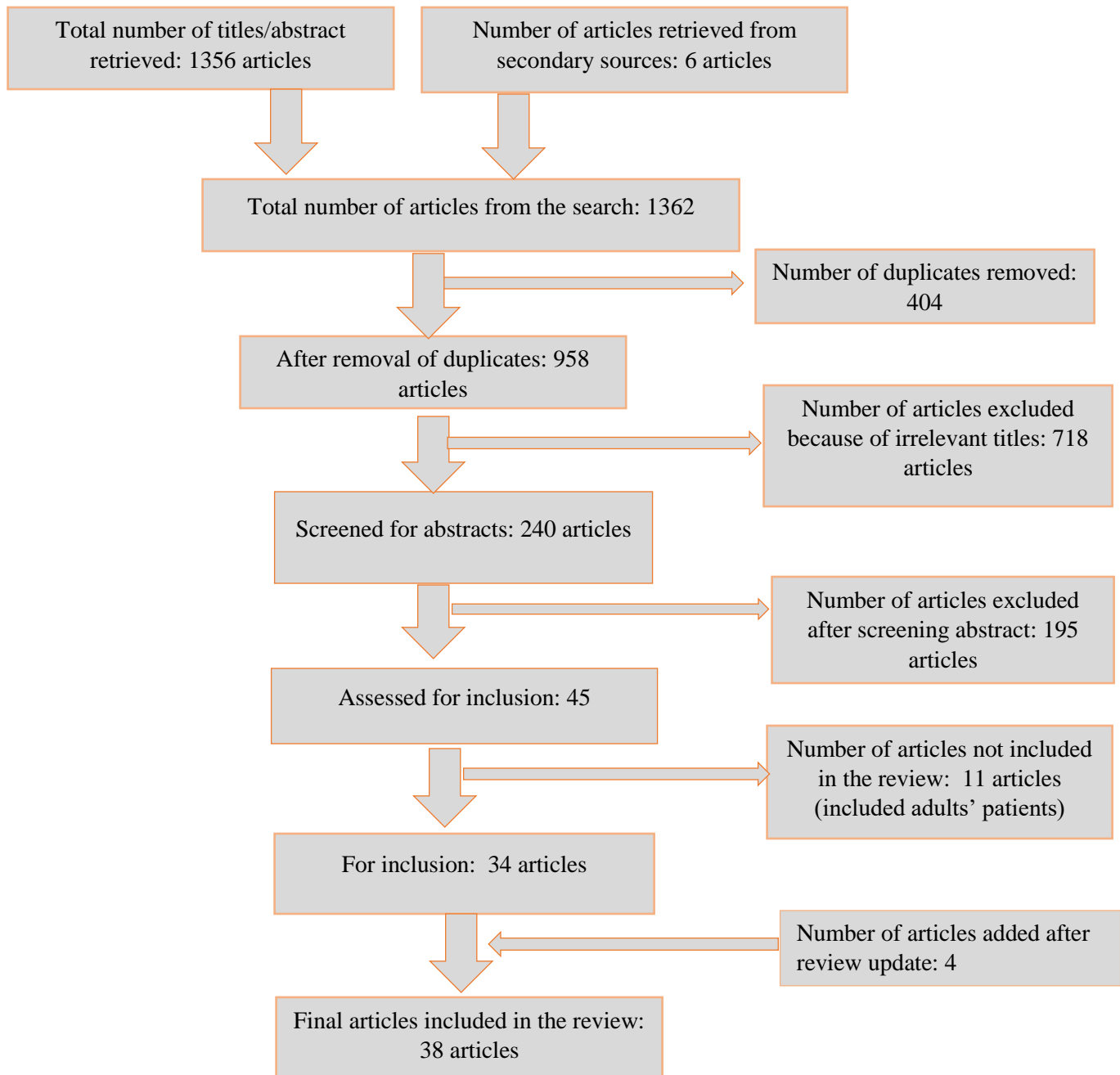
- Studies of OL and UL use of medicines in adults.
- Studies in out-patient and community care settings.
- Studies where the full text article was not available in English.
- Editorials, correspondences and opinions.

Data was extracted and screened for inclusion by the researcher; however the included studies were further reviewed by the supervisory team to ensure validity. The quality of the studies was assessed using Critical Appraisal Skills Programme (CASP) checklist. References of the included studies were also searched for other articles. The review was updated in October 2017.

### **2.3 Results**

In the literature search between January 1997 and February 2016, 1,362 articles were obtained. Duplicates and articles with irrelevant titles were removed, and inclusion and exclusion criteria were applied. Thirty-four papers were included in the initial review. Four more papers were included following an updated literature search covering the period up to October 2017. A summary following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Moher et al., 2009) is provided in Figure 2.1.





**Figure 2:1: Flow diagram of literature search outcome**

### **2.3.1 Settings of included studies**

#### **2.3.1.1 Studies conducted in neonatal units**

Of the 38 studies included in this review, ten were conducted in neonatal units including intensive care units (Carvalho et al., 2012; Conroy et al., 1999; Cuzzolin & Agostino, 2016; Kieran et al., 2014; Laforgia et al., 2014; O'Donnell et al., 2002; Oguz et al., 2012) ) (Table 2.1):

**Table 2:1: Studies conducted in neonatal units**

<b>Author, Year/ Country</b>	<b>Design</b>	<b>Duration</b>	<b>No. of prescriptions reviewed</b>	<b>No. of patients</b>	<b>Main findings</b>
<b>Cuzzolin &amp; Agostino, 2016, Italy</b>	Prospective cross-sectional survey	1 day survey	720 prescriptions corresponding to 79 drugs	220 neonates	191 (26.5 %) were license, 529 (73.5 %) were OL or UL. 193/220 newborns (87.7 %) received at least one OL/UL prescription. Most common categories of OL use were age (34.4 %) and dosing frequency (20.6 %).
<b>Schweigertova et al., 2016, Slovak Republic</b>	Cross-sectional study	6 months	962 prescriptions corresponding to 97 different medications	202 hospitalised newborns	43% were OL and 4.8% as UL. At least one OL or UL drug was given to 88.6% of patients.
<b>Laforgia et al., 2014 Italy</b>	Prospective observational study	1 month	483 prescriptions for 87 different drugs	126 neonates	88.6% were licensed and 11.4% were UL. Among licensed medicines, 37.4% were used as OL (range 27.3- 53.4%). Each patient was exposed to three different medicines
<b>Kieran et al 2014 Ireland</b>	Prospective study	2 months	900 prescriptions of 69 different drugs	110 neonates	29 (42%) were licensed, 13 (19%) were UL, and 27 (39%) were OL. 45 infants (44%) received both an OL and UL medicines.
<b>Oguz et al 2012, Turkey</b>	Prospective observational cohort study	24 hours	1315 prescriptions of 93 different drugs	464 neonates	62.3% were OL and UL
<b>Carvalho et al., 2012, Brazil</b>	Observational cohort study	6 weeks	318prescriptions	61 neonates	UL medicines made up 7.5% of prescriptions; OL medicines made up 27.7%. Only 13 patients with appropriate use of medications (21%).
<b>Lass et al., 2011 Estonia</b>	Prospective cohort study	6 months	1981 prescriptions of 115 products	490 neonates	1729 (87%) of 1981 prescriptions were OL or UL medicines. All preterm, and 97% of treated term neonates received at least one OL or UL medicine.
<b>Dell'Aera et al., 2007 Italy</b>	Cross- sectional pilot and prospective study	2months	176 prescriptions for 61 different drugs	34 new-borns	Medicines were licensed in 88%, and UL in 12% of cases. In licensed medicines, 37.5% were used following the terms of marketing authorization

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<b>O'Donnell et al., 2002 Australia</b>	Prospective cohort study	10 weeks	1442 prescriptions	97 infants with 101 admissions	High percentage of OL and UL medicines' use in neonatology 42% of the total prescriptions were licensed, 11% were UL, and 47% were OL 80% of infants received UL or OL medicine, and rose to 93% of extremely low birth weight infants.
<b>Conroy et al., 1999 UK</b>	Prospective chart review	13weeks	455 prescriptions	70 neonates	90% (63) received at least one OL or UL medicine. 54.7% (249) were OL, 9.9% (45) were UL, and 35.4% (161) were licensed.

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Four studies were undertaken in NICU and other wards (Table 2.2) (Lindell-Osuagwu et al., 2009; Lindell-Osuagwu et al., 2014; Mukattash et al., 2016; Porta et al., 2010;). A summary is provided in Table 2.2.

**Table 2:2: Studies conducted in neonatal intensive care units and other neonatal wards**

<b>Author, Year/Country</b>	<b>Design</b>	<b>Duration</b>	<b>No. of prescriptions reviewed</b>	<b>No. of patients</b>	<b>Main findings</b>
<b>Lindell-Osuagwu et al., 2014 Finland</b>	Prospective study	2 weeks	1054 prescriptions for 119 patients	123 patients 0-18 years	Patients with prescription for OL/UL medicine were significantly higher in 2011 compared to 2001 (p< 0.001). Prescriptions for UL medicines was significantly higher in children < 2years than in older children in both years (21% vs. 5% in 2011 and 24% vs. 3% in 2001, P < 0.001).
<b>Lee et al 2013 Malaysia</b>	Prospective observational explanatory study	2 months	1295 prescriptions for 168 patients	194 patients aged 1 month to 18years	353 (27.3%) were UL, 442 (34.1%) were OL. 44% of patients received at least one medicine for UL use, and 82.1% of patients received at least one medicine for OL use
<b>Porta et al., 2010 Three European countries- Italy, UK, Greece,</b>	Prospective study	2 weeks	1244 antibiotic prescriptions	616 children aged 0 to 17 years	OL antibiotic use is very common among European paediatric patients
<b>Lindell-Osuagwu et al 2009 Finland</b>	Prospective study	2 weeks	629 prescriptions for 108 patients	141 patients aged 0- 18 years	321 (51%) were for licensed medicines, 226 (36%) were OL and 82 (13%) were UL medicines. 24% of 108 children received licensed medicines; 66% received OL; 33% received UL medicines.

### **2.3.1.2 Studies carried out in paediatric intensive care units & other paediatric wards**

Four studies in were carried out in Paediatric Intensive Care Unit (PICU) and other wards (Berdkan et al., 2016; Garcia-Lopez et al., 2017; Jobanputra, Save & Bavdekar, 2015; Lee et al., 2013). The four studies are included in Table 2.3.

**Table 2:3: Studies carried out in paediatric intensive care units & other paediatric wards**

<b>Study Year/Country</b>	<b>Design</b>	<b>Duration</b>	<b>No. of prescriptions reviewed</b>	<b>No. of patients</b>	<b>Main findings</b>
<b>Garcia-Lopez et al., 2017 Spain</b>	Prospective observational	6 weeks	696 prescriptions involving 102 medicines	42 patients aged 0- 18years old	8.6% of total prescription were UL and 53.9% were OL use. Main reasons for OL use were indication, age and dose.
<b>Berdkan et al., 2016, Lebanon</b>	Retrospective analysis	10 months	2054 prescribed medicines	500 patients Aged 0- 16years old	11.1% and 15.8% of medicines prescribed were UL according the French Medical Regularity Authority and the Food and Drug Administration (FDA) respectively. 30.2% were OL and 33.5% were OL according to the French Medical Regularity Authority and FDA respectively.
<b>Jobanputra, Save &amp; Bavdekar, 2015, India</b>	Prospective observational	12 months	1789 prescriptions	482 aged 28 days to 12years	738(41.25%) were OL and 376(21.01%) were UL. OL medicines use was highest in infants (56.52%) with indication outside the license (32.37%) being the commonest category of OL medicines' use across all age groups.
<b>Lee et al 2013 Malaysia</b>	Prospective observational explanatory study	2 months	1295 prescriptions for 168 patients	194 patients aged 1 month to 18years	353 (27.3%) were UL and 442 (34.1%) were OL. 44% of patients received at least one medicine for UL use, and 82.1% of patients received at least one medicine for OL use



### 2.3.1.3 Studies carried out in emergency units

Three studies were carried out in paediatric emergency units (Czarniak et al., 2015; Taylor et al., 2015; Morales-Carpi et al., 2010); these are summarised in Table 2.4.

**Table 2:4: Studies carried out in emergency units**

<b>Study Year/Country</b>	<b>Design</b>	<b>Duration</b>	<b>No. of prescriptions reviewed</b>	<b>No. of patients</b>	<b>Main findings</b>
<b>Czarniak et al., 2015, Australia</b>	Retrospective chart review	12 months	2,654 prescriptions for 330 drugs	699 patients aged 0-18years	1905 (71.8) were licensed, 681 (25.7%) were OL and 68 were UL. Infants and children had the most OL prescription (31.7% and 35.9% respectively) and highest UL prescribing (7.2%) occurred in infants (p < 0.0001).
<b>Taylor et al., 2015, Australia</b>	Retrospective observational	12 months	6786 medicines administered	3343 aged 0-17years	2072 (30.5%) were OL/UL. 1213 (36.3%) of the patients were prescribed OL/UL.
<b>Morales-Carpi et al 2010 Spain</b>	Prospective observational and descriptive study	14 months	667 prescriptions for 336 children	462 children Aged 0- 14 years old.	Of the 152 formulations prescribed, 107 were used in OL manner.

#### **2.3.1.4 Studies carried out in general and surgical paediatric wards**

Majority (17) of the studies were conducted in general paediatric wards, surgical, and nephrology wards (Ballard et al., 2013; Bellis et al., 2013; Berg & Tak, 2011; Conroy et al., 2000; Craig, Henderson & Magee, 2001;; Di Paolo et al., 2006; Dos Santos & Heineck, 2012; Gavrilov et al., 2000; Gomes et al., 2015; Hsien et al., 2008; Joret-Descout et al., 2015; Neubert et al., 2004; Palcevski et al., 2012; Saiyed, Lalwani & Rana, 2015; Shah et al., 2010; Turner et al, 1999; Yasinta et al., 2015). A summary is provided in Table 2.5.

**Table 2:5: Studies carried out in general and surgical paediatric wards**

<b>Study Year/Country</b>	<b>Design</b>	<b>Duration</b>	<b>No. of prescriptions reviewed</b>	<b>No. of patients</b>	<b>Main findings</b>
<b>Gomes et al., 2015, Brazil</b>	Prospective cross-sectional	6 months	1,158 corresponding to 65 drugs	320 aged 28 months to 14 years	57.2% were in-label, 36.4% were OL, and 6.3% were UL. Prevalence of UL and OL medicines' use was 20.9% and 77.8% respectively.
<b>Joret-Descout et al., 2015, France</b>	Retrospective cross-sectional	1 day	315 prescription medicines	120 aged 1-16 years	190/60.3 % were licensed, 115/36.5 % were OL and 10/3.2 % were UL. 54 % of patients received an OL/UL medicine.
<b>Saiyed, Lalwani &amp; Rana, 2015, India</b>	Prospective non-interventional	6months	1,645 medications administered	320 aged 0 to 12 years	70% of 1645 medications were OL. ADRs occurred in 47 (10.85%) out of 320 patients. No. of OL medicines significantly increased the hazard of an ADR hazard ratio (P = 0.002). Most common ADRs were macupapular rash, chills, ataxia and pyrexia.
<b>Yasinta et al., 2015, China</b>	Retrospective review	1 year	1424 corresponding to 35 drugs	385 aged 1months-18 years old	16.64% of 1424 prescriptions were OL, and 31.43% of 35 medicines were prescribed in OL manner. 40.78% of 385 patients received OL nephrology medicines.
<b>Ballard et al., 2013 Australia</b>	Retrospective review	7 weeks	887 medicines	300 patients aged 0- 12 years old	32% of medicines were OL 57.3% of patients received an off-label medicine of the 106 different medicines,
<b>Bellis et al., 2013, UK</b>	Nested case-control study within a prospective cohort study	12months	10,699 different drugs	1388 patients aged between 0 to 16 years and 11 months.	6980 (68.8%) of the total medicines were licensed, 2407 (23.7%) were OL, and 758 (7.5%) were UL. 435 (6.2%) of all medicines were implicated in at least one definite or probable ADR. 298 (12.4%) of OL medicines and 113 (14.9%) of UL medicines were associated with ADRs.
<b>Dos Santos &amp; Heineck 2012</b>	Cross-sectional descriptive prospective study	3 months	342 prescriptions of 2026 items	342 patients aged 0 to 14 years	12% of prescriptions were UL, and 39% were OL 95.3% of patients received OL or UL medicine

<b>Brazil</b>					
<b>Palcevski et al., 2012</b> <b>Croatia</b>	Prospective cross-sectional study	1 day each month for 12 months	1643 prescriptions Of 198 different drugs	691 patients aged 1 day to 20 years old	46% of the different drugs were OL or UL. 48% of patients received at least one OL or UL medicine. 25% of all the prescriptions were either OL or UL.
<b>Berg &amp; Tak 2011</b> <b>Netherland</b>	Retrospective Analysis of electronic prescriptions ordering system	2 weeks	268 drug prescriptions	39 patients aged 0.25-17 years old	87% of patients received OL or UL medicine 59% of children received at least two UL medicines
<b>Shah et al., 2010</b> <b>Northern Ireland &amp; Singapore</b>	Prospective cross-sectional study	4 weeks	2073 medicines NI 674 medicines Singapore	389 children in NI; 252 children in Singapore (authors did not specify age of children)	More medicines were prescribed in an OL and UL manner in NI (10.4% and 32.6% respectively) compared to Singapore (1.3% and 20.6% respectively).
<b>Hsien et al., 2008</b> <b>Germany</b>	Prospective observational study	6 months	1,812 prescriptions representing 211 different drugs	417 patients aged 0- 18 years	31% of all were OL. 61% of 417 patients received at least one OL prescription. The percentage of OL prescriptions among the five most frequently prescribed medicines groups were: cardiovascular medicines, 60%; anti-infectives, 42%; respiratory medicines, 30%; medicines for GIT, 25%; analgesics and antipyretics, 3%.
<b>Di Paolo et al., 2006</b> <b>Switzerland</b>	Prospective study	6 months pilot study	483 prescriptions	60 patients aged 0 to 18 years	51% (247) prescriptions were licensed, 24% (114), were UL and 25% (122) were OL. All patients received at least one UL or OL medicine.
<b>Neubert et al., 2004,</b> <b>Germany</b>	Prospective pharmacoepidemiological	8 months	740 drug prescriptions	178 patients aged 0- 18 years old	198 (27.7%) medicines were used in either OL or UL manner. 46 ADRs were observed in 31 patients (17.4%); ADRs were associated with 5.6% of the 517 licensed medicines prescriptions, and with 6.1% of the 198 OL or UL medicine prescriptions.

	Cohort-based survey				
<b>Craig, Henderson &amp; Magee, 2001, Northern Ireland</b>	Prospective study	2 months	237 prescriptions	74 patients aged from one week old to 13 years	77.2% medicines were licensed; 22.8% prescriptions were non-licensed (3.4% were UL and 19.4% were OL).
<b>Gavrilov et al., 2000 Israel</b>	Retrospective analysis of medical records	2 months	222 medicine prescriptions	132 patients aged 1 month to 18 years	8% of the 222 medicines were UL and 26% were OL. 42% of children received either OL or UL medicine.
<b>Conroy et al., 2000, 5 European countries</b>	Prospective study	4 weeks	2262 drug prescriptions	624 patients aged 4 days to 16 years	1036 (46%) of all prescribed medicines were either UL or OL. 67% (421) of patients received an UL or OL medicine.
<b>Turner et al., 1999, UK</b>	Prospective surveillance study	13 weeks	4,455 drug courses	936 patients aged from 1 day to 18 years	48% (507) out of 1046 admitted patients received one or more OL or UL medicine. ADRs occurred in 11% (116) of the 1046 admissions. ADRs were associated with 112 (3.9%) of the 2881 licensed medicines, and 6% (95) of the 1574 OL/UL medicines.

### 2.3.2 Definition of off-label and unlicensed use

Among the studies included in this review, there were variations in the definition of OL and UL medicines' use. Majority of the studies (26) defined OL and UL use based on the country's national formulary and the information provided in the SPCs; 10 studies adopted the Turner et al. (1998) definition of OL and UL medicines' use, while two studies adopted the Neubert et al (2008) definition. Table 2.6 includes studies and definition the authors adopted.

**Table 2:6: Definitions of off-label and unlicensed medicines in the included studies**

<b>Definition of OL/UL</b>	<b>Number of studies</b>	<b>Authors/Year</b>
<b>National formulary and/or SPC</b>	26	(Bellis et al., 2013; Carvalho et al., 2012; Cuzzolin & Agostino, 2016; Dell'Aera et al., 2007; Di Paolo et al., 2006; Dos Santos & Heineck, 2012; Gomes et al., 2015; Hsien et al., 2008; Jobanputra, Save & Bavdekar, 2015; Kieran et al., 2014; Laforgia et al., 2014; Lee et al., 2013; Morales-Carpi et al., 2010; Mukattash et al., 2016; Neubert et al., 2004; Oguz et al., 2012; Palcevski et al., 2012; Porta et al., 2010; Saiyed, Lalwani & Rana, 2015; Schweigertova et al., 2016; Shah et al., 2010; Ballard et al., 2013; Berg & Tak, 2011; Czarniak et al., 2015; Taylor et al., 2015; Yasinta et al., 2015)
<b>Turner's definition</b>	10	(Berdkan et al., 2016; Craig, Henderson & Magee, 2001; Conroy et al., 2000; Conroy et al., 1999; Gavrillov et al., 2000; Joret-Descout et al., 2015; Lindell-Osuagwu et al., 2014; Lindell-Osuagwu et al., 2009; O'Donnell et al., 2002; Turner et al., 1999)
<b>Neubert's definition</b>	2	(Garcia-Lopez et al., 2017; Lass et al., 2011)

### **2.3.3 Studies that investigated prevalence of off-label and unlicensed medicines use**

Thirty-four studies investigated the prevalence of OL and UL medicines use in paediatrics (Table 2.1). Some of the studies reported prevalence of OL and UL medicine use separately while others reported it together. Among the studies conducted in NICU, Lass et al., 2011 reported the highest combined OL/UL prevalence of 87%, Cuzzolin & Agostino, 2016 and Oguz et al., 2012 reported combined OL/UL prevalence of 73.5% and 62.3% respectively. Among the nine studies conducted in NICU, Conroy et al., 1999 reported highest OL prevalence of 54.7% and lowest UL prevalence of 9.9%. Up to 100% of patients in this setting received at least one OL or UL medicine (Conroy et al., 1999; Kieran et al., 2014; Lass et al., 2011; O'Donnell et al., 2002). In the paediatric general ward, high prevalence OL and UL medicines use is also reported. In a prospective study of 342 patients, Dos Santos & Heineck (2012) reported that 95.3% of patients received UL or OL medicines. Prevalence of OL and UL medicine use in this setting is reported to be between 25% - 77% (Di Paolo et al., 2006; Gomes et al., 2015) and 3.2% - 24% (Joret-Descout et al., 2015; Di Paolo et al., 2006). OL and UL medicines use is therefore a common practice among all paediatric settings with higher incidence reported in intensive care units.

### **2.3.4 Studies that investigated safety issues associated with the use of off-label and unlicensed medicines**

Four studies (Bellis et al., 2013; Neubert et al., 2004; Turner et al., 1999; Saiyed, Lalwani & Rana, 2015) investigated adverse drug reactions (ADRs) associated with the use of OL and UL medicines' use in paediatrics. The four studies were all of prospective design.

In a prospective study of 1,046 admissions in which 48% of the patients received one or more OL or UL medicines, ADR occurred in 11% of the admissions. Approximately 4% of the ADRs were associated with licensed medicines and 6% was associated with OL/UL medicines (Turner et al., 1999). In a related study of 320 patients, 70% of prescribed medicines were OL. ADRs occurred in 10.8% of the patients, with the most common ADRs being macupapular rash, chills, ataxia and pyrexia (Saiyed, Lalwani & Rana, 2015). Bellis et al. (2013) reported 12.4% ADR with OL and 14.9% ADR with UL medicines compared with 6.2% with licensed medicine. The study reported a prevalence of 23.7% for OL and 7.5% for UL medicines. A summary of studies that investigated ADRs is provided in Table 2.7.



**Table 2:7: Studies that investigated adverse drug reactions associated with use of off-label and unlicensed**

<b>Study/Year Country</b>	<b>Design</b>	<b>Definition</b>	<b>Duration</b>	<b>Setting</b>	<b>No. of prescriptions reviewed</b>	<b>No. of patients</b>	<b>Main findings</b>
<b>Saiyed, Lalwani &amp; Rana, 2015, India</b>	Prospective non-interventional	OL use of medicines was based on authors' categorisation.	6months	paediatric ward	1,645 medications administered	320 aged 0 to 12 years	70% of medicines were OL. 51 ADRs occurred in 10.85% out of 320 patients. OL caused 367% ADRs; licensed medicines resulted in 33% of ADRs. ADR increased with increase in number of OL medicines (P = 0.002).
<b>Bellis et al., 2013, UK</b>	Nested case-control study within a prospective cohort study	OL and UL use of medicines was based on information obtained from the SPCs.	12months	Medical ward	10,699 different medicines	1388 patients aged between 0 to 16 years and 11 months.	68.8% of medicines were licensed; 23.7% were OL, and 7.5% were UL. 6.2% of licensed medicines caused at least one definite or probable ADR; 12.4% of OL medicines and 14.9% of UL medicines caused at least one definite or probable ADR respectively.
<b>Neubert et al., 2004, Germany</b>	Prospective pharmacoepidemiological Cohort-based survey	OL and UL classified based on information obtained from Fachinfo compact disc 2001.	8months	Paediatric isolation ward	740 drug prescriptions	178 patients aged 0- 18 years old	27.7% medicines were used in OL and/or UL manner. 46 ADRs were observed in 31 patients (17.4%); ADRs were associated with 5.6% of the licensed prescriptions, and with 6.1% of the OL or UL prescriptions.
<b>Turner et al., 1999, UK</b>	Prospective surveillance study	Turner et al. 1998 definition	13 weeks	surgical, medical, neonatal surgical, cardiac intensive care and	4,455 drug courses	936patients aged from 1day to 18 years	48% (507) out of 1046 admitted patients received one or more OL or UL medicine. ADRs occurred in 11% (116) of the 1046 admissions. ADRs were associated with 3.9% of licensed medicines, and 6% of OL/UL medicines.

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general  
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## 2.4 Discussion

This review adds to existing body of literature in confirming a high prevalence of OL and UL medicines use among paediatric patients in different paediatric settings. In 2007, the European Medicines Agency introduced a legislation, the Paediatric investigation Plan (PIP) that encourages inclusion of children in clinical trials (European Medicines Agency, 2007). This was to ensure sufficient paediatric formulations in the market, and to minimise OL and UL prescribing in paediatrics. Lindell-Osuagwu et al. (2009) reported that the proportion of prescriptions for OL use in different paediatric settings was 58% prior to the PIP legislation. A repeat study 10 years after the first found that the proportion of prescriptions for OL use was 79% (Lindell-Osuagwu et al., 2014). Although Lindell-Osuagwu et al reports show increase in OL prescribing following PIP legislation, Van Riet-Nales et al (2011) reported an improvement in development of newer types of paediatric dosage forms, such as mini-tablets or oro-dispersible films. The authors however concluded that there is still need for further research in paediatric medicines.

Paediatric medicines research is influenced by recent legislation to develop age-appropriate formulations; however, there are many challenging factors that affect designing suitable formulations for the paediatric population (Buckley et al., 2017). These factors include the heterogeneity of paediatric population especially in swallowing abilities, taste preferences, and dosage requirements (Buckley et al., 2017). To develop age-appropriate medicines therefore, collaboration between experts (formulators, clinicians, toxicologists and medicines' disposition scientists) for production of suitable amount of excipients, dosing regimen, duration of treatment, route of administration, as well as the indication is needed (Schmitt, 2015). Another factor that affects design of age-appropriate medicines is excipients selection. This is because there is a lack of specific standards regarding the safety of the excipients commonly used in the different groups

of paediatric populations as some excipients are implicated in safety incidents when used in paediatric population while they used safely in adults (Fabiano et al., 2011). The consequence of these challenges is that, there is lack of paediatric age-appropriate formulations and OL and UL medicines' use remains a problem in paediatric practice. Thus, most of medicines used for paediatric patients are used in an OL and/or UL manner with regard to age, indication, dosage and frequency (Ballard et al., 2013; Bellis et al., 2013; Conroy et al., 1999; Conroy et al., 2000; Di Paolo et al., 2006; Hsien et al., 2008; O'Donnell et al., 2002; Porta et al., 2010).

A higher prevalence of OL and UL medicines' use is reported in the neonatal intensive care unit than in other paediatric settings (Cuzzolin & Agostino, 2016; Lass et al., 2011; Lindell-Osuagwu et al. 2014; Oguz et al., 2012). The paediatric population with highest exposure to OL and UL medicines is neonates, particularly preterm neonates with all preterm neonates reported to receive at least one OL or UL medicine (Lass et al., 2011). That is because preterm neonates usually have very low body weight which affects absorption, distribution, metabolism and extraction of medicines. Underdeveloped organs, decrease in body water and co-morbidities during the developmental stages lead to further changes of the pharmacokinetics in this group of patients.

There were variation in definitions and classifications of OL and UL between the authors. Although Neubert et al. (2008) published a consensus definition of OL and UL use of medicines, most of the studies defined OL and UL use based on national formulary and/or SPCs while others adopted the Turner et al. (1998) definition. Thus, there is currently no consensus on the definition of OL and UL medicines use in paediatric. This can makes the judgement on OL and UL use limited to authors' classifications and categories, which made the comparison of published studies difficult. This review highlights the need for a consensus definition of OL and UL medicine use in

paediatrics and a uniform method of reporting OL and UL prevalence and safety to enable comparison.

OL and UL medicines prevalence is reported differently between authors. Whilst some authors report combined OL/UL prevalence (Lass et al., 2011; Cuzzolin & Agostino, 2016; Oguz et al., 2012), others report OL and UL separately (Conroy et al., 1999; Lee et al., 2013; O'Donnell et al., 2002; Turner et al., 1999). Thus, it is again difficult to compare the results between different studies.

The different studies employed different designs (prospective and retrospective). The study's design usually has a major effect in achieving the desired outcomes. Both prospective and retrospective designs involved review of drug charts and/or medical notes and databases. Variation in methods investigating the same subject can lead to variation in the results obtained.

Although there is high prevalence of use of OL and UL medicines in children in different in-patient care settings, problems associated with their use are low (Taylor et al., 2015). Medicines related problems (MRPs) comprised of Adverse drug reactions (ADRs), adverse drug events (ADEs), and medication errors (MEs), however the four studies included in this review assessed one aspect of the MRPs associated with the use OL and UL medicines (ADRs). The prevalence of ADRs associated with the use of OL and UL medicines are higher when compared with licensed medicines (Neubert et al., 2004; Turner et al., 1999). The risk of ADRs to OL and UL medicines increases with increased number of OL and UL used (Saiyed, Lalwani & Rana, 2015). ADR was classified as definite, probable or possible (Turner et al., 1999). OL and UL medicines are reported to be associated with higher prevalence of definite or probable ADRs (Bellis et al., 2013). Despite the fact that OL and UL medicines' use is common in paediatrics, it poses safety implications because of the major differences between children and adults in their pharmacokinetics and

pharmacodynamics. Thus, safety studies to explore all aspects of OL associated problems are important for this population. There is also the need for a holistic view at the problems that are associated with the use of OL and UL medicines in this patient population by assessing other aspects of MRPs.

A major limitation of this review is that it only focused on studies of OL and UL use in in-patient paediatrics settings, thus the findings may not present the overall picture of the prevalence and problems associated with OL and UL use of medicines in the paediatric patients in other settings. Another limitation of this review is that a meta-analysis of included studies could not be performed. This was due to the variation in OL and/or UL definitions, author's methodologies, participants age-groups, and settings.

Findings of this systematic review confirms results of previous reviews, and revealed high prevalence of use OL and UL medicines in paediatric in-patients. While there is high prevalence of use of OL and UL, problems associated with their use were low, and comprised mainly of ADRs, such as, macupapular rash, chills, ataxia and pyrexia. Further studies are required to evaluate the safety and effectiveness of OL and UL medicines use in this setting by investigating all other aspects of MRPs.

## **2.5 Chapter summary**

This chapter describes the systematic literature review that was undertaken to determine the prevalence of OL and UL medicines, and problems associated with the use of OL and UL medicines in paediatric patients.

- Findings of the review show high prevalence of OL and UL medicines use among paediatric patients, especially those admitted to intensive care units.

- There was no consensus on the definition of OL and UL use of medicines among the authors of the included studies
- There were no studies that investigated MRPs associated with use of OL and UL medicines in paediatric patients, however ADRs have been reported to be higher with the use of OL and UL medicines when compared with licensed medicines.
- This review therefore highlights the need for further research to investigate all aspects of MRPs associated with the use of OL and UL medicines in paediatric patients.

## **2.6 Research rationale, aim and objectives**

From the literature review, no study was found that investigated all aspects of MRPs associated with the use of OL and UL medicines in paediatric patients. Thus conducting a research to explore all aspects of MRPs associated with the use of OL and UL medicines in order to produce recommendations for improving paediatrics' practice is justified.

### **2.6.1 Research Questions**

1. What is the prevalence of MRPs associated with the use of OL and UL medicines in paediatric in-patients?
2. What are the types of MRPs associated with the use of OL and UL medicines in paediatric in-patients?
3. What is the severity of the identified MRPs?

### **2.6.2 Research Aim**

To investigate MRPs associated with the use of OL and UL medicines in paediatrics in-patients admitted to intensive care units (ICUs) of a paediatric hospital, London, United Kingdom.

### **2.6.3 Research objectives**

- To determine the prevalence of OL and UL medicines use, particularly problems associated with the use of OL and/or UL medicines in patients admitted to ICU of the paediatric hospital.
- To identify the type of MRPs experienced by patients admitted to ICU of the hospital.
- To categorise these MRPs according to their severity.
- To produce a list of recommendations to prevent MRPs associated with OL and UL medicines' use in paediatrics.



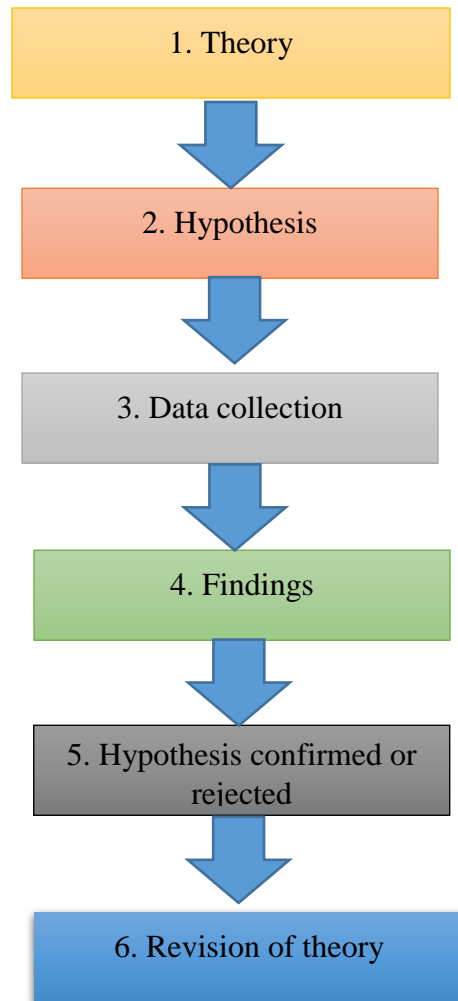
## **Chapter 3: Methodology**

### **3.1 Introduction**

Research is the systematic and rigorous process of enquiry, which aims to describe phenomena and to develop and test explanatory concepts and theories (Hunter & Long, 1993). Research is a comprehensive area that is informed by several elements. Some of these include theory, epistemology, and ontology. In the following sections, these different elements that inform choice of research methods and designs will be discussed.

#### **3.1.1 Relationship between theory and research**

Theory can be defined as a generalisation about a phenomenon, an explanation of how or why something occurs. It can also be defined as a widely accepted principle or explanation of nature (Creswell, 2003). Theory as well as background literature provide the basis and justification for conducting research. Based on the influence of theory, research can be divided into two main categories which are deductive and inductive research. Theories generate hypotheses that can be proven or disproved by research. In conducting research, the researcher can draw on theoretical ideas or what is known about a particular area in order to deduce a hypothesis; this is termed deduction (Bryman, 2015). After a hypothesis is deduced, data are collected in relation to concepts that have been made up from the hypothesis. Findings from data collected are then used to confirm or reject the hypothesis. Figure 3.1 shows the process of deduction and relationship between theory and research.



**Figure 3:1: The process of deduction (Sources: Bryman, 2015, Social research strategies**

On the other hand, induction involves observation of phenomenon of interest. This is followed by collection of data and generalisations based on findings from data. Once a set of initial data has been collected, further data are then collected to establish conditions in which a theory will or will not hold (Bryman, 2015).

### **3.1.2. Epistemology**

Epistemology is one of the branches of philosophy that is concerned with study of knowledge. It is concerned with what should be regarded as an acceptable source of knowledge. There are two

epistemological positions that have been adopted in the study of knowledge, these include positivism and interpretivism (Bowling, 2009; Bryman, 2015).

Positivism assumes that true knowledge is obtainable through experiment and observation on the basis of experience of senses (Guba & Lincoln, 1994). The positivist approach to enquiry has directed research in the natural sciences (e.g. bio-medicine) (Bowling, 2009). Positivism is related to an empiricist and deterministic philosophy that assesses cause and effect relationships, and seeks to measure in quantitative terms, observe and make objective predictions of relationships in the variables (Cook, 2015). Positivism is the world of science and testing hypotheses. In the positivist world, researchers are objective and strive to minimise sources of bias wherever they can. In other words, researchers exist apart from their data (Guba & Lincoln, 1994). Positivism aims to discover laws using quantitative methods to prove facts.

Quantitative research is therefore an empirical and systematic research into the phenomena that are observable. It involves either measuring certain characteristics in the population, counting these characteristics and/ or transferring these characteristics to numbers (Shagoury, & Power, 2012). Quantitative research methods include experiments which include randomised control trial (RTC), before-after, after-only, and time series; survey (cross-sectional and longitudinal surveys); computational and mathematical modelling and ex-post facto research (Bowling, 2009; Shagoury, & Power, 2012). Quantitative studies start with a predicament statement as well as include the hypothesis development, a literature evaluation and a quantitative statistics investigation (Creswell, 2003). Consequently, the approach will be objective; generate hypotheses and test them without any bias.

Interpretivism is an epistemological position often assumed by social scientists. It assumes that the study of social reality should not be subjected to the similar methods of research employed in

the natural sciences (Bryman, 2015). Interpretivists therefore hold the view that researchers need to be conscious of the fact that our language, ideas and concepts lead to our thoughts regarding the social world (Nelson, Groom & Potrac., 2014). For interpretivists, the research is interactive and jointly participative by the researcher and participants, thus the researchers' opinions are the key element in concluding findings (Bryman, 2015). Methods commonly employed are qualitative.

Qualitative research therefore investigates how people see or interpret events or how they make sense of their experience and the world around them. It describes and explains rather than count data (Goertz, & Mahoney, 2012). Methods of qualitative research include observation/ethnography, interviews, focus group, grounded theory study, and content analyses (Bowling, 2009). All qualitative strategies focus on three steps including namely: describing, explaining and interpreting composed data (Creswell, 2003).

### **3.1.3. Ontology**

Ontology is the study of beings and it attempts to identify things that are in existence around us. Essentially, it is the study of beings and their relative similarities and differences. Ontology attempts to respond to questions that start with 'what.' The subject is concerned with whether things exist or do not exist. The main positions in ontology include objectivism and constructivism (Charlwood et al., 2014). Objectivism assumes that social phenomena and their meanings have an existence that is independent or separate from human actors (Goldkuhl, 2012). The objectivists rely on quantitative methods. Constructivism focuses on how humans form meaning relative to interaction of their ideas and experiences. Constructivism advocates learning to be an active process in which learners make discovery of facts, concepts and principles for themselves. Thus, intuitive thinking is a main feature in constructivism (Fosnot, 2005). Constructivists argue that

human beings construct their own social realities in relation to one another. The goal of constructivist research is to gain understanding, as opposed to prediction. Qualitative research leans towards constructivism (Bowling, 2009; Bryman, 2015). The table below (Table 3.1) shows differences between quantitative and qualitative research:

**Table 3:1: Comparisons between quantitative and qualitative studies**

<b>Qualitative study</b>	<b>Quantitative study</b>
<b>Based on subjective data obtained through the scientific literature, focus groups and in-depth interviews.</b>	Based on objective (numeric) data obtained through the scientific literature, structured observations and interviews.
<b>Inductive: Generates hypothesis/ theories.</b>	Deductive: Tests hypothesis/ theories and concepts.
<b>Subjective: Provides the viewpoint of the researcher.</b>	Objective: Provides observed effect regardless of the research viewpoint.
<b>Text based.</b>	Number based.
<b>Comprehensive information from smaller sample size.</b>	Partial information with larger sample size.
<b>Open ended questions and unstructured/ semi-structured response.</b>	Closed ended questions and structured response.
<b>No statistical data analysis.</b>	Statistical data analysis.

While research methods have been broadly classified into two (quantitative and qualitative), there is increasing emphasis on the use of mixed methods in pharmacy practice research.

According to Leech & Onwuegbuzie (2008), mixed methods research is the research that involves collecting, analysing, and interpreting both quantitative and qualitative data in a single study or in a series of studies that investigate the same phenomenon. According to Agency for Healthcare Research and Quality (AHRQ), using mixed methods strengthens and enhances validity of a study and offset weaknesses and limitations of certain research methods (AHRQ, 2013). Mixed method approach also enables the researcher to collect comprehensive data from different perspectives, which helps to reduce the researcher’s personal bias.

This research followed a positivist approach because it sought to measure certain characteristics (medicines related problems (MRPs) associated with the use of off-label (OL) and unlicensed (UL) medicines) in a certain population (paediatric in-patients) by counting these characteristics. Thus, quantitative method was employed in this research.

Quantitative methods provide the researcher the ability to capture and measure data. The relationship between dependent and independent variable is studied in a comprehensive manner. Hence, it is to the advantage of the researcher that the study is objective in terms of its findings and outcomes. The method is also used in the testing of hypotheses of experiments owing to its utility of statistical tools to establish relationship between data set. The key disadvantage of quantitative method is that the context of experiment or study is not taken into account when using statistical analysis. Quantitative method does not evaluate elements in natural settings or comprehends meaning of different aspects as it is in qualitative methods. Another disadvantage is that there may be an element of unintentional bias as statistical results may lead to correlation. However, correlation may not imply causality as can be deduced from outcomes (Goertz, & Mahoney, 2012).

Quantitative research can employ experimental or observational designs. Experimental studies involve manipulation and randomisation of subjects while observational studies do not involve intervention or experiments and are conducted under a physical appearance of the researcher and document the phenomena of the interest without bias (Creswell, 2003; Smith, 2002). Observational studies can be cross-sectional (data is collected from population of interest at one point in time), or longitudinal (data is collected two or more times from the same population over a specified period) (Bowling, 2009). Observational studies can be conducted prospectively (where data

collection takes place over the forward passage of time) or retrospectively (data is collected from a phenomenon that occurred in the past).

Prospective and retrospective cohort studies have different strengths and weaknesses. The major strength of a prospective cohort study is the accuracy of data collection with regard to exposures, confounders, and endpoints, but this is realised at the cost of an inevitable loss of efficiency, for this design is both expensive and time-consuming because of a usually long follow-up period. Vice versa, the retrospective design is a very time-efficient and elegant way of answering new questions with existing data, but one has no choice other than to work with what has been measured in the past, often for another purpose (e.g. patient care) than the one under investigation.

Retrospective cohort studies have the following distinct advantages when compared with prospective cohort studies (Sedgwick, 2014):

- can be conducted on a larger scale
- achieve greater variability
- require less time to complete
- fewer ethical objections
- better for analysing multiple outcomes.
- generally less expensive because outcome and exposure have already occurred, and the resources are directed at mainly collection of data

On the other hand, retrospective studies have disadvantages when compared to prospective studies. These disadvantages include that some key statistics cannot be measured, and significant biases may affect the selection of controls (selection bias and miss-classification or information bias).

With retrospective studies, the temporal relationship is frequently difficult to assess. Also, those who conduct retrospective studies cannot control exposure or outcome assessment but instead need to rely on others for accurate recordkeeping. That is particularly problematic because it can be very difficult to make accurate comparisons between the exposed and the non-exposed subjects. Retrospective studies may also need very large sample sizes for rare outcomes (Creswell, 2003). In retrospective studies bias is introduced in the sample selection; whereas in prospective studies it is introduced in outcome judgment (Gerhard, 2008). Table 3.2 summarises key elements of prospective and retrospective studies (Koop & Strang, 2001; Mann, 2003; Weinger, Slagle, Jain, & Ordonez, 2003):

**Table 3:2: Comparison of the key elements of retrospective and prospective studies**

<b>Key element</b>	<b>Prospective</b>	<b>Retrospective</b>
<b>Exposure</b>	Assessed at the time the study commences	Assessed in the past.
<b>Direction</b>	Forward	Backward
<b>Sample selection</b>	Samples are selected from the available participants	Samples are selected from the available data
<b>Ethical requirements</b>	More ethical requirements	Less ethical requirements
<b>Data collection</b>	Data is collected by the researcher	Data is already available for the researcher
<b>Data analysis</b>	Analysis of the outcome and underlying factors	Analysis of the outcome and underlying factors.
<b>Duration</b>	Longer study duration	Shorter study duration
<b>Cost</b>	More expensive	Less expensive
<b>Outcome</b>	The outcome is pursued throughout the study	The outcome has already occurred
<b>Intervention</b>	Intervention is possible	Intervention is not possible

While it is easier and less expensive to conduct a retrospective study, in this research both retrospective and prospective methods were employed to generate robust data and compare results from the different designs. Also because this is the first study to investigate MRPs associated with the use of OL and UL medicines, both methods were adopted to strengthen the findings.



## 3.2 Assessing quality in research

### 3.2.1 Validity

Validity refers to the extent to which the findings of a study are a true reflection of phenomena under study (Bryman, 2015). Validity refers to the degree in which test or measure device is truly measuring what we intended it to measure. It demonstrates the integrity of findings that concluded from the research. Types of Validity are (Bryman, 2015):

- Internal validity: is concerned with the causal relationship between two or more variables in the study.
- External validity or generalisability: is concerned with whether the findings can be generalised beyond the specific research context. The most important factors that determine the generalisability of study findings are the sampling strategies, procedures and sizes, and response rates (e.g. surveys), and representativeness and completeness of data (e.g. databases). If probability sampling strategy is employed; and there is comprehensiveness of databases and sampling frames, good response rates (surveys) and steps are taken to ensure data collected are valid, findings should be generalisable to the population from which the sample was drawn.
- Construct validity: is the term given to a test that measures a construct accurately and there are different types of construct validity, mainly concurrent, content and predictive validity.

In this research, a content validity was performed for the data collection form, identification of MRPs, causes of MRPs, intervention and outcome of MRPs, severity and preventability of MRPs.

### **3.2.2 Reliability**

Reliability refers to the extent to which procedures, measures and data are reproducible. Methods of testing reliability include test-retest, alternate form and internal consistency (Bowling, 2009). In this research, method adopted to check reliability was test-retest of the data collection form.

### **3.3 Sampling in research**

In research, sampling technique used depends on the type of research employed. In quantitative research, probability sampling techniques such as simple random sample, systematic sample, stratified sampling, cluster sampling are employed. Non-probability sampling techniques, such as, convenience sampling, purposive sampling and snowballing technique are employed in qualitative studies (Smith, 2002). For the purpose of this study, random sampling was used as it demonstrates no bias, and all participants have the same chance of selection, and equal probability to be included.

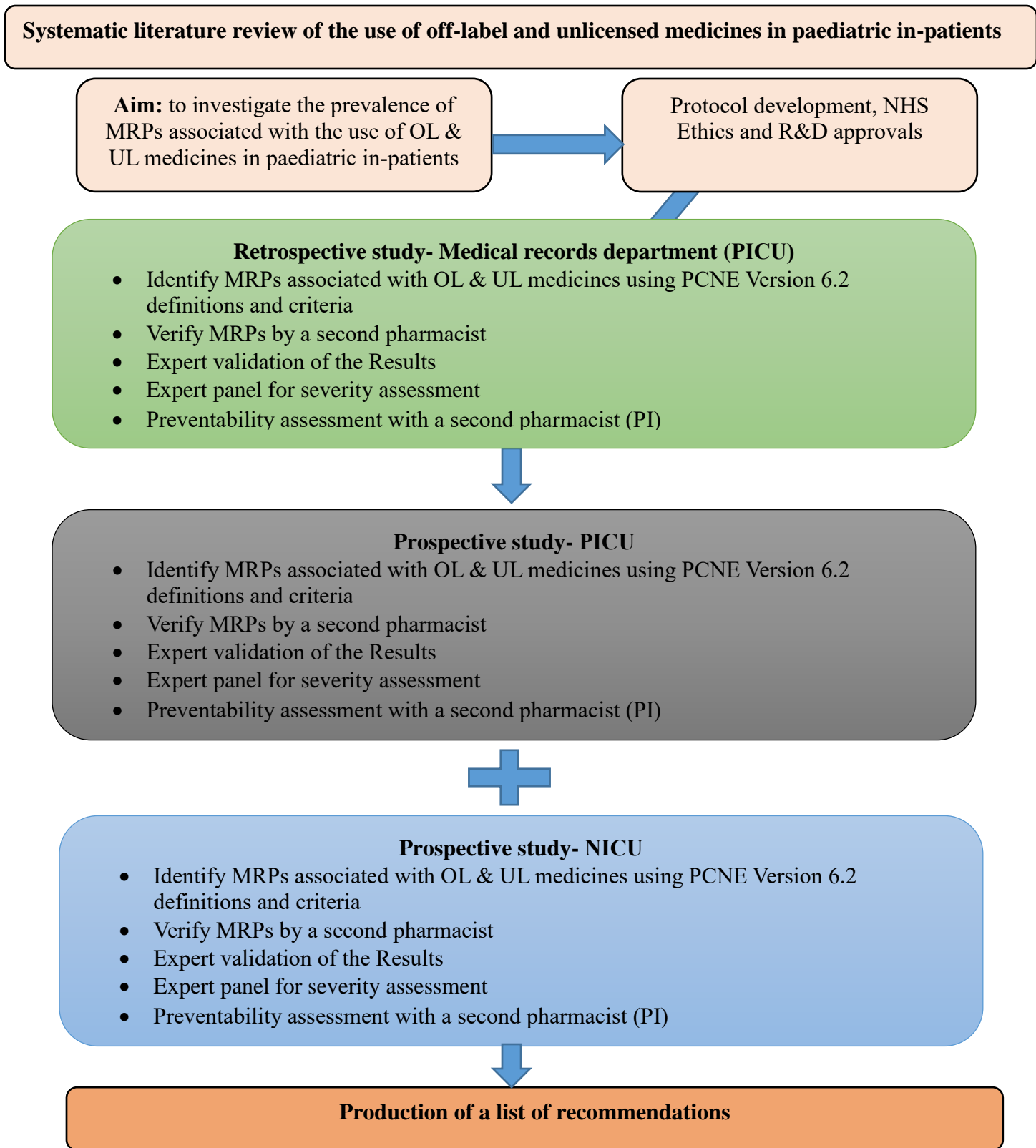
### **3.4 Study framework**

Research framework is defined according to Liehr and Smith (1999) as a structure that provides guidance for the researcher as study questions are fine-tuned, methods for measuring variables are selected and analyses are planned. Once data are collected and analysed, the framework is used as a mirror to check whether the findings agree with the framework or whether there are some discrepancies; where discrepancies exist, a question is asked as to whether or not the framework can be used to explain them (Smith, 2002).

As indicated in Chapter 2, section 2.6, the aim of this research was to investigate MRPs in paediatric patients admitted to paediatric intensive care units (PICU) and neonatal intensive care unit (NICU) of a paediatric hospital.

The research was undertaken in two different phases: retrospective and prospective. The retrospective phase involved review of medical case notes of patients admitted into PICU between April and September 2014. This was carried out between March and August 2015.

The prospective phase was divided into two studies and was conducted in the two units (PICU & NICU). The first study was undertaken in PICU for a period of six months from October 2015 to March 2016, and the second study was undertaken in NICU over a six months period from January 2016 to June 2016. The studies covered different periods to ensure data collected included information from different seasons' epidemiological illnesses. The figure below shows the timing and phases of the studies:



**Figure 3:2: Medicines related problems study framework**

### **3.5 Study Setting**

The use of OL and UL medicines is common in paediatric healthcare settings. However, a systematic review assessing OL/UL prescription in paediatrics found higher rates in hospital versus community and primary care settings (Pandolfini & Bonati, 2005). In hospital settings, OL/UL prescription was found to be higher in paediatric and neonatal intensive care units than in general paediatric wards. Ninety percent of patients admitted to NICU are reportedly prescribed OL and/or UL medicines, while 67% of patients admitted to PICU are prescribed OL and/or UL medicine (Conroy, McIntyre & Choonara, 1999; Conroy et al., 2000). Therefore, the choice of the study setting (ICUs in secondary care setting) was based on the findings in literature, and was not based on the advantages and disadvantages of conducting research on primary and secondary care settings.

### **3.6 Research Tools**

In this research, the Pharmaceutical Care Network Europe (PCNE V6.2) classification was used. The following section provides a brief description of PCNE.

#### **3.6.1 Pharmaceutical Care Network Europe**

The PCNE was established in 1994 by European researchers on pharmaceutical care. The first classification scheme for medicines related problems was produced in 1999 (Pharmaceutical Care Network Europe, 1999). The main aim of the classification system was to ensure an international standard system, which enable health care professionals to compare results from research, studies between different settings and different countries. This classification system has been updated several times, and different versions has been developed such as Version 5 and Version 6.01. According to the published studies, the PCNE classification version 5.00 has been used in the

hospital setting and in nursing homes (Lampert et al., 2008, Brulhart and Wermeille 2011) and the version 5.01 in community pharmacies during dispensing (Eichenberger et al., 2010), in medication review clinics (Chan et al., 2012) and among diabetics (van Roozendaal and Krass 2009).

The latest version was produced in 2010 defining MRPs as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” (PCNE, 2010). This latest classification scheme differs from the previous versions as it has separated the medicines’ problems from causes. It also has an open hierarchical structure for each category, which consists of type of problems, causes of the problems, interventions taken to solve the problems, and the outcome. The hierarchical structure also uses a coding system to facilitate data recording.

While PCNE has been adopted by several researchers to evaluate MRPs, it is not without limitations. For example, Chan et al. (2012) in their study reported that several MRPs could not be classified into any existing PCNE categories. The authors also reported that the tool did not have a good indicator for poor medication adherence (that is, drug not taken/administered), consequently, they introduced a new category. Also Lampert, Kraehenbuehl & Hug (2008) in a study conducted in a hospital setting concluded that the PCNE system lacked some MRP’ categories such as incompatibilities, application errors or faulty transcriptions. In a related study to classify MRPs in community pharmacies, the authors introduced extra problems’ categories in the PCNE classification tool in order to capture all the identified MRPs (Eichenberger et al., 2010).

Although the authors of studies described in the preceding paragraph identified problems that could not be classified into any PCNE category, the tool has been used in studying MRPs in paediatric in-patients because of its versatility (Rashed et al, 2012; Ibrahim et al., 2013). The

PCNE was therefore adopted as the tool of choice for this research project. In addition, the coding system and hierarchical structure facilitates the data collection.

The PCNE classification system was used concurrently with the Naranjo Scaling system of probability where there was more than one cause and where there was a strong existence of probability.

### **3.6.2 Causality assessment**

Causality assessment is the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event, and it assesses the relationship between a medicine treatment and the occurrence of an adverse event (Macedo, 2005). When an adverse event occurs in a patient, it may be difficult to determine whether the event was caused by a certain medicine in the presence of a complex therapy. Naranjo and colleagues have developed a probability scale, the Naranjo Adverse Drug Reaction Probability Scale (Naranjo Scale) (Appendix 2), to assess the probability that a drug administered in therapeutic doses caused an adverse event thereby classifying the event as an adverse drug reaction (ADR). This scale helps to reach a valid and reliable judgement of causes of adverse events via some questions and points, which are based on scoring system, and classified the causes of ADRs as definite, probable, possible and doubtful (Naranjo, 1981).

Due to the fact that MRPs have no probability scale of causality, the Naranjo scale was used to identify the medicines that were associated with the identified MRPs. This scale was preferred because in practice, different forms of the same medicine might be used at the same time, or more than one medicine might be implicated in an adverse event or MRP. However there are many other causality systems in the literature, the most widely used scales are Naranjo Algorithm and World Health Organisation Collaborating Centre for International Drug Monitoring, the Uppsala

Monitoring Centre system (WHO–UMC) (WHO, 1975). This system classified causes of ADRs as certain, likely, possible, unlikely, conditional and un-assessable. In this research project, Naranjo scale was preferred over the WHO system because the scale is easy to understand and the questions are straightforward thus, allowing meaningful conclusions to be drawn. After identifying the problems and their causes, the severity of these problems are of high importance to the health care professionals. As well as causality assessment, there is no severity scaling system for MRPs and so using adverse reactions and adverse events severity scoring system was the only choice. Thus, National Patients Safety Agency Level of harm was used to categorise the clinical significance of the identified medicines related problems.

### **3.6.3 National Patient Safety Agency Level of Harm**

The NPSA level of harm was developed to assess patient safety incidents. The level of harm is categorised into five as follow (NPSA, 2011):

- **No harm:**
  1. Impact prevented – any patient safety incident that had the potential to cause harm but was prevented, resulting in no harm to people receiving NHS-funded care.
  2. Impact not prevented – any patient safety incident that ran to completion but no harm occurred to people receiving NHS-funded care.
- **Low harm:** Any patient safety incident that required extra observation or minor treatment and caused minimal harm, to one or more persons receiving NHS-funded care.
- **Moderate harm:** Any patient safety incident that resulted in a moderate increase in treatment and which caused significant but not permanent harm, to one or more persons receiving NHS-funded care.



- **Severe harm:** Any patient safety incident that appears to have resulted in permanent harm to one or more persons receiving NHS-funded care.
- **Death:** Any patient safety incident that directly resulted in the death of one or more persons receiving NHS-funded care.

Although the NPSA system clearly defines all the different levels of harm, some confusion might still occur with regard to potential problems that did not reach the patient because some professionals might still evaluate the harm had it occurred. The assessment whether it is based on the actual or potential harm is challenging. Thus, clear communication and good explanation of how to use the system is crucial. The severity scoring in this research was done by a panel of experts consisting of consultant clinical pharmacist, a consultant paediatrician and a nurse.

#### **3.6.4 Preventability**

Preventability of the identified MRPs was assessed by the researcher and the clinical consultant pharmacist using Schumock and Thornton preventability scale (Schumock and Thornton, 1992). The Schumock and Thornton preventability scale is a validated scale and has been previously in paediatric MRPs studies (Rashed et al., 2012; Easton et al., 2004; Easton et al., 2003). Table 3.3 below describes the Schumock and Thornton preventability scale.

**Table 3:3: Schumock and Thornton preventability scale**

<b>Definitely Preventable</b>
<b>1. Was there a history of allergy or previous reactions to the drug?</b>
<b>2. Was the drug involved inappropriate for the patient's clinical condition?</b>
<b>3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?</b>
<b>4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?</b>
<b>5. Was there a known treatment for the adverse drug reaction?</b>
<b>Probably Preventable</b>
<b>6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?</b>
<b>7. Was a drug interaction involved in the ADR?</b>
<b>8. Was poor compliance involved in the ADR?</b>
<b>9. Were preventative measures not prescribed or administered to the patient?</b>
<b>Not preventable If all above criteria not fulfilled</b>

Details of the use of the three tools used in this research are presented in chapters 4, 5 and 6.

### **3.7 Ethical considerations**

Ethical approval for this research was sought and obtained from the University of Hertfordshire (Protocol Number: LMS/PG/00290) (appendix 3). Application was also made to the NHS REC Committee (NRES Committee North West - Greater Manchester South) (appendix 4) and an approval was obtained (15/NW/0263) (appendix 5). Application for access (appendix 6) was made to the Research and Development department of the hospital, a letter of access was obtained, (RJ115/N167). All patients' relevant information was protected through different numbers of measures: Confidentiality agreement was signed by the researcher, patients' information were anonymised, and electronic devices, where the data were stored, was a password protected. Data collected did not include any identifiers or patients' identifiable information and all the collected parameters were anonymised. All the collected data will be destroyed after three years following

project completion. This research project was sponsored by the University of Hertfordshire (Appendix 7&8).

Explicit patients' consent was not required as that will limit the number of records to be reviewed as this study is a non-interventional study. The researcher was given an honorary contract and considered as a member of staff accountable to the consultant pharmacist, who was the local collaborator and principal investigator of the project. This honorary contract gives permission for viewing patients' case-notes. In addition, this study, aimed to establish the prevalence of medicines related problems associated with unlicensed and off-label medicines' use in paediatrics, and if patient consent is required, this will affect the true number as not all patients may agree to a record review. In the event that the researcher identified an MRP that was clinically significant, the researcher would contact the pharmacist in charge of the unit, who would be responsible to deal and liaise with the clinical team to resolve the problem. The researcher also undertook an extensive training in line with the local policy to take a professional position in event that identified MRP might result in a serious harm to the patient. With regard to near misses and potential MRPs, the researcher was obligated to report to the head of the unit who was responsible for entering the data in the local incidents reporting system (DATIX).

### **3.7.1 Implications of General Data Protection Regulations on research**

The new General Data Protection Regulations (GDPR) introduces protection of data subjects especially, the paediatric population. All subject data should be collected for specified and legitimate purposes and should be processed only for the stated purposes and not any incompatible purposes. Data size also should be minimised and limited to what is necessary. Consent should be obtained and freely given in an unambiguous, specific and clear affirmative action and needs to be

documented from a person who holds a parental responsibility of a child age under 13 years old, and an assent form must be signed by children over 13 years old. This might limit the sample size of paediatric patients in research on new medicinal products because of complexity of obtaining consent. However this ensure maximum protection for paediatric patients who participate in research studies and harmonisation of subject data which in turn will improve research quality and data will be treated fairly with minimum bias. Also, third parties will not be involved and there will be a high level of transparency of information of included participants.

### **3.8 Chapter summary**

This chapter described the core elements that guide this research. The specific methods and the tools employed in this research are described. The steps taken to ensure this research complied with ethical requirements are also described. In the next chapter, description of the first study is provided.

## **Chapter 4: Retrospective study of off-label & unlicensed medicines' related problems in paediatric intensive care unit**

### **4.1 Introduction**

In Chapter 1, section 1.10.3, it was found that a limited numbers of studies have investigated medicine related problems (MRPs) in the paediatric population. MRP was associated with 4.3% of paediatric hospital admissions in a study that sought to determine the frequency of paediatric hospital admissions due to MRPs (Easton, 2004). In a related study, 3.3% of emergency department admissions were associated with MRPs (Easton, 2003). Another study, which investigated MRPs in paediatric patients, found that the overall MRPs incidence in the United Kingdom was 39.4% among paediatric patients admitted to Paediatric Intensive Care Unit (PICU), Neonatal Intensive Care Unit (NICU) and general medical ward. The highest incidence of MRPs from the overall study cohort was reported from PICU (59.7%) (Rashed et al., 2012b). MRP is a broad term that includes adverse drug reactions (ADRs) and medication errors that can lead to treatment effectiveness' problems (PCNE, 2010). While some studies have looked at ADRs associated with use of OL and UL medicines in paediatric in-patients (Turner et al., 1999; Rashed et al., 2012a), no study was found that investigated MRPs associated with the use of off-label (OL) and unlicensed (UL) medicines in paediatric patients. The Pharmaceutical Care Network Europe (PCNE) classification system classifies MRPs into four domains, including treatment effectiveness (healthcare professional domain), adverse drug reactions (drug domain), treatment costs (economic domain), and others (patients and/or unclear problem domain) (PCNE, 2010). For the purpose of this project, MRPs due to OL and UL medicines use in paediatric inpatients was studied from healthcare professionals' perspective.

## **4.2 Aim**

The aim of this retrospective study was to investigate MRPs associated with the use of OL and UL medicines in paediatric patients who were admitted to PICU of a paediatric hospital between April and September 2014.

## **4.3 Objectives**

- To determine the prevalence of OL and UL medicines use in PICU of the hospital.
- To determine the prevalence of MRPs in the unit.
- To determine the prevalence of MRPs associated with the use of OL and UL medicines in this unit of the hospital.
- To assess the severity of the identified MRPs.

## **4.4 Methods**

### **4.4.1 Study setting**

The setting of this study is a 140-bed paediatric teaching hospital. The hospital has two intensive care centres, paediatric and neonatal intensive care units.

### **4.4.2 Study population and sampling procedure**

In this retrospective study, data was collected from the medical records department of the hospital. Case notes of patients aged 0-18 years old, who were admitted to PICU between April and September 2014 were reviewed. Case notes for review were identified by members of the audit department of the hospital; the researcher then applied a computer random sampling to obtain the required sample size.

#### 4.4.3 Inclusion and exclusion criteria

Case notes of patients who were under 18 years old and were admitted to PICU and on medicines were included. Case notes of deceased patients were excluded as there was no access to their case notes. Also case notes of patients who were on nutritional products but not medicines were excluded.

#### 4.4.4 Sample size

A study conducted by Conroy et al. reported that 67% of patients who were admitted to PICU received either off-label and/or unlicensed medicines (Conroy et al., 2000). The literature review of this thesis found no studies that investigated MRPs associated with the use of OL and UL medicines in paediatric population. Consequently, the sample size calculation was powered around the number of patients who were admitted to PICU, and prescribed OL and/or UL medicines. The sample size for this retrospective study was calculated as follows (Ausvet, 2014):

$n = Z_{\alpha/2}^2 * p * (1-p) / MOE^2$ , where:

$Z_{\alpha/2}$  is the critical value of the normal distribution based on the width of 95% confidence interval  
= 1.96

MOE is the margin of error = 0.07 (or 7%)

P is the sample proportion = 0.67 (67% of patients in PICU received either OL/UL medicines).

Assuming that similar prevalence reported by Conroy et al. might be found in the study setting, the sample size for this retrospective study was calculated to be 176 patients' case notes. The sample size was then inflated by 10% to make up for case notes that might have missing information, thus the sample size for this retrospective study was 194 case notes.

#### **4.4.5 Power calculation for sample size**

A power calculation was performed for the sample size in order to ensure the quality of the research. The results were retrieved via statistical method by STATA, and it demonstrated a high level of accuracy (99.2%).

#### **4.4.6 Ethical considerations**

Ethical approval for this study was obtained from University of Hertfordshire, NHS Research Ethics Committee (REC) and Research and Development (R&D) department as described in Chapter 3 section 3.6. To ensure confidentiality of patient information, the research signed a confidentiality agreement. Data collected did not include any patients' identifiable information; all parameters collected were presented anonymously. Data collected were stored in password-protected devices. Explicit patients' consent was not required in this study because this was a non-interventional study.

The following section describes a feasibility study conducted to validate data collection.

#### **4.4.7 Development of a data collection form to identify medicines related problems in paediatric in-patients**

A data collection form that incorporated all types of MRPs associated with the use of OL and UL medicines in paediatric in-patients was designed. This feasibility study was conducted at the beginning of the retrospective study (Phase 1) in order to assess the practicality of the data collection form and to ensure the accuracy of information collected. The feasibility study was carried out by the researcher. Findings of the study facilitated the development of the tool to be used for data collection.



#### **4.4.7.1 Process of assessing the practical use of the data collection form**

The parameters included in the form were: patients' demographics including age, weight, height, gender and ethnicity. It also included: medicine name, date prescribed, route of administration, dose, frequency, duration, indication, and whether the medicine is licensed, unlicensed or off-label. MRPs were categorised according to the PCNE classification system version 6.2 (PCNE, 2010). Licensing status of medicines was assessed using Summary of Product Characteristics (SPC) of medicines obtained from the Electronic Medicines Compendium.

#### **4.4.7.2 Outcome of the feasibility study**

The form was initially used to collect data from medical records, drug charts and laboratory data of five patients. Some changes were made to the form (example, ethnicity was removed as it was not reported in most of the case notes). The second version of the form was used to collect data from 15 medical case-notes. Further changes were made to the layout of the form; the final version of the form was produced (appendix 9). The form was validated by a consultant clinical pharmacist with expertise in patient and medication safety, who was also the principal investigator in this study.

#### **4.4.8 Data collection**

Data collection included the retrieval of information from medical records, drug charts and laboratory data. Patients' medical notes were obtained from the Medical Records Department of the hospital. Data retrieved included: patient age, weight, height, gender, length of stay and medications. Intensive chart review method was adopted as it has been used in a previous study in paediatric population (Ghaleb et al., 2010). Medicines dosage forms, route of administration, indication, dose, frequency and duration were retrieved. Medicines were classified as licensed, off-

label and unlicensed according SPC as well as the Turner et al. (1998) classification of OL and UL use of medicines. Age was categorised into five different groups according to International Conference of Harmonization Guideline E11 as follows: preterm newborn infants, term newborn infants (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 –11 years) and adolescents (12 to 17 years) (ICH, 2001). Diagnosis and co-morbidities were categorised according to the International Classification of Diseases version 10 (WHO-ICD, 2014).

Definition and classification of MRPs was based on the PCNE classification version 6.2, which defines MRP as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (PCNE, 2010). When an MRP was identified, Naranjo scale was used to identify the medicines that were associated with the identified MRPs. The details including the type of MRP, causes, interventions and outcome of the interventions were recorded. An example of how MRPs were identified is provided in the Table 4.1.

**Table 4:1: Identification of medicines related problems**

Identification of medicines related problems			
<b>Patient details</b>		<b>Medical diagnosis &amp; co-morbidities</b>	
<b>Study ID</b>	188	Elective admission for atrial sept-ostomy, respiratory distress, high pulmonary pressure.	
<b>Age</b>	1 week	Allergy was unknown at the beginning then the patient developed a skin reaction.	
<b>Weight</b>	2.8kg		
<b>Height</b>	Not recorded		
<b>Gender</b>	F		
<b>Length of stay</b>	3days		
<b>Medications</b>			
<b>Name of medicine</b>	<b>Dose</b>	<b>Frequency</b>	<b>Route of administration</b>
<b>Flucloxacillin</b>	150mg	<b>Bd</b>	Iv
<b>Morphine 3mg/50ml</b>	10/mcg/kg/hr	<b>Cont</b>	Iv
<b>Dopamine100microgr:</b>	10micro/Kg/min	<b>Cont</b>	Iv
<b>Gentamicin</b>	26mg	<b>Od</b>	Iv
<b>Benzympenicillin</b>	165mg	<b>Tds</b>	Iv
<b>Fentanyl</b>	3mcg	<b>Stat</b>	Iv
<b>Ketamine</b>	3mg	<b>Stat</b>	Iv
<b>Paracetamol</b>	50mg	<b>Qds</b>	Ng tube
<b>Cefotaxime</b>	150mg	<b>Stat</b>	Iv
<b>Clinical narrative</b>			
<b>The patient developed severe skin reaction after administration of flucloxacillin. The medicine was stopped and the patient was prescribed chlorphenarmin injections. Penicillin allergy was indicated in the patient's case following the reaction to flucloxacillin.</b>			

Data were stored electronically after review of the drug charts and medical notes in the audit office in the hospital. The data were coded anonymously to ensure patients confidentiality. To ensure validity of the identified MRPs, a consultant clinical pharmacist was asked to review the problems, causes, interventions and outcome during meetings with the researcher.

To assess the severity of the identified MRPs, the National Patient Safety Agency categorisation for the level of harm was used. Table 4.2 shows the National Patient Safety Agency categorisation for the level of harm.

**Table 4:2: National Patient Safety Agency categorisation for level of harm**

<b>Level of Harm</b>	<b>Definition</b>
<b>No Harm</b>	A situation where no harm occurred: either a prevented patient safety incident or no harm patient safety incident.
<b>Low</b>	Any unexpected or unintended incident which required extra observation or minor treatment and caused minimal harm, to one or more persons.
<b>Moderate</b>	Any unexpected or unintended incident which resulted in further treatment, possible surgical intervention, cancelling of treatment, or transfer to another area and which caused short term harm, to one or more persons.
<b>Severe</b>	Any unexpected or unintended incident which caused permanent or long term harm, to one or more persons.
<b>Death</b>	Any unexpected or unintended incident which caused the death of one or more persons.

A panel of three experts consisting of a consultant paediatrician, a consultant clinical pharmacist and a medicines' safety and retrieval practitioner nurse assessed 10% percent of the identified MRPs. In this study, only 10% of identified MRPs were assessed for severity because of time constraints on the part of the experts invited. Secondly, no specific cut off for the number of cases for severity scoring was identified in literature. The consultant clinical pharmacist, who was also the principal investigator of this study, identified and recruited the other two experts using convenient sampling technique. Although the three experts had different backgrounds, it was important to explore opinions of experts from different professions to minimise bias. The experts rated the level of harm of each problem individually. Kappa test was used in order to assess the experts' agreement on severity. The test is measured on a scale ranging up to a maximum agreement of one. Table 4.3 provides an interpretation of Kappa test ranges (<https://wwwusers.york.ac.uk/~mb55/msc/clinimet/week4/kappash2.pdf> ).

**Table 4:3: Kappa test for level of agreement**

<b>Value of Kappa</b>	<b>Strength of agreement</b>
<b>&lt; 0.20</b>	<b>Poor</b>
<b>0.21 – 0.40</b>	<b>Fair</b>
<b>0.41 – 0.60</b>	<b>Moderate</b>
<b>0.61 – 0.80</b>	<b>Good</b>
<b>0.81 – 1.00</b>	<b>Very Good</b>

Preventability of identified MRPs was assessed by the researcher and the clinical consultant pharmacist using Schumock and Thornton preventability scale.

#### **4.4.9 Data analysis**

Data collected were analysed using computer programmes including Excel, Statistical Package for the Social Sciences (SPSS) and STATA. Descriptive statistics including frequencies, medians, standard deviation, and interquartile range were performed. Data were presented as numbers and percentages. Chi-squared test was used to detect significant differences for categorical variables while Kruskal–Wallis rank and Wilcoxon Rank-Sum (Mann–Whitney U) were used to determine significant differences between numerical variables. For all tests,  $p < 0.05$  was selected as the level of statistical significance.

Data analysis regarding MRPs was divided into nine parts:

- Number of patients who developed MRPs due to different licensing status of medicines, the total number of medicines prescribed during the study period, and comparison of licensed, UL and OL medicines use and their associated problems using the Chi-square test.

- Prevalence of licensed, UL and OL medicines use in the different age groups and the associated problems.
- Occurrence of MRPs between genders using Chi-square test.
- MRPs categories in patients and the medicines associated with them.
- The association between MRPs and the length of stay (LOS) in the hospital using Kruskal-Wallis.
- The relationship between the number of medicines and the number of MRPs using Pearson test.
- MRPs causes, interventions and outcome using the PCNE classification system V 6.2.
- Severity of the identified MRPs using Kappa test.
- Preventability of MRPs using Schumock and Thornton Preventability Scale.

## **4.5 Results**

### **4.5.1 Patients' demographics**

A total number of 194 case-notes of paediatric patients who were admitted to PICU between April and September 2014 were reviewed over a 3-month period. In the study cohort, majority were infants (35%) and children (30%). Table 4.4 summarises different age groups in the study cohort.

**Table 4:4: Different age groups of the study population**

<b>Age group</b>	<b>Age range</b>	<b>Number of patients (n), Percentage (%)</b>
<b>Preterm new born neonates</b>	Less than 38 weeks	15 (8)
<b>Term new born neonates</b>	0- 27 days	35 (18)
<b>Infants</b>	28 days- 2 years	69 (35)
<b>Children</b>	2 years- 12 years	58 (30)
<b>Adolescents</b>	12 – 18 years	17 (9)

\*Analysis involved descriptive statistics (frequencies and percentages)

The most common diagnoses were congenital malformations abnormalities (n=113 patients), diseases of the respiratory system (n=22), and certain infectious and parasitic diseases (n=19). From the 113 patients who were diagnosed with congenital malformations abnormalities, 90% (n= 102/113) were born as premature neonates. The average length of stay was 3days (range 2-20 days;  $M = 3$ ,  $SD \pm 2.9$ ). Table 4.5 summarises the study participants' diagnosis and number of patients who developed MRPs with each diagnosis.

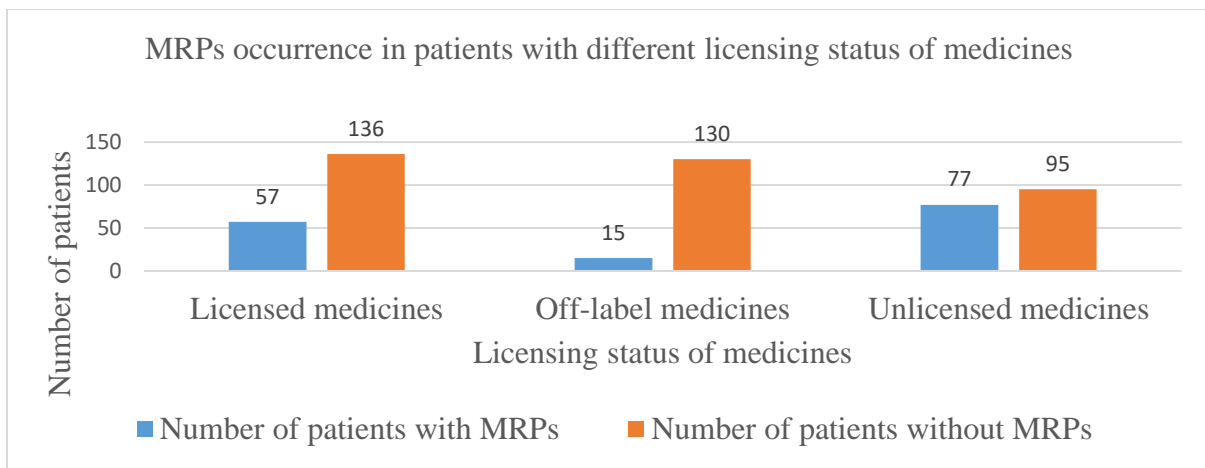
**Table 4:5: Patients' diagnosis and number of medicines related problems**

<b>Diagnosis</b>	<b>Number of patients</b>	<b>Number of patients with MRPs</b>
<b>Congenital malformations abnormalities</b>	113	71
<b>Certain infectious and parasitic diseases</b>	22	10
<b>Diseases of the respiratory system</b>	19	6
<b>Disease of blood and blood-forming organs</b>	16	7
<b>Certain conditions within perinatal period</b>	15	4
<b>Disease of the digestive system</b>	9	4
<b>Neoplasms</b>	3	2

\*Analysis involved descriptive statistics (frequencies and percentages)

#### 4.5.2 Medicines related problems in patients in relation to the different licensing status of medicines

From the total number of patients, 53% (n= 102/194) developed at least one MRP during admission. Thirty percent (n= 57/193) of patients who received licensed medicines developed MRPs. Forty-five percent (n= 77/172) of patients who received UL medicines developed MRPs and 10% (n= 15/145) of patients who received OL medicines developed MRPs. The proportion of patients who experienced MRPs due to licensed, UL and OL medicines are summarised in Figure 4.1.



**Figure 4:1: Medicines related problems in patients in relation to different medicines' licensing status**

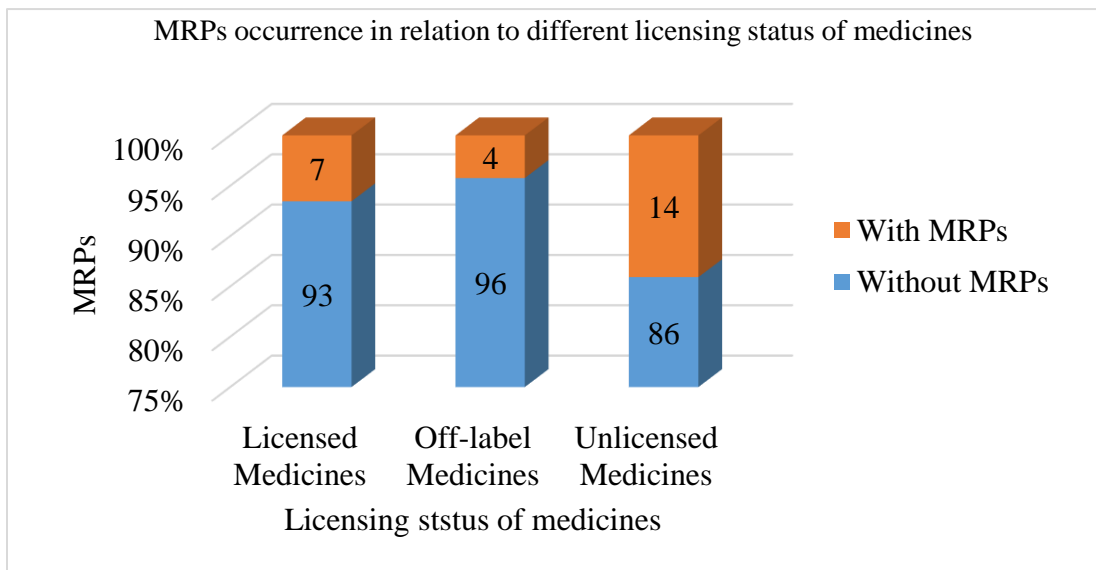
#### 4.5.3 Medicines related problems occurrence in relation to different licensing status of medicines

A total of 2,000 medicines were prescribed to the 194 patients, out of which 54.3% (n= 1085/2000) were licensed and 45.7% (n=915/2000) were OL and UL; 17.7% were OL (n= 354/2000), and



28% were UL (561/2000). Eight percent of the total number of medicines were associated with MRPs (n= 165/2000).

Fourteen percent of UL medicines was associated with MRPs; 4% of OL medicines was associated with MRPs while 7% of licensed medicines was associated with MRPs. MRPs were therefore more common with the use of UL medicines,  $p < 0.001$ . However, there was no significant difference between MRPs occurrence with licensed and OL medicines,  $p = 0.11$ . The proportion of licensed, UL and OL medicines prescribed and the proportion implicated in MRPs are summarised in Figure 4.2.



**Figure 4:2: Medicines related problems occurrence in relation to different medicines licensing status**

#### 4.5.4 Medicines related problems in different age groups

With respect to the occurrence of MRPs with use of licensed, OL and UL medicines in the different age groups, the results showed that use of OL medicines was significantly associated with

occurrence of MRPs in younger paediatric patients; 21% in preterm, 10% in term babies, but lower than 3% in older paediatric patients;  $p < 0.001$ . Summary of results is shown in Table 4.6.

**Table 4:6: Occurrence of medicines related problems in relation to the use of licensed, off-label and unlicensed medicines in the different age groups**

Medicine licensing status	MRP occurrence	Age categories					P-value
		Preterm new born N (%)	Term new born N (%)	Infant N (%)	Children N (%)	Adolescent N (%)	
<b>Licensed</b>	No MRP	50 (100)	154 (92)	392 (93)	318 (95)	100 (92)	0.16
	MRP	0 (0)	14 (8)	31 (7)	17 (5)	9 (8)	
<b>Off-licence</b>	No MRP	15 (79)	81 (90)	137 (99)	78 (100)	28 (97)	<b>&lt;0.001</b>
	MRP	4 (21)	9 (10)	1 (1)	0 (0)	1 (3)	
<b>Unlicensed</b>	No MRP	8 (73)	99 (86)	200 (88)	136 (83)	39 (89)	0.51
	MRP	3 (27)	16 (14)	28 (12)	27 (17)	5 (11)	

Analysis involved descriptive statistics (frequencies and percentages)

#### **4.5.5 Medicines related problems occurrence between genders in relation to different licensing status of medicines**

Eight percent of all medicines that were prescribed to male patients were associated with MRPs (n= 89/999medicines). Also 8% of the total medicines that were given to females' patients were associated with MRPs (n= 76/836medicines).

There was no significant difference in occurrence of MRPs with licensed, UL and OL medicines between the genders (Table 4.7). However, male patients tended to have more MRPs with use of UL medicines than female patients did, 52% versus 37%.

**Table 4:7: Medicines related problems occurrence between genders in relation to different licensing status medicines**

Medication	MRP	Male N (%)	Female N (%)	P-value
<b>Licensed</b>	No MRP	74 (73)	62 (67)	0.37
	MRP	27 (27)	30 (33)	
<b>Off-label</b>	No MRP	68 (88)	62 (91)	0.57
	MRP	9 (12)	6 (9)	
<b>Unlicensed</b>	No MRP	42 (48)	53 (63)	<b>0.04</b>
	MRP	46 (52)	31 (37)	

Analysis involved chi-square test

#### 4.5.6 Medicines related problems categories and associated medicines

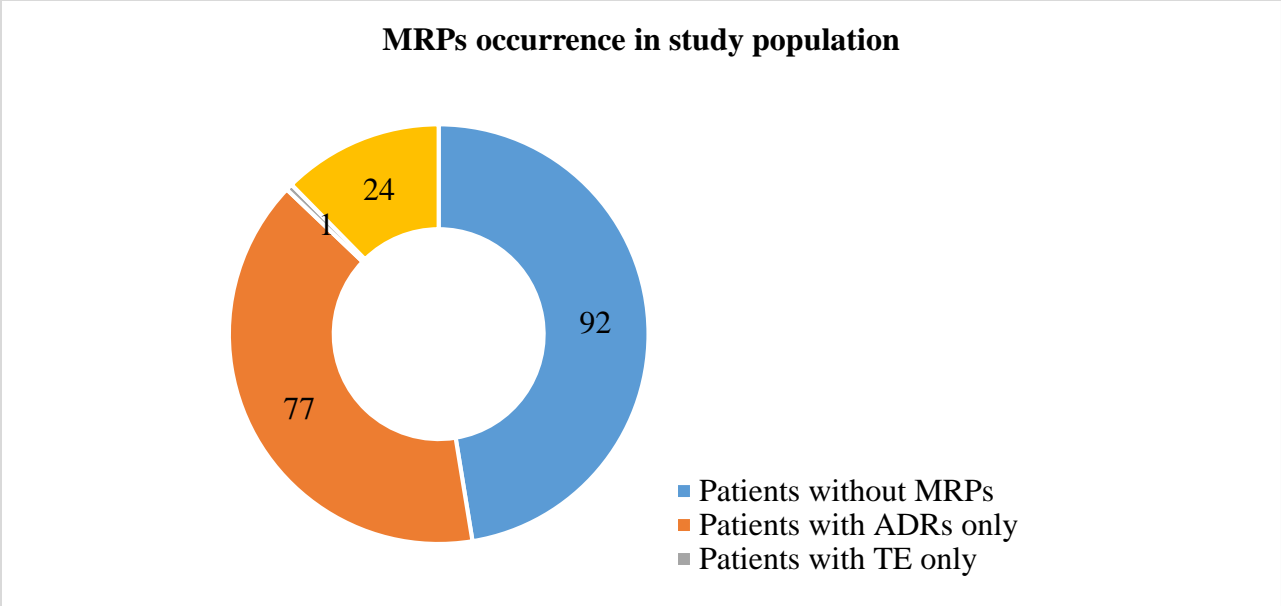
Where MRPs occurred, ADRs constituted 84% of the total number of MRPs (n=138/165); and treatment effectiveness problems accounted for 16% (27/165) of the identified MRPs. The sub-domain of the problems is summarised in Table 4.8.

**Table 4:8: Medicine related problems categories**

Primary domain	Code	Sub-domain	Number
<b>Treatment effectiveness problems</b>	P1.1	No effect of drug treatment	2
	P1.2	Effect of drug treatment not optimal	24
	P1.3	Wrong effect of drug treatment	1
<b>Adverse drug reactions</b>	P2.1	Non-allergic adverse drug event	60
	P2.2	Allergic adverse event	23
	P2.3	Toxic adverse event	1

Analysis involved descriptive statistics (frequencies and percentages)

Of the 194 patients in this study, 53% (n= 102) experienced at least one MRP. The proportion of patients who experienced different types of MRPs is shown in the figure below:



TE: treatment effectiveness; ADR: adverse drug reaction; MRPs: medicine-related problems

**Figure 4:3: Different medicines related problems categories in patients**

The most common prescribed medicines in the study population were morphine, paracetamol, clonidine, furosemide, spironolactone and potassium chloride. Using the Naranjo scale, morphine and furosemide were implicated in MRPs, 50% (n= 83/165) and 26% (n= 43/165) respectively. In appendix 10, a list of all the medicines with their licensing status is provided. Table 4.9 summarises the medicines that were frequently associated with problems; Table 4.10 includes the medicines that were associated with problems in different age groups.

**Table 4:9: The most frequently prescribed medicines**

Medicine	Licensing status	Number of times prescribed	Number of patients	Number of times associated with MRPs	Number of patients with MRPs
Morphine	UL	193	151	79	77
Morphine	L	11	11	4	4
Paracetamol	L	120	119	1	1
Clonidine	UL	146	135	0	0
Furosemide	L	110	102	43	43
Potassium chloride	L	74	71	1	1

Analysis involved descriptive statistics (frequencies and percentages)

**Table 4:10: Medicines associated with problems in different age groups**

Age-group	Medicines associated with MRPs		Number of MRPs	Category of MRP
	Name	Licensing status		
<b>Pre-term</b>	Paracetamol	OL	4	TE
	Morphine	UL	3	ADR
<b>Term</b>	Morphine	UL	16	ADR
	Paracetamol	OL	9	TE
	Furosemide	L	8	ADR
	Flucloxacillin	L	3	ADR
	Gentamicin	L	2	TE
<b>Infants</b>	Morphine	UL	31	ADR
	Furosemide	L	24	ADR
	Sytron	L	1	ADR
	Fentanyl	OL	1	ADR
	Co-amoxiclav	L	1	TE
<b>Children</b>	Morphine	UL	28	ADR
	Furosemide	L	7	ADR
	Gentamicin	L	3	TE
	Azithromycin	L	1	TE
	Salbutamol	L	1	ADR
<b>Adolescents</b>	Morphine	UL	5	ADR
	Furosemide	L	4	ADR
	Dihydrocodiene	L	1	ADR
	Tranexamic Acid	OL	1	ADR
	Oxycodiene	L	1	ADR

\*ADR= Adverse Drug Reaction, L= Licensed, OL= Off-label, TE= Treatment Effectiveness problems, UL= Unlicensed.

#### 4.5.7 Medicines related problems and the length of stay

The association between the occurrence of MRPs and length of hospital stay (LOS) was examined. The average LOS was 3days (range 2-20 days;  $M = 3$ ,  $SD \pm 2.9$ ). There was a significant association between MRPs and LOS. The longest LOS was found in those with 2+ MRPs, where the median LOS was 4 days. Fewer MRPs occur with LOS shorter than two days. The results are summarised in Table 4.11.

**Table 4:11: Relationship between medicines related problems and the length of stay**

Category	Number patients	LOS Median (IQR)	P-value
No MRPs	92	2 (2, 4)	
1 MRP	52	3 (2, 4)	<0.001
2+ MRPs	50	4 (4, 6)	

Analysis involved Kruskal-Wallis test. IQR- Inter quatile range

#### 4.5.8 Medicines related problems and number of medicines

The average number of medicines per patient was 10.3 ( $SD= 4.7$ ). There was positive correlation between the number of medicines and the number of MRPs. The number of MRPs increased with increase in the number of medicines (correlation coefficient 0.47,  $p<0.001$ ). This is shown in Table 4.12 below.

**Table 4:12: Relationship between medicines related problems and number of medicines**

Number of MRPs	Number of patients	Number of medicines per patient Mean (SD)
0	92	8.4 (4.9)
1	52	10.8 (2.8)
2	40	12.4 (3.7)
3	7	15.3 (4.4)
4	3	20.0 (2.6)
5	0	-

Analysis involved Pearson test.

#### 4.5.9 Medicines related problems' causes, interventions and outcome

One hundred and sixty-five medicines were associated with 165 MRPs, which were mainly treatment effectiveness problems and adverse drug reactions. Overall, 231 causes were identified for the 165 identified MRPs using the PCNE V6.2 classification system. The most frequent causes were medicine selection; dose selection; treatment duration; logistics of prescribing errors, and others. Table 4.13 describes the causes and categories.

**Table 4:13: Causes of medicines related problems**

Primary domain	code	Sub-domain	Number of causes
<b>Drug selection</b>	C1.1	Inappropriate drug (Contra-indication)	19
	C1.6	Too many drugs prescribed for indication	21
	C3.1	medicine dose too low	40
<b>Dose selection</b>	C3.2	medicine dose too high	60
	C3.5	No therapeutic monitoring	2
	C3.7	Deterioration of disease requiring dose adjustment	2
<b>Treatment duration</b>	C4.2	treatment duration too long	53
<b>Logistics</b>	C6.2	prescribing errors	22
<b>Others</b>	C8.2	No obvious cause	10

Analysis involved descriptive statistics (frequencies and percentages)

The identified MRPs required 215 interventions; some of the MRPs required more than one intervention. As this was a retrospective study, interventions were counted from drug charts and patients' case-notes at the medicines level. All interventions resulted in positive outcome and MRPs were resolved. Table 4.14 below summarises type and number of interventions.

**Table 4:14: Medicine related problems' interventions**

Primary domain	Code	Sub-domain	Number of interventions
<b>At medicine level</b>	I13.2	Dosage changed	102
<b>At medicine level</b>	I13.3	Formulation changed	19
<b>At medicine level</b>	I13.5	Drug stopped	49
<b>At medicine level</b>	I13.6	New medicine started	45

Analysis involved descriptive statistics (frequencies and percentages)

#### **4.5.10 Medicines related problems severity**

Using the NPSA level of harm, 5% of identified MRPs were rated by experts as causing no harm (n= 9/165); 71% resulted in low harm (n= 117/165), and 24% caused moderate harm (n= 39/165).

An example of an MRP case study that was sent to the experts is shown in the Table 4.15.



**Table 4:15: An example case study for medicines related problems severity**

<b>Severity of MRPs/ Case no. 2</b>			
<b>Patient details</b>		<b>Medical diagnosis &amp; Co-morbidities</b>	
Study ID	3	Elective admission for cardiac surgery, born as ex-premature (32/40).	
Age	6 year		
Weight	31 Kg		
Height	127 cm		
Gender	Male		
Length of stay	2days		
Allergies	NKDA		
<b>laboratory tests: only Abnormal results are reported</b>			
Parameter	Abnormal Results	Results after intervention	
Potassium	3.1mmol/L	3.5mmol/L	
<b>Medication history</b>			
Name of medicine	Dose	Frequency	Route of administration
CEFUROXIME	750mg	Stats	Iv
CHLORPHENIRAMINE	1mg	Od	Iv
FUROSEMIDE	10mg	Bd	Iv
IBUPROFEN	150mg	Od	Ngt
MORPHINE 50mg/50ml	20mcg/kg/hr	Con	Inf
PARACETAMOL	460mg	Qds	Po
SPIRONOLACTONE	10mg	Bd	Iv
POTASSIUM CHLORIDE	5mmol	Stats	Iv
<b>Clinical narrative</b>			
The patient was on the correct dose of furosemide and the level of potassium dropped to 3.1, and required intravenous potassium chloride, which successfully increased level back to 3.5.			
<b>Experts' opinion</b>			
<b>Medicine related problem (MRP):</b> “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”. (Pharmaceutical Care Network Europe, 2010)			
<b>Please rank the harm caused by the MRP identified based on NPSA scale of harm, insert ✓</b>			
<ul style="list-style-type: none"> <li>• No harm (The incident caused no harm)</li> <li>• Low (Any patient safety incident that required extra observation or minor treatment, and caused minimal harm to the person(s) receiving NHS funded care) ✓</li> <li>• Moderate (Any patient safety incident that resulted in a moderate increase in treatment, and which caused significant but not permanent harm to the person receiving NHS funded care)</li> <li>• Severe (Any patient safety incident that resulted in permanent harm to the person(s) receiving NHS funded care)</li> </ul>			

Each member of the panel rated all the 17 MRPs individually (Appendix 11). A summary of the number of responses in each category for each panel member is shown in Table 4.16.

**Table 4:16: Experts’ panel severity scoring of medicine related problems**

<b>Expert</b>	<b>No harm N (%)</b>	<b>Low N (%)</b>	<b>Moderate N (%)</b>
<b>Consultant pharmacist</b>	1 (6%)	12 (71%)	4 (24%)
<b>Consultant paediatrician</b>	1 (6%)	12 (71%)	4 (24%)
<b>Nurse</b>	1 (6%)	12 (71%)	4 (24%)

Analysis involved descriptive statistics (frequencies and percentages)

The MRPs were categorised in terms of the agreement between the three experts. A summary of the number and percentage of MRPs in each category is shown in the Table 4.17.

**Table 4:17: Level of agreement between assessors**

<b>Level of agreement</b>	<b>Number (%)</b>
<b>All members in agreement</b>	15 (88)
<b>Two in agreement, one disagreement</b>	2 (12)
<b>All three members in disagreement</b>	0 (0)

The kappa statistic was calculated to be 0.82, with a 95% confidence interval from 0.59 to 1.00.

This value implies very good agreement between the three experts.

#### **4.5.11 Medicines related problems preventability**

Using the Schumock and Thornton preventability scale, approximately 30.3% (50/165) of MRPs were deemed preventable.

In Table 4.18, a case vignette that illustrates the most common prescribed medicines and associated problems, problem categories, severity and preventability is presented.

**Table 4:18: Examples case studies of the most common prescribed medicines and associated problems**

<b>Case</b>	<b>Medicine associated with MRP</b>	<b>licensing status</b>	<b>MRP Category</b>	<b>MRP Severity</b>	<b>MRP Preventability</b>
<b>A patient aged 5days (4kg) was admitted for Cardiac surgery, Co-arctation of the Aorta, Ventricular Septal Defect. The patient developed allergy after administration of morphine, and settled after being given Chlorpheniramine injections.</b>	Morphine	L	ADR	Low harm from the three experts	Non-preventable
<b>A patient aged 2weeks (3kg) electively admitted for coarctation of the aorta surgery. The patient was on the correct dose of morphine but developed signs of seizures, respiratory depression and agitation. The patient recovered after being administered Naloxone intravenously.</b>	Morphine	UL	ADR	Moderate harm from the three experts	Non-preventable
<b>A patient aged 6weeks (4.5kg) was admitted for cardiac surgery, tricuspid valve atresia. The patient was on the correct dose of intravenous furosemide and the potassium level dropped to 3mmol/L, and required intravenous Potassium Chloride which successfully increased level back to 3.6mmol/L.</b>	Furosemide	L	ADR	Low harm from the three experts	Non-preventable
<b>A patient aged 6days (2kg), who was born at 36weeks gestational age, was electively admitted for cardiac management; Coarctation of Aorta and Left atrial isomerism. The patient was prescribed 16mg of gentamicin 8mg/kg. A lower dose of Gentamicin was given (10mg), instead of 16mg due to wrong calculation.</b>	Gentamicin	UL	Treatment effectiveness	Pharmacist: low harm Nurse: low harm Paediatrician: no harm	Preventable
<b>A patient aged 1day (3.1kg), was admitted due to suspected sepsis. The patient developed severe skin reaction after administration of Flucloxacillin.</b>	Flucloxacillin	UL	ADR	Pharmacist: moderate harm Nurse: moderate harm Paediatrician: moderate harm	Non-preventable

<p><b>A patient aged 5days (3.5kg) was electively admitted for cardiac surgery. The patient received a high dose of paracetamol (75mg) instead of the correct dose (26.5mg) due to wrong calculations.</b></p>	<p>Paracetamol OL</p>	<p>Treatment effectiveness problem</p>	<p>Pharmacist: moderate harm Nurse: moderate harm Paediatrician: low harm</p>	<p>preventable</p>
<p><b>A patient aged 6weeks (4.5kg) was admitted for cardiac surgery, tricuspid valve atresia. The patient was on the correct dose of intravenous furosemide. The potassium level dropped and required intravenous potassium chloride tds. The dose of potassium chloride was insufficient due to the frequency, and then changed to a continuous infusion which successfully increased level back to 3.6mmol/L.</b></p>	<p>Potassium chloride L</p>	<p>Treatment effectiveness problem</p>	<p>Low harm from the three experts</p>	<p>preventable</p>

## 4.6 Discussion

The main objectives of this study were to determine the prevalence of OL and UL medicines' use in patients who were admitted to PICU and MRPs that were associated with their use. Findings of this study showed that the most common diagnosis in the study population were congenital malformations abnormalities, diseases of the respiratory system, certain infectious and parasitic diseases. The average length of stay in this population was 3 days.

Of the 2,000 medicines that were prescribed to the study population, 54.3% were licensed (n= 1085), 17.7% (n= 354) were OL and 28% (n= 561) were UL. A previous study had reported prevalence of 19% and 39% for UL and OL medicines respectively among neonates (Kieran et al., 2014). A related study reported a prevalence of 11.1% for UL medicines and 30.2% for OL medicines in paediatric patients aged 0- 16 (Berdkan et al., 2016). Although the prevalence of UL and OL obtained in this study is not closely comparable with those reported by Kieran et al., 2014 and Berdkan et al., 2016, it however confirms the use of OL and UL medicines is common in paediatric practice.

In this study, 53% of the total number of patients developed at least one MRP. Findings of this study is similar to that of Rashed et al. (2012) that reported MRPs incidence of 59.7% in PICU in a prospective study to determine the epidemiology of MRPs. The similarity in findings may be due to the fact this study, like Rashed et al. was conducted in a similar setting, although the Rashed et al.'s study was conducted prospectively.

Eight percent of the total number of medicines were associated with MRPs (n=165/2000); 14% of UL were associated with MRPs (n=79/561) and 4% of OL medicines were associated with

MRPs (n= 15/354), while 7% of licensed medicines were associated with MRPs (n=71/1085). From the total number of MRPs (165), 43% were associated with licensed medicines, while 57% were associated with OL and UL medicines (9% and 48% respectively). While no study was identified in the literature to compare these findings, studies of ADRs, a subset of MRPs have been carried out. These studies reported higher incidence of ADRs with the use of OL and/or UL medicines when compared to licensed medicines (Neubert et al., 2004; Saiyed, Lalwani & Rana, 2015). Turner et al. (1999) reported ADRs were associated with 3.9% of 2881 licensed medicine prescription and 6% of 1574 UL medicine prescriptions in their study. Using the PCNE classification system, the main types of problems found in this study were ADRs and treatment effectiveness problems. The identified MRPs were predominantly ADRs (84%) and included non-allergic, allergic and toxic adverse drug reactions. They were type A reactions (dose-dependent, predictable or augmentations of known pharmacologic effects of the medicine). This highlights the importance of accurate dose calculation and adjustment as well as clinical monitoring in the paediatric population especially due to changes in pharmacokinetics of medicines during development. Most of the ADRs were associated with the use of morphine and furosemide, and were extension of these medicines' pharmacological effect which would normally occur regardless of the licensing status. On the other hand, treatment effectiveness problems (16%) were mostly classified as effect of medicine treatment not optimal, wrong effect of medicine treatment caused by the dose selection; medicine dose too low; medicine dose too high; treatment duration too long and prescribing errors. This is because of the challenges encountered with OL and UL prescribing in the treatment of paediatric population where there is lack of age-appropriate formulations, insufficient information for paediatric prescribing, and downscaling from adult doses which possess a risk of mistakes in dose calculations. Also,

prescribing for this group of patients is determined by other factors such as age, weight and body surface area (Wong et al., 2004). Although ADRs would occur regardless of the licensing status, treatment effectiveness problems are affected by the licensing status of the medicines. This is because prior to obtaining marketing authorisation, pharmaceutical companies are required to show evidence of efficacy and safety through clinical trials to regulatory agencies. Participants in these trials are often adults, thus prescribing information on dosing; adverse effects etc. are for adults, sometimes with a warning that safety in paediatric patients has not been established.

When such medicines are used in UL and/or OL manner, there is the risk of error in dose calculation and manipulation to a dosage form that is suitable for the paediatric patients.

Among the study population, there was no statistically significant difference in occurrence of MRPs between different age groups. Non-significant difference in overall MRPs between the age groups has been previously reported (Rashed et al., 2012). There was however a difference in occurrence of MRPs between age groups due to different licensing status of medicines, with the highest number of MRPs occurring in pre-term and term neonates with the use of OL medicines. Thus, OL use of medicines are associated with MRPs in younger paediatric patients when compared with older ones. Bellis et al. (2013) found that medicines licensed in children but given to children below the minimum age had the greatest odds of being implicated in ADRs supports finding of this study. In the UK, the age group of 0-4 years was reported to be most vulnerable for medicines' incidents (NPSA, 2011). This finding can be explained by the high prevalence of OL medicines use in this age group. Conroy et al. (1999) in their study of the prevalence of OL medicines in neonates admitted to NICU found that 90% of neonates received at least one UL or OL medicine. A related study of prevalence of OL medicines in neonates reported that 80% of infants received UL and/or OL medicine; this rose to 93% in extremely low birth weight infants

(Lindell-Osuagwu et al., 2009). This is because of the high level of OL prescribing in this age group due to the limited number of age-appropriate medicines, the complexity of prescribing and the paediatrics physical development.

Findings of this study showed that there was no difference in the MRPs occurrence between the genders. Eight percent of all medicines prescribed were implicated in MRPs in male and female patients respectively. There was also no difference in occurrence of MRPs with licensed, UL and OL medicines between the genders. This agrees with a previous study that reported no difference in MRPs incidents between males and females participants (Rashed et al., 2012). This implies that occurrence of MRPs is not influenced by gender, that is, both male and female patients will experience MRPs to the same degree whether the medicine is licensed, OL or UL.

Besides assessing prevalence of use of OL and UL medicines, and the associated problems, this study also looked at the relationship between length of stay and polypharmacy. There was a significant association between MRPs and LOS as the number of MRPs increased with the increase in LOS. Findings of this study also showed a positive correlation between the number of MRPs and the number of medicines given to patients. These findings are supported by a related study which found that if the average number of prescriptions per patient was  $\geq 5$  prescriptions, the patient was more likely to experience an MRP (Rashed et al., 2012). This is because of the possibility of drug-drug interaction, drug- disease interaction as well as the age of the patient (the very young patients tend to have more MRPs because of the underdeveloped organs).

Of the 165 MRPs identified in this study, only 24% were rated as moderate harm, 76% ranged between no-harm and low harm. While there were variations in the rating of the severity of MRPs



between the assessors, there was a good level of agreement (82%) from Kappa analysis. This finding is supported by a previous study that found that 72.2% of MRPs were minor (n= 345/478) and 27% were moderate (n= 129/478) (Rashed et al., 2012). This study also showed that 30.3% of the identified MRPs were preventable (n= 50/165). In their study, Rashed et al. (2012) found that 80.3% of MRPs were preventable (n= 384/478); Easton et al. (2003) found that 51.3% of MRPs were preventable; Easton et al. (2004) also found that 46.9% of the MRPs were preventable. This can be explained by the difference in methodologies that were adopted as Rashed et al. and Easton et al. studies were conducted prospectively while this study was of a retrospective design.

In this study, MRPs associated with UL medicines were higher when compared with OL medicines. To reduce incidence of MRPs with use of UL medicines, the paediatric population should be included in clinical trials in compliance with legislation, including the Paediatric Investigation Plan (PIP). Because UL and OL medicines' use is a routine practice in management of paediatric illnesses, it is not feasible to obtain parents' consents in the busy atmosphere in PICU. This highlights the need to establish a monitoring policy in PICU when UL medicines are prescribed. This policy should include education of parents so they could participate in monitoring any MRP that may result from UL medicines use.

#### **4.7 Strengths and limitations**

This is the first study to investigate MRPs associated with the use of OL and UL medicines in paediatric patients admitted to intensive care units. The intensive chart review method adopted has been reported as the most appropriate and gold standard in pharmaco-epidemiological studies (Ghaleb et al., 2010). Although this study was conducted in only one centre, the use of power

calculation in determination of sample size and randomisation enhanced the generalisability of findings.

The major limitation of this study is that deceased patients' records were not reviewed. Thus, there might be bias in the clinical significance level as it was not certain if there is any MRP incident that led to death. Another limitation is that patients were moved between the two intensive care units, and that might affect any finding regarding a specific setting. Also poor documentation was found to be a major limitation of this study. There was no previous study to compare results with regard to MRPs associated with OL and UL medicines in paediatric patients. This study therefore draws the attention of paediatric health care professionals to the need to promote research into this area. Nonetheless, paediatric population is in need for more innovations in research and development.

#### **4.8 Implication of study findings in practice**

In this study, the identified MRPs were ADRs which were due to pharmacological effects of prescribed medicines, and treatment effectiveness problems which resulted from prescribing errors, medicine dose too low, medicine dose too high, or duration too long. While ADRs may not be readily preventable, treatment effectiveness problems are preventable. This implies that standard reference sources, such as SPCs should be incorporated into routine practice to minimise errors in dose calculations. There should also be a procedure that ensures dosing for paediatric patients is double checked as it always involves small decimal calculations to reduce the chances of mistakes. Also, continuous monitoring and dose adjustment are necessary for paediatric patients according to the clinical response.

It is important to have a tool to identify MRPs and practitioners should be trained to use the tool for early identification of MRPs. The identified MRPs should always be reported to the hospital incident reporting system. MRPs were found to be higher with off-label and unlicensed medicines when compared to licensed medicines, thus regular education programme to increase the awareness of MRPs associated with OL and UL medicines might help to reduce the number of MRPs in this population. This will in turn contribute to improving the paediatric healthcare quality by decreasing MRPs-related mortality, morbidity and financial burdens.

#### **4.9 Conclusion**

This study was undertaken to investigate MRPs associated with the use of off-label and unlicensed medicines in paediatric patients admitted to intensive care unit.

- A total of 2,000 medicines were prescribed to 194 patients of which 54.3% were licensed, 17.7% were off-label, and 28% were unlicensed.
- 53% of the total number of patients developed at least one MRP.
- A total of 165MRPs were identified; 43% were associated with licensed medicines and 57% were associated with off-label and unlicensed medicines (9% and 48% respectively).
- The identified MRPs were predominantly ADRs (84%) and treatment effectiveness problems (16%).
- Morphine and furosemide were found to be commonly associated with the identified MRPs.
- There was no statistically significant difference in occurrence of MRPs between different age groups however; OL use of medicines was associated with more MRPs in younger paediatric patients when compared with older ones.

- Of 165 identified MRPs, 24% were rated as moderate harm, 76% ranged between no-harm and low harm; 30.3% of the identified MRPs were preventable.

Findings of this retrospective study facilitated sample size determination for the prospective phase. The prospective phase was divided into two different studies in both PICU and NICU because an electronic prescribing was adopted in NICU by the time of the data collection. The next chapter describes a prospective study to determine prevalence of MRPs with the use of off-label and unlicensed medicines in patients admitted to PICU of the hospital.

## **Chapter 5: Prospective study of medicines' related problems associated with off-label & unlicensed medicines in paediatric intensive care unit**

### **5.1 Introduction**

The use of unlicensed and/or off-label medicines in paediatric population has been associated with a number of adverse incidents (Bellis et al., 2013; Turner et al. 1999). This is because most of the medicines used in paediatrics have not studied in this population; their use is based on data obtained from the adult population. An Australian study has found that 4.3% of paediatric admissions and 3.3% of A&E visits were related to MRPs (Easton, 2003; Easton, 2004). A related study found that the overall incidence of medicines related problems (MRPs) was 59.7% in paediatric patients who were admitted to intensive care unit (Rashed et al., 2012).

In Chapter 4, findings of the retrospective study to identify MRPs associated with the use of off-label and unlicensed medicines in paediatric intensive care unit (PICU) were presented. In this chapter, data was collected prospectively. Findings of the literature review of this thesis showed that both prospective and retrospective study designs have been employed in the studies of prevalence of off-label and unlicensed medicines' use in paediatric population. Although the use of different study design in investigation of the same subject may lead to variation in results, in this thesis, both retrospective and prospective design were employed to allow comparison of results as this is the first study to investigate MRPs associated with the use of off-label and unlicensed medicines in paediatric in-patients. Findings of the retrospective study were used for determination of sample size for the two prospective studies (PICU and Neonatal Intensive Care Unit, NICU).

## **5.2 Aim**

To prospectively investigate medicines related problems (MRPs) associated with the use of off-label and unlicensed medicines in patients admitted to paediatric intensive care unit (PICU) of the paediatric hospital.

## **5.3 Objectives**

- To determine prospectively the prevalence of OL and UL medicines use in PICU.
- To determine the prevalence of MRPs in this unit.
- To determine the prevalence of MRPs associated with OL and UL medicines use in this unit of the hospital.
- To assess the severity of the identified MRPs.

## **5.4 Method**

### **5.4.1 Study Setting**

This study was performed at the PICU, which serves patients from South London and South East England. The hospital's intensive care unit is considered as one of the leading intensive care units in the UK; the 20-bed PICU is considered as one of the important cardiac units in the country (Tomlin, S., personal communication).

### **5.4.2 Study population and sampling procedure**

Medical case notes of patients aged 0-18 years old admitted to PICU between October 2015 and March 2016 were reviewed. On the first day of data collection (12.10.15), all patients aged 0-18 years admitted into the unit that day were recruited into the study. All new patients were subsequently recruited as they were admitted with the assistance of the unit's administrative officer

who helped to identify new admissions. When up to 10 recruitments were made, the researcher would wait for some old patients to be discharge before further recruitment was made.

### **5.4.3 Inclusion & exclusion criteria**

Patients who were less than 18 years old and admitted to PICU and on medicines were included in the study. Patients who were admitted for less than 24 hours were excluded from the study. Also patients who were on nutritional products only were excluded. Patients who were isolated and there was no access to their medical case notes were also excluded.

### **5.4.4 Sample size**

The sample size was calculated based on the findings from the retrospective study. The results showed that MRPs was observed in 53% of patients who were admitted to PICU. All patients received licensed, UL and/or OL medicines; however the number of patients who experienced MRPs due to OL and UL medicines was higher than the number of patients who experienced MRPs in association with licensed medicines. The results also showed that MRPs associated with the use of OL and UL medicines were higher when compared with the use of licensed medicines.

The sample size for the prospective phase was calculated based on the difference in the percentage of patients with an MRP between licensed and OL and/or UL medicines. Level of significance was set at 5% and 95% power, it was calculated that 220 patients were required. This sample size was increased by 5% to allow for missing data. Thus, a total of 234 patients' case notes were reviewed. This prospective phase was conducted in two settings, PICU and NICU. Ratio of admission between these two settings is known to be 3:2 (Tomlin, S.). Consequently, 147 patients' case notes were reviewed from PICU and 87 patients' case notes from NICU.

A power calculation was performed for the sample size in order to ensure the quality of the research. The results were retrieved via statistical method by STATA, and it demonstrated a high level of accuracy (98.8%).

#### **5.4.5 Ethical considerations**

Ethical approval for this study was obtained from University of Hertfordshire, NHS REC, and Research and Development (R&D) department as described in section chapter 3 section 3.6. To ensure patient information were protected, the researcher was required to sign a confidentiality agreement. Patient information collected did not include any identifiers; data was anonymised and stored in password-protected devices. Explicit patients' consent was not required as that will limit the number of records to be reviewed as this study was a non-interventional study. In the event that the researcher identified an MRP that was clinically significant, the researcher was required to contact the pharmacist-in-charge of the unit, who would take appropriate steps to resolve the problem.

The following section describes a feasibility study conducted to validate data collection.

#### **5.4.6 Feasibility study: Development of a data collection form to identify medicines related problems in paediatric inpatients**

Development of data collection form for this phase was the same as the retrospective study. However, other parameters were included; these were changes of doses, dosage form, duration or frequency were also recorded daily. Introduction of new medicines, and/or stopping of any treatment was recorded as well as the associated problems. MRPs were categorised according to the Pharmaceutical Care Network Europe classification system version 6.2 (PCNE, 2010). Licensing status of medicines was assessed using Summary of Product Characteristics (SPC) of medicines that was obtained from the Electronic



Medicines Compendium. The form was initially used to collect data from ten patients' medical case-notes. Some changes were made to the form (example, introduction of comments about intervention). The second version was then used to collect data from 20 medical case-notes (appendix 12). The form was validated by a consultant clinical pharmacist with expertise in patient and medication safety, who was also the principal investigator in this study.

#### **5.4.7 Data collection**

Data collection included retrieval of information from patients' case notes, drug charts and laboratory results. Intensive chart review method was adopted as it has been used in a previous study in paediatric population (Ghaleb et al., 2010). Information was obtained from drug charts and medical case-notes daily from the day of admission until discharge or a maximum of 28 days. Patients who were discharged from PICU to other paediatric wards were classified as new patients in case of re-admission after more than 24 hours. Most of the new admissions were included, however when the number of patients exceeded more than ten patients, the researcher would wait until discharge of some patients before including new admissions.

Medicines were classified as licensed, off-label and unlicensed according to SPC with regard to age, dose, form and indication. Age was categorised according to the International Conference of Harmonization Guideline E11 (ICH, 2001). Diagnosis and co-morbidities were categorised according to the International Classification of Diseases version 10 (WHO-ICD, 2014).

MRPs definition and classification were based on the PCNE classification system, version 6.2 (Appendix 1). MRPs identification was as described in Chapter 4 (Table 4.1). When an MRP was identified, then the details including the type of MRP, causes, interventions and outcome of the interventions were recorded. Medicines associated with MRPs were identified using Naranjo

ADRs Probability Scale (appendix 2). The three experts who assessed severity of MRPs in the retrospective study were asked to assess the severity of random 10% of identified MRPs using the National Patients Safety Agency level of harm. The experts were recruited to explore opinions from different backgrounds; their participation in the retrospective study also enhanced their knowledge on MRPs severity scoring. The experts rated the level of harm of each problem individually. The level of agreement between the assessors was then measured using Kappa test. Preventability of MRPs was assessed using Schumock and Thornton Preventability Scale. Data was stored electronically and coded anonymously to ensure patients confidentiality. To ensure validity of the identified MRPs, a consultant clinical pharmacist was asked to review the problems, causes, interventions and outcome during meetings with the researcher.

#### **5.4.8 Data analysis**

Data collected were analysed using computer programmes including Excel, Statistical Package for the Social Sciences (SPSS) and STATA. Descriptive statistics including frequencies, medians, standard deviation, and interquartile range were performed. Data are presented as numbers and percentages. Chi-squared test was used to determine statistical significance for categorical variables while Kruskal–Wallis rank and Wilcoxon Rank-Sum (Mann–Whitney U) was used to determine statistical significance between numerical variables. For all tests, level of significance was set at  $p < 0.05$ .

Data analysis was divided into nine parts as in Chapter 4 and included the following:

- Number of patients who developed MRPs due to different licensing status of medicines, the total number of medicines prescribed during the study period, and comparison of

licensed, UL and OL medicines use and their associated problems using the Chi-square test.

- Prevalence of licensed, UL and OL medicines use in the different age groups and the associated problems.
- Occurrence of MRPs between genders using Chi-square test.
- MRPs categories in patients and the medicines associated with them.
- The association between MRPs and the length of stay (LOS) in the hospital using Kruskal-Wallis.
- The relationship between the number of medicines and the number of MRPs using Pearson test.
- MRPs causes, interventions and outcome using the PCNE classification system V 6.2.
- Severity of the identified MRPs using Kappa test.
- Preventability of MRPs using Schumock and Thornton scale.

## **5.5 Results**

### **5.5.1 Patients' demographics**

Data was collected from 147 patients of patients who were admitted to PICU over a 6-month period. In the study cohort, majority were infants (37%) and children (39%). Most of patients (78%) were born premature. Characteristics of the patient are summarised in Table 5.1.

**Table 5:1: Patients' demographics**

<b>Patients characteristics</b>	<b>Category</b>	<b>Number of patients, (%)</b>
<b>Age group</b>	New born neonates	23(16)
	Infant	55(37)
	Children	57(39)
	Adolescents	12(8)
<b>Gender</b>	Male	78(53)
	Female	69(47)
<b>Gestation period at birth</b>	Mature	32(22)
	Born Premature	115(78)

\*Analysis involved descriptive statistics (frequencies and percentages)

Patients were categorised according to their diagnosis. Table 5.2 gives information on the three most common diagnoses.

**Table 5:2: The most common diagnosis in the study population**

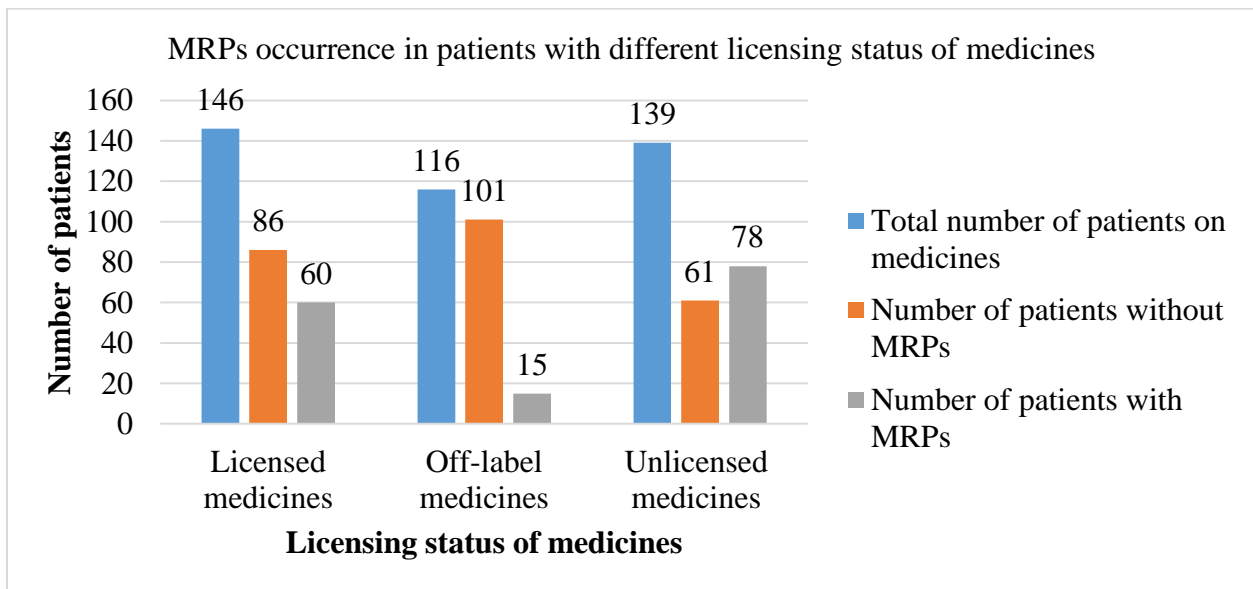
<b>Diagnosis</b>	<b>Number of patients (%)</b>	<b>Number of patients without MRP (%)</b>	<b>Number of patients with MRP (%)</b>
<b>Congenital malformations abnormalities</b>	94 (64)	22 (23)	72 (77)
<b>Diseases of the respiratory system</b>	17 (12)	12 (29)	10 (71)
<b>Certain infectious and parasitic diseases</b>	13 (9)	9 (69)	4 (31)

\*Analysis involved descriptive statistics (frequencies and percentages)

About two-thirds (64%) of the patients were diagnosed with congenital malformations abnormalities; 77% of the total number of patients had an MRP. Just over 10% of patients were diagnosed with diseases of the respiratory system, and within this group, over two-thirds (71%) of the total number of patients had an MRP. Less than 10% of patients were diagnosed with certain infectious and parasitic diseases and less than a third (31%) had an MRP within this category.

### 5.5.2 Medicines related problems in patients in relation to the different licensing status of medicines

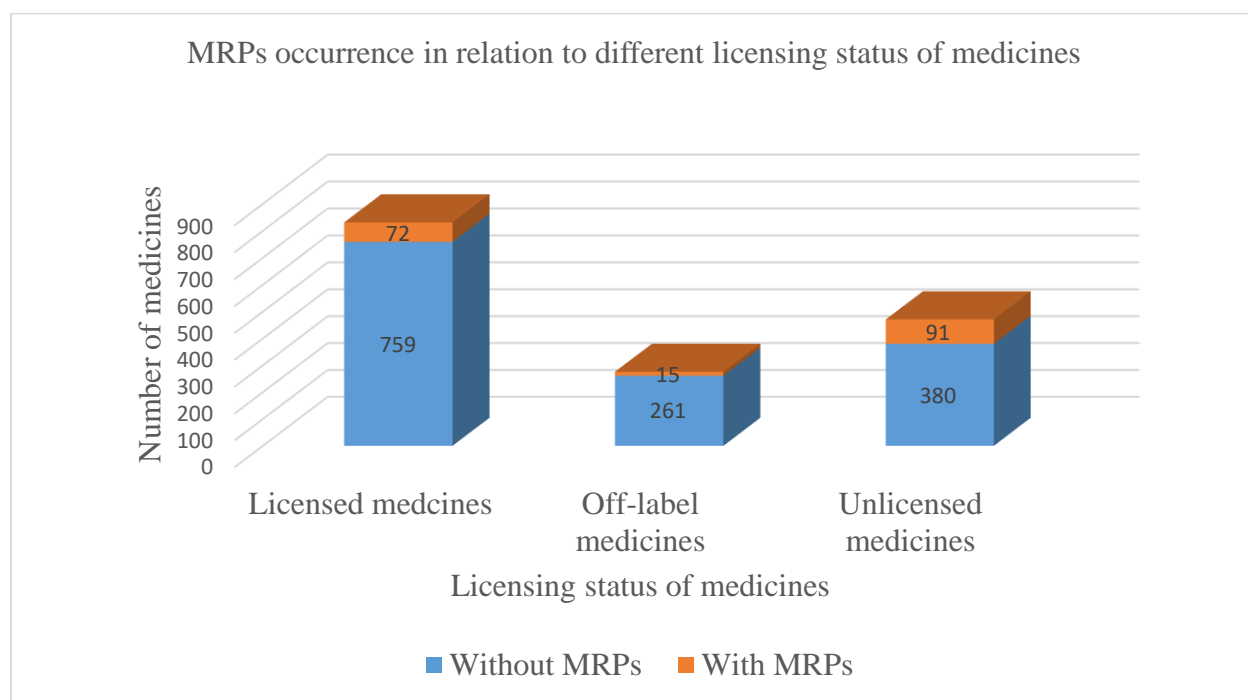
Approximately 79% of patients (n= 116/147) received OL medicines and 95% of patients (n= 139/147) received UL medicines. Results of this study showed that 66% of patients had an MRP (n= 97/147); 56% of patients who received UL medicines had an MRP (n= 78/139); 13% of patients who received OL medicines had an MRP (n= 15/116); 41% of patients who received licenced medicines had an MRP (n= 60/146). Figure 5.1 provides a summary of the MRPs in patients in relation to the different licensing status of medicines.



**Figure 5:1: Medicines related problems in patients in relation to the different licensing status of medicines**

### 5.5.3 Medicines related problems occurrence in relation to different licensing status of medicines

A total of 1,578 medicines were prescribed to the 147 patients in this study. Eleven percent (n=178/1578) of the medicines were associated with MRPs. With regard to the different licensing status of medicines, the results showed that 5.4% (15/276) of OL medicines and 19.3% (91/471) of UL medicines were associated with MRPs, while 9% of licensed medicines associated with MRPs. A significant difference,  $p < 0.001$  was observed between the two groups (licensed medicines and OL/UL medicines). Figure 5.2 shows MRPs occurrence due to different licensing status of medicines.



**Figure 5:2: Medicines related problems occurrence in relation to different licensing status of medicines**

#### 5.5.4 Medicines related problems occurrence in different age groups

Among the study population, the mean age was 46 months (*SD* 55 months; range 0.01-216). MRP occurrence in the different age groups was compared using chi-square test. There was a significant difference in MRPs occurrence between the different age groups,  $p < 0.002$ , with new born patients being the most exposed to MRPs; 16% ( $n = 45$ ). Summary is shown in Table 5.3.

**Table 5:3: Medicines related problems occurrence in different age groups**

Medicines	Number of medicines in new born patients (%)	Number of medicines in infant (%)	Number of medicines in Children (%)	Number of medicines in adolescent (%)
<b>Without MRPs</b>	231 (84)	536 (89)	522 (91)	111 (90)
<b>With MRPs</b>	45 (16)	68 (11)	52 (9)	13 (10)

\*Analysis involved descriptive statistics (frequencies and percentages)

A significant difference was also found in MRPs occurrence due to different licensing status of medicines between the age groups. Fifteen percent of OL medicines given to new-born patients were associated with MRPs compared to 5% or lower in all other groups,  $p < 0.001$ . There was however no difference in occurrence of MRPs with licensed and UL medicines between different age groups. Table 5.4 describes MRPs occurrence in different age groups.

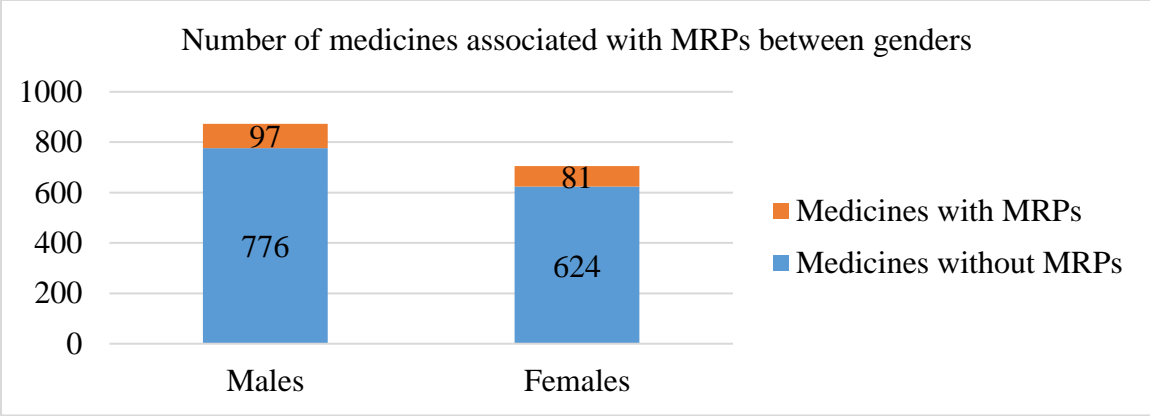
**Table 5:4: Medicines related problems in different age groups with different licensing status of medicines**

Medicine licensing status	MRP occurrence	Age categories				P-value
		Neonates N (%)	Infant N (%)	Children N (%)	Adolescent N (%)	
<b>Licensed</b>	No MRP	99 (87)	288 (92)	309(93)	63(89)	0.16
	MRP	15(13)	26(8)	23(7)	8(11)	
<b>Off-licence</b>	No MRP	64 (85)	101(97)	78(100)	18(95)	<b>&lt;0.001</b>
	MRP	11(15)	3(3)	0(0)	1(5)	
<b>Unlicensed</b>	No MRP	68(78)	147(79)	135(82)	30(88)	0.51
	MRP	19(22)	39(21)	29(18)	4(12)	

### **5.5.5 Medicines related problems between genders in relation to different licensing status of medicines**

A Chi-square test was carried out to compare the occurrence of MRPs between genders. The results showed no significant difference in occurrence of MRPs between male and female,  $p=0.81$ , (11% versus 11%). The figure below shows the proportion of medicines that associated with MRPs in genders.





**Figure 5:3: The proportion of medicines that were associated with medicines related problems between genders**

There was also no significant difference in occurrence of MRPs due to the different medicines licensing status between genders as shown in Table 5.5.

**Table 5:5: Medicines related problems occurrence between genders with different licensing status medicines**

Medicines licensing status	MRP	Male N (%)	Female N (%)	<i>P</i> -value
Licenced	No MRP	427 (92)	332 (91)	0.57
	MRP	38 (8)	34 (9)	
Off-label	No MRP	151 (94)	110 (95)	0.87
	MRP	9 (6)	6 (5)	
Unlicensed	No MRP	198 (80)	182 (82)	0.63
	MRP	50 (20)	41 (18)	

Analysis involved chi-square test

### 5.5.6 Medicines related problems categories and associated medicines

Of the 1,578 medicines prescribed to the study population, 11% were associated with 178 MRPs, of which 83% (n=147/178) were classified as ADRs and 17% (n= 30/178) were classified as treatment effectiveness problems. The sub-domain of the problems is summarised in Table 5.6.

**Table 5:6: categories of medicines related problems**

<b>Primary domain</b>	<b>Code</b>	<b>Subcategory</b>	<b>Number</b>
<b>treatment effectiveness problems</b>	P1.1	No effect of drug treatment	1
	P1.2	Effect of drug treatment not optimal	28
	P1.3	Wrong effect of drug treatment	1
<b>adverse drug reactions</b>	P2.1	Non-allergic adverse drug event	69
	P2.2	Allergic adverse event	77
	P2.3	Toxic adverse event	1

The Naranjo scale was used to identify medicines associated with MRPs. Among the study population, the most commonly prescribed medicines were morphine, paracetamol, clonidine, furosemide and spironolactone. Morphine was prescribed 172 times to 127 patients with MRPs occurring in 62% of the patients (n= 79). A complete list of medicines with their licensing status and associated problems is shown in Appendix 13. Table 5.7 summarises the medicines that were frequently associated with problems; Table 5.8 shows the medicines that were associated with problems in different age groups.

**Table 5:7: Medicines frequently associated with problems**

Medicine	Licensing Status	Number of times medicine prescribed	Number of patients	Number of times medicine associated with MRPs	Number of patients developed MRPs
<b>MORPHINE</b>	UL	164	127	80	77
<b>CLONIDINE</b>	UL	121	114	4	4
<b>PARACETAMOL</b>	L	105	104	3	3
<b>FUROSEMIDE</b>	L	92	86	48	48

Analysis involved descriptive statistics (frequencies and percentages)

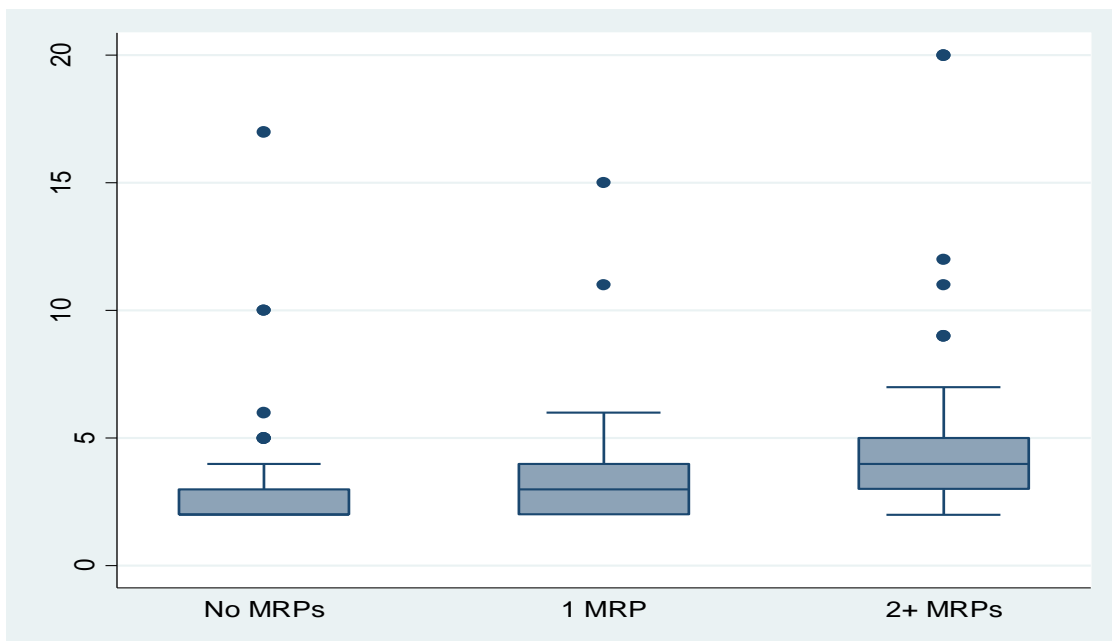
**Table 5:8: Medicines associated with problems in different age groups**

Age-group	Medicines associated with MRPs		Number of MRPs	Category of MRP
	Name	Licensing status		
<b>New born (*)</b>	Morphine	UL	17	ADR
	Furosemide	L	12	ADR
	Paracetamol	OL	10	TE
	Gentamicin	L	2	TE
	Vancomycin	UL	1	TE
<b>Infants</b>	Morphine	UL	33	ADR
	Furosemide	L	21	ADR
	Vancomycin	L	4	ADR & TE
	Clonidine	UL	3	ADR
	Flecainide	OL	1	TE
<b>Children</b>	Morphine	UL	28	ADR
	Furosemide	L	9	ADR
	Gentamicin	L	3	TE
	Salbutamol	L	2	ADR
	Co-Amoxiclav	L	2	TE
<b>Adolescents</b>	Furosemide	L	6	ADR
	Morphine	UL	4	ADR
	Tranexamic Acid	OL	1	ADR
	Gentamicin	L	1	TE
	Paracetamol	L	1	TE

(\*) Term and pre-term babies were combined together as only a small number of pre-terms

### 5.5.7 Medicines related problems occurrence and length of stay

The association between the occurrence of MRPs and the length of stay (LOS) in hospital was examined. The mean LOS was 4.0 days ( $SD= 3.1$  days; range 2-20). The Kruskal-Wallis test showed a significant association between MRPs and LOS,  $p < 0.05$ . Patients with two or more MRPs had longer LOS. Figure 5.4 is a graphical illustration of MRPs occurrence and LOS of the study participants.



**Figure 5.4: Length of stay in study population**

### 5.5.8 Medicines related problems occurrence and number of medicines

The results showed that the average number of medicines per patient was 10.7 ( $SD= 4.5$ ,  $IQR= 8$  to 13). The results also showed that there was an association between number of medicines and number of MRPs. There was a positive correlation between the two measures, with a correlation coefficient of 0.51, which was statistically significant ( $p < 0.001$ ). Table 5.9 shows the occurrence of MRPs with number of medicines.

**Table 5:9: Relationship between number of medicines related problems and number of medicines**

Number of MRPs	Number of patients	Number of medicines per patient, Mean (SD)
<b>0</b>	50	8.4 (4.6)
<b>1</b>	43	10.6 (3.2)
<b>2</b>	35	11.6 (2.9)
<b>3</b>	14	14.9 (4.7)
<b>4</b>	3	15.7 (6.1)
<b>5</b>	1	23.0 (-)
<b>&gt;5</b>	1	18.0 (-)

Analysis involved Pearson test.

### 5.5.9 Medicines related problems' causes, interventions and outcome

In this study, 11% of the total number of medicines was associated with 178MRPs (treatment effectiveness problems and ADRs). The total number of causes was 267 causes, including medicine selection; dose selection; treatment duration; logistics of prescribing errors, and others.

Table 5.10 shows the causes and categories.

**Table 5:10: Medicines related problems causes**

Primary domain	Code	Subcategory	Number
<b>Drug selection</b>	C1.1	Inappropriate drug (Contra-indication)	12
	C1.6	Too many drugs prescribed for indication	13
	C3.1	medicine dose too low	29
<b>Dose selection</b>	C3.2	medicine dose too high	37
	C3.5	No therapeutic monitoring	5
	C3.7	Deterioration of disease requiring dose adjustment	59
<b>Treatment duration</b>	C4.2	treatment duration too long	44
<b>Logistics</b>	C6.2	prescribing errors	39
<b>Others</b>	C8.2	No obvious cause	29

Analysis involved descriptive statistics (frequencies and percentages)

These MRPs required 201 interventions; some of the MRPs required more than one intervention. Approximately 31% (n= 62/201) of all interventions were carried out at the prescriber level and were done by the pharmacist in charge of the unit (that is, the interventions were recommended by the pharmacist and approved by the prescriber).

Sixty-nine percent (n= 139/201) of the interventions were carried out at the medicine level (that is, dose changed, formulation changed, medicine stopped and new medicine started).

At the medicines level, 36% (n= 50/139) of interventions were carried out by the pharmacist while 64% (n= 89/139) were carried out by other healthcare professionals. All interventions resulted in a positive outcome and the identified MRPs were resolved. Table 5.11 below summarises the different types of interventions of the identified MRPs.

**Table 5:11: Medicines related problems interventions**

Primary domain	Code	Subcategory	Number
<b>At prescriber level</b>	I1.3	Intervention proposed, approved by Prescriber	62
	I13.2	Dosage changed to	31
<b>At drug level</b>	I13.3	Formulation changed to	23
	I13.5	Drug stopped	29
	I13.6	New drug started	56

Analysis involved descriptive statistics (frequencies and percentages)

#### **5.5.10 Medicines related problems severity**

The severity scoring of identified MRPs (178) showed that 6% (n= 11/178) were no harm, 72% (n= 128/178) were of low harm and 22% (n= 39/178) were of moderate harm. An example of MRP case study that was sent to experts is shown in Table 5.12 below.

**Table 5:12: An example case study for medicines related problems severity**

Severity of MRPs/ Case no. 16			
Patient details		Medical diagnosis & Co-morbidities	
Study IDP	153	Admitted for removal of spinal correctional instrumentation, GORD, Epilepsy	
Age	15years		
Weight	38kg		
Gender	M		
Length of stay	5days		
Allergies	Morphine allergy		
Medication history			
Name of medicine	Dose (mg)	Frequency	Route of administration
Teicoplanin	380mg	Stats	Iv
Enoxaparin	20U	Od	Sc
Paracetamol	500mg	Qds	Iv/peg
Cholocalcefirol	400iu	Od	Po
Oxycodiene	2.5mg	Qds	PEG
Diclofenac sodium	30mg	Tds	Po
Gentamicin	95mg	Stats	Iv
Vancomycin	570mg	Tds	Iv
Movicol	2sachets	Bd	Po
Nystatin	1ml	Bd	Po
Omeprazol	20mg	Od	Po
Domperidone	10ml	Qds	Po
Clinical narrative			
The patient has GORD, and developed severe stomach pain and vomiting after taking diclofenac sodium orally.			
Medicine related problem (MRP): “A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”. (Pharmaceutical Care Network Europe, 2010)			
Please answer the following question by either YES or No			
Does the case include any MRP based on the attached PCNE classification tool?			
Please rank the harm caused by the MRP identified based on NPSA scale of harm, insert ✓			
<ul style="list-style-type: none"> <li>• No harm (The incident caused no harm)</li> <li>• Low (Any patient safety incident that required extra observation or minor treatment, and caused minimal harm to the person(s) receiving NHS funded care) ✓</li> <li>• Moderate (Any patient safety incident that resulted in a moderate increase in treatment, and which caused significant but not permanent harm to the person receiving NHS funded care)</li> <li>• Severe (Any patient safety incident that resulted in permanent harm to the person(s) receiving NHS funded care)</li> </ul>			

None of the MRPs was rated as severe or death; thus only three levels were observed in the data.

Table 5.13 shows summary of experts' rating.

**Table 5:13: Experts' panel severity scoring of medicines related problems**

<b>Scorer</b>	<b>No harm Percentage % (n)</b>	<b>Low Percentage % (n)</b>	<b>Moderate Percentage % (n)</b>
<b>Consultant pharmacist</b>	6 (1)	72 (13)	22 (4)
<b>Consultant paediatrician</b>	6 (1)	72 (13)	22 (4)
<b>Nurse</b>	6 (1)	72 (13)	22 (4)

Analysis involved descriptive statistics (frequencies and percentages)

The identified MRPs were summarised in terms of whether all three experts agreed, 2 of the three experts agreed, or all the 3 experts disagreed. Using the Stata software, Kappa test was used to calculate the level of agreement between the three experts. The kappa test result was found to be 0.83 (95% CI; 0.6-1.0). This value implies very good agreement between the three experts.

Summary of agreements of experts is shown in Table 5.14.

**Table 5:14: Experts' agreement**

<b>Level of agreement</b>	<b>Percentage % (n)</b>
<b>All members in agreement</b>	89 (16)
<b>Two in agreement, one disagreement</b>	11 (2)
<b>All three members in disagreement</b>	0 (0)

### 5.5.11 Medicines related problems preventability

Assessment of preventability using Schumock and Thornton Preventability Scale 34% of the identified MRPs were found to be preventable (n= 61/178). Table 5.15 shows a summary of case vignettes of the most common prescribed medicines and associated problems, problem categories, severity and preventability:



**Table 5:15: Examples of case vignettes of most common prescribed medicines and associated problems**

Case	Medicine associated with MRP	licensing status	MRP Category	MRP Severity	MRP Preventability
<b>A patient aged 22days (3kg) was admitted for Cardiac surgery. The patient developed sign of seizures after IV morphine was administered. The patient recovered after the medicines was stopped.</b>	morphine	UL	ADR	Pharmacist: low harm Nurse: low harm Paediatrician: no harm	Non-preventable
<b>A patient aged 12years (33kg) electively admitted for coarctation of the aorta surgery. The patient developed severe allergic reaction which required administration of chlorpheniramine injection.</b>	morphine	L	ADR	Low harm from the three experts	Non-preventable
<b>A patient aged 4months was admitted for cardiac surgery. The patient was on the correct dose of intravenous furosemide and the potassium level dropped to less than 3mmol/L; administration of intravenous Potassium Chloride successfully increased level back to 3.6mmol/L.</b>	furosemide	L	ADR	Low harm from the three experts	Non-preventable
<b>A patient aged 1days who was born at 36weeks gestational age with a weight of less than 2kg was electively admitted for suspected sepsis. The patient was prescribed 20mg/kg every 8 hours, however the patient was received 20mg/kg every 4hours</b>	paracetamol	UL	Treatment effectiveness	No harm from the three experts	Preventable

## 5.6 Discussion

The main objectives of this prospective study were to determine the prevalence of MRPs in the PICU, and the prevalence of MRPs associated with off-label and unlicensed medicines use. Like the retrospective study (Chapter 4), the most common diagnosis among the 147 patients included in the study were congenital malformations abnormalities, diseases of the respiratory system, and certain infectious and parasitic diseases. There was high rate of off-label and unlicensed medicines' use among the study population as 79% of the patients received off-label medicines while 95% received unlicensed medicines. This finding is in agreement with a previous study of 342 patients, which reported that 95.3% of the patients admitted to PICU received unlicensed and/or off-label medicine (Dos Santos & Heineck, 2012). Out of the 1578 medicines prescribed, approximately 47% were off-label and/or unlicensed. A previous study has reported similar finding; 46% of medicines were unlicensed or off-label (Palcevski et al., 2012). In comparison with the retrospective study, the proportion of off-label and/or unlicensed was 46%. Findings from literature and the retrospective and prospective studies showed consistency in the use of OL and UL medicines among paediatric in-patients. Approximately 50% of medicines used in treatment of paediatric in-patients are either off-label and/or unlicensed, therefore off-label and unlicensed use of medicines remains a major issue in paediatric practice.

Among the 147 patients, 66% developed MRPs. In the retrospective study, 53% of the 194 patients developed MRPs. Findings of this study are therefore supported by a study to determine MRPs incidence in PICU which reported 59.7% incidence rate of MRPs (Rashed et al., 2012).

In this prospective study, 11% of the medicines were associated with MRPs; 5.4% (15/276) of OL medicines and 19.3% (91/471) of UL medicines were associated with MRPs, while 9% of licensed medicines associated with MRPs. At the time of literature review of this thesis, no study was found to compare these findings. However, the results of the retrospective study showed similar findings with 8% of the total number of medicines associated with MRPs; 10.3% of OL and UL medicines associated with MRPs, and 7% of licensed medicines associated with MRPs. Of the total number of the identified MRPs, this study found that 83% were ADRs (Type A reactions, which are extension of the medicine's pharmacology), while 17% were treatment effectiveness problems (result from prescribing and other errors). This result suggests that proper dose calculations and monitoring is required to minimise treatment effectiveness problems. In comparison with the retrospective study, ADRs were 84% and treatment effectiveness problems were 16%. Previous studies have reported higher prevalence of ADRs with use of OL and/or UL medicines when compared to licensed medicines (Neubert et al., 2004; Saiyed, Lalwani & Rana, 2015; Turner et al., 1999). Although MRPs (mostly ADRs) occurred more with the use of off-label and/or unlicensed medicines than with licensed medicines, other factors including pharmacological effects of the medicines may have accounted for the occurrence. Medicine selection, dose selection, treatment duration, and logistics (prescribing errors) were found to be the causes of treatment effectiveness problems. This is because of the challenges of prescribing for this population where there are limited availability of formulations and insufficient information of the prescribed medicines.

Among the study population, the age group most prone to MRPs were new-born patients (0-28days),  $p < 0.001$ . As noted in a previous study (Cuzzolin & Agostino, 2016), this age group is the most exposed to off-label and unlicensed medicines. This may explain why incidence of MRPs

are higher in this age group due to the pharmacokinetic changes (absorption, distribution, elimination) during maturation. Also, the lack of information on prescribed medicines, and the factors that influence prescribing in this group (age, weight, body surface area and physical development) (Wong et al., 2004) may predispose this age group to development of MRPs. It has also been reported that children who are aged between 0-4 years are the most vulnerable group for medicines' incidents (NPSA, 2011).

Like the retrospective study, there was no significant difference in occurrence of MRPs between genders. Non-significant difference in occurrence of MRPs between male and female has previously been reported (Rashed et al., 2012). These findings imply that gender may not be a risk factor for development of MRPs with the use of off-label and unlicensed medicines, or other medicines in paediatric in-patients.

In this prospective study, morphine, paracetamol, clonidine, furosemide and spironolactone were the most commonly used medicines among the study population; with MRPs occurring in 62% of patients who received morphine. This is similar to findings of the retrospective study. High occurrence of ADRs with use of morphine in paediatric patients has also been reported in a related study (Rashed et al., 2012).

Like the retrospective study, results from this study showed that there was significant association between LOS and number of MRPs,  $p < 0.05$ . Patients with longer LOS had two or more MRPs. A previous study has found that LOS is a risk factor for ADRs (Weiss et al., 2002). Findings of this study also showed that the number of MRPs increased with the number of medicines. Polypharmacy has been previously identified as a one of the main risk factors for occurrence of MRPs, including ADRs (Rashed et al., 2012; Weiss et al., 2002; Zopf et al., 2008).

Assessment of severity and preventability of identified MRPs showed that 72% of MRPs were of low harm, 22% of MRPs were of moderate harm and 6% posed no harm. Thirty-four percent of the identified MRPs were preventable especially treatment effectiveness problems which were caused by dosing problems and prescribing errors. These findings may not be very close to those of Rashed et al. (2012), who reported 67.7% preventable MRPs. That is because this study was conducted in PICU while Rashed et al (2012) study of MRPs was conducted on different wards including medical ward where the highest percentage of MRPs was identified.

MRPs associated with OL and UL medicines were found to be higher when compared with licensed medicines. A number of measures can be introduced to minimise the risk associated with these problems. These include inclusion of paediatric patients in clinical trials of new medicinal products, healthcare professionals should be encouraged to minimise medicines manipulations, and close monitoring for paediatric patients who are prescribed OL and/or UL medicines.

### **5.7 Strength and limitations**

The methodology adopted in this study was intensive chart review, which has been recognised as the gold standard in pharmaco-epidemiological studies. Prospective observational intensive chart review method gave more chance to detect off-label and unlicensed medicines' use than the retrospective study, as poor documentation was found as one of the limitations in retrospective chart review. Also unlicensed medicines in form of specials and extemporaneous medicines were easier to identify than in retrospective review as the researcher was able to detect which type of medicines were used.

Although this study was conducted in only one centre, the use of power calculation in determination of sample size and randomisation enhanced the generalisability of findings. The

major limitation of this study is that not all patients were included; the researcher had to stop recruiting patients when the recruited patients were more than ten patients. Other limitation was that isolated patients were not included as there was no access to their room or their case notes.

### **5.8 Implication of study findings in practice**

In this study, the identified MRPs were ADRs which were due to pharmacological effects of prescribed medicines and they are often not be preventable, and treatment effectiveness problems which resulted from prescribing errors, medicine dose too low, medicine dose too high, or duration too long. Treatment effectiveness problems are however preventable. Summary of product characteristics should be incorporated into routine practice as well as local guidelines to minimise errors in dose calculations. Double-checking of dose calculation by two or more healthcare professional should be introduced in routine practice. MRPs were found to be higher with OL and UL medicines when compared to licensed medicines, thus regular education programme to increase the awareness of MRPs associated with OL and UL medicines might help to reduce the number of MRPs in this population. Regular incident reporting of MRPs and near misses will help in minimising their occurrence. This will contribute to improving paediatric practice and decrease MRPs-related mortality, morbidity and financial burdens.

### **5.9 Conclusion**

This study was carried out prospectively to investigate the prevalence of medicines related problems associated with the use of off-label and unlicensed medicines in patients admitted to paediatric intensive care unit of a paediatric hospital.

- A total of 1,578 medicines were prescribed to the 147 patients in this study.
- 66% of the study participants were developed MRPs

- 11% of the medicines were associated with MRPs.
- 5.4% of off-label medicines and 19.3% of unlicensed medicines were associated with MRPs, while 9% of licensed medicines associated with MRPs.
- 83% of the identified MRPs were ADRs and 17% were treatment effectiveness problems.
- Morphine and furosemide were found to be commonly associated with the identified MRPs.
- Longer length of stay and polypharmacy were found to contribute to occurrence of MRPs.
- While less than half of identified MRPs were preventable, none was rated as being of severe harm to patients.

At the time of this study, an electronic prescribing system was implemented in the neonatal intensive care unit (NICU); therefore a separate study was conducted to investigate MRPs associated with the use of OL and UL medicines and to ascertain whether the electronic prescribing has an impact MRPs occurrence or not. The next chapter describes the prospective study that conducted in NICU.

## **Chapter 6: Prospective study of off-label & unlicensed medicines' related problems in neonatal intensive care unit**

### **6.1 Introduction**

In this chapter, findings of a prospective study undertaken in the Neonatal Intensive Care Unit (NICU) are presented. Over the past five years, there has been increasing emphasis on adoption of digital technology across the NHS to improve the quality of care, and increase patient safety and service efficiency (NHS England, 2012; NHS England, 2014). More recently, the Francis Inquiry Report into the failings of Mid Staffordshire NHS Foundation Trust highlighted the need for common information practices, and feeding of performance information into shared databases for monitoring purposes through introduction of electronic patient information systems (NHS, 2013). Consequently, the Secretary of State announced the Safer Hospitals, Safer Wards Technology Fund in May 2013. The objective of the fund was to assist NHS organisations to move from paper-based to paper-light and effectively paperless, integrated digital care records (IDCRs). It also supports those organisations that seek to achieve demonstrable improvements in efficiency, quality and safety through introduction of electronic prescribing (e-prescribing) within acute settings and community settings (NHS, 2013). Implementation of e-prescribing has the following advantages (NHS, 2013):

- improves the legibility and completeness of prescriptions and makes information about medicines available to the healthcare team at all times.
- the need to move paper prescriptions around an organisation is removed,
- patient safety issues associated with poor handwriting are addressed,
- the quality of care is improved as queries are reduced and efficiencies delivered as paper is no longer chased



- local formulary implementation is supported by reminders at the point of prescribing reducing the need to constantly update prescribers about local policy
- the use of decision support provides additional support for prescribers
- guided prescribing can help to reduce inappropriate dosing,
- facilitates correct drug selection and reduce the incidence of incorrect selection when an allergy or contraindications are present.

At the time of this research, the NICU of the hospital had migrated to electronic medical record, called Medchart. Although findings of the studies in Chapters 4 and 5, and literature showed that the use of off-label/unlicensed (OL/UL) medicines is highest among neonates, and incidence of MRPs is also highest among neonates, it was decided to further conduct a study in NICU. This was to ascertain if implementation of Medchart have any effect on the occurrence of medicines related problems (MRPs).

## **6.2 Aim**

The aim of this prospective study was to investigate MRPs associated with the use of OL and UL medicines in neonates' admitted to NICU at a paediatric hospital.

## **6.3 Objectives**

- To determine the prevalence of OL and UL medicines use in NICU.
- To determine the prevalence of MRPs in this unit.
- To determine the prevalence of MRPs associated with the use of OL and UL medicines in this unit of the hospital.
- To assess the severity of the identified MRPs.

## **6.4 Method**

### **6.4.1 Study setting**

This study was carried out at the NICU which serves patients from South London and South East England. The NICU is considered as one of the leading intensive care units in the UK (Tomlin, S., personal communication).

### **6.4.2 Study population and sampling procedure**

In this prospective study, data was collected from electronic medical records between December 2015 and May 2016; drug charts and laboratory results were reviewed. Fluids recorded in paper-charts were also reviewed. A computer random sampling was applied in selection of participants' case-notes.

### **6.4.3 Inclusion & exclusion criteria**

Patients who were admitted to NICU in the 6 months period of data collection and were on medicines were included in the study. Patients who were admitted for less than 24 hours and patients who were on nutritional products only were excluded from the study.

### **6.4.4 Sample size**

Determination of sample size for this study is as described in Chapter 5. Sample size was calculated to be 87 patients.

### **6.4.5 Ethical considerations**

Ethical approval for this study was obtained from University of Hertfordshire, NHS REC, and Research and Development (R&D) department as described in Chapter 3 Section 3.6. To ensure

patient information was protected, the researcher was required to sign a confidentiality agreement. Patient information collected did not include any identifiers; data was anonymised and stored in password-protected devices. Explicit patients' consent was not required as that will limit the number of records to be reviewed as this study is a non-interventional study. In the event that the researcher identified an MRP that was clinically significant, the researcher was required to contact the pharmacist in charge of the unit, who would take appropriate steps to resolve the problem.

#### **6.4.6 Data collection**

At the time of this study, the NICU had implemented electronic prescribing. The system allows both prescribing and reconciliation to be done electronically. All patient data including the NHS number, hospital number, date of birth, gestational age, diagnosis, allergies, medication history, and current medications was captured. Medicines names, doses by age or body weight, and other relevant information are incorporated in the software. The system raises alerts for contraindications, incorrect doses, and wrong calculations of medicines. All requested investigations and/or examination, test' results and further referrals of each patient are accessible when a user logs into electronic medical chart. Patients' allergy status is indicated in red at the top of each page of the medical chart. Any changes in patient's medical condition(s) and treatment(s) are updated electronically. When pharmacists make changes to the existing treatment plan, they are required to sign for these changes as well as the daily reconciliation of medicines. While majority of prescribing in NICU was done electronically, however intravenous fluids as well as medicines given via intravenous fluids were prescribed using paper chart. Information was obtained from medical electronic patients' notes and fluid charts every day from the day of admission until discharge or a maximum of 28days. Patients who were discharged from NICU to other paediatric wards were classified as new patients in case of re-admission into NICU after

more than 24hours. Data collection form used in this study was the same as the one used in the prospective study in PICU (Appendix 12). Data collected included patient demographics: age, weight, height, weight on birth, and gender. Patients' medical history, diagnosis, co-morbidities, and allergy status were recorded. Doses, dosage form, frequency, duration, and indications for each prescribed medicine were also recorded. Medicines were classified as licensed, OL and UL according to SPC with regards to age, dose, form and indication. Age was categorised according to the International Conference of Harmonization Guideline E11 (ICH, 2001). Diagnosis and co-morbidities were categorised according to the International Classification of Diseases version 10 (WHO-ICD, 2014).

MRPs definition and classification were adopted from the PCNE classification version 6.2 (Appendix 1). MRPs identification was as described in Chapter 4 (Table 4.1). When an MRP was identified, then the details including the type of MRP, causes, interventions and outcome of the interventions, were recorded. Medicines that were associated with problems were identified using the Naranjo ADRs Probability Scale (appendix 2). A panel of experts was asked to assess severity of MRPs using the National Patients Safety Agency level of harm (NPSA, 2009). The experts who also participated in previous two studies were recruited via convenient sampling technique with the principal investigator.

Preventability of MRPs was also assessed using Schumock and Thornton Preventability Scale. Data was stored electronically and coded anonymously to ensure patients confidentiality. To ensure validity of the identified MRPs, a consultant clinical pharmacist was asked to review the problems, causes, interventions and outcome during meetings with the researcher.

#### **6.4.7 Data analysis**

Data collected were analysed using computer programmes including Excel, Statistical Package for the Social Sciences (SPSS) and STATA. Descriptive statistics including frequencies, medians, standard deviation, and interquartile range, were performed. Data are presented as numbers and percentages. Chi-squared test was used to detect significant differences for categorical variables while Kruskal–Wallis rank and Wilcoxon Rank-Sum (Mann–Whitney U) used to determine significant differences between numerical variables. For all tests  $p < 0.05$  was selected as the level of statistical significance.

Data analysis was divided into eight parts including the following:

- Number of patients who developed MRPs due to different licensing status of medicines, the total number of medicines prescribed during the study period, and comparison of licensed, UL and OL medicines use and their associated problems using the Chi-square test.
- Occurrence of MRPs between genders using Chi-square test.
- MRPs categories in patients and the medicines associated with them.
- The association between MRPs and the length of stay (LOS) in the hospital using Kruskal-Wallis.
- The relationship between the number of medicines and the number of MRPs using Pearson test.
- MRPs causes, interventions and outcome using the PCNE classification system V 6.2.
- Severity of the identified MRPs using Kappa test.
- Preventability of MRPs was using Schumock and Thornton scale Preventability.

## 6.5 Results

### 6.5.1 Patients' demographics

Approximately 76% (n= 66/87) of the 87 patients were born as pre-mature neonates; 52% (n= 45/87) were male. Seventy five percent (n= 65/87) of the patients were referred to the hospital from other hospitals by South Thames Retrieval Services (STRS); 24% (n= 21/87) were admitted from the maternity department; one patients was admitted from the A&E department.

The most common diagnosis was respiratory system diseases. Ninety percent (n= 78/87) of the patients developed MRPs. All patients received at least one OL and/or UL medicine. Table 6.1 gives an overview of MRPs occurrence in patients.

**Table 6:1: Medicines related problems occurrence in study population**

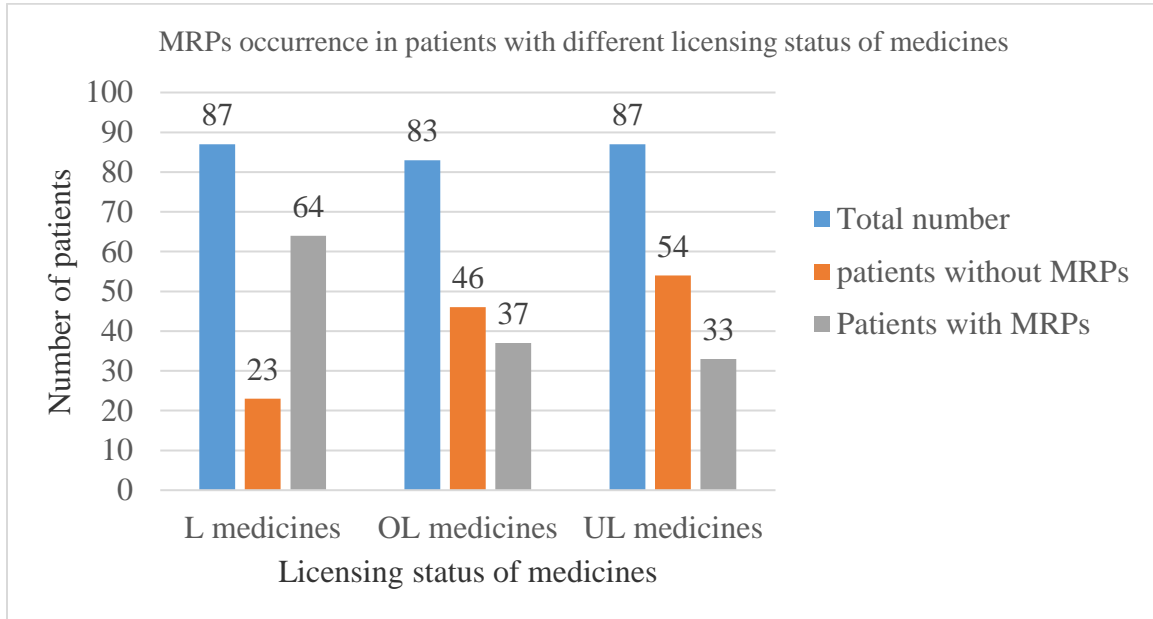
Variable	Category	Number of patients (%)
<b>MRP</b>	No MRP	9 (10%)
	MRP	78 (90%)
<b>Type of MRP</b>	ADR only	78 (100%)
	TE problems only	0 (0%)
	ADR and TE	0 (0%)

\*Analysis involved descriptive statistics (frequencies and percentages)

### 6.5.2 Medicines related problems in patients in relation to different licensing status of medicines

Seventy-four percent of patients who received licensed medicines experienced MRPs; 45% of patients who received OL medicines experienced MRPs; and 33% of patients who received UL medicines experienced MRPs. Neonates who were born as premature babies were found to have a

higher rate of problems (n= 57patients) when compared to patients who were born as mature babies (n=21patients). Figure 6.1 provides information on MRPs occurrence in patients who received medicines' with different licensing status.

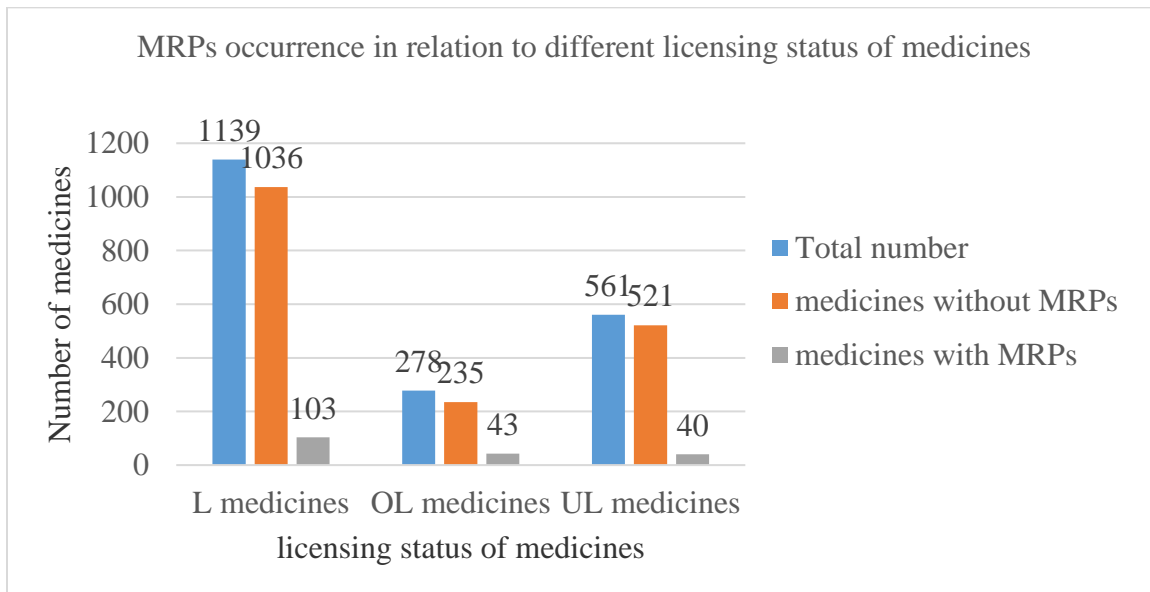


**Figure 6:1: MRPs in patients in relation to different licensing status of medicines**

### 6.5.3 Medicines related problems occurrence in relation to different licensing status of medicines

A total number of 1,978 medicines were prescribed to the study population, of which approximately 58% (n= 1,139) were licensed medicines, 14% (n= 278) were OL medicines and 28% (n= 561) were UL medicines. Nine percent (n= 186/1978) of the total number of medicines were associated with MRPs.

Comparison of MRPs occurrence between medicines' licensing status showed that 9% (n=103/1,139) of licensed medicines were associated with MRPs; 15% (n=43/278) of OL were associated with MRPs, and 7% (n= 40/561) of UL medicines were associated with MRPs. MRPs were higher with OL medicines than licensed or UL medicines,  $p < 0.001$ . Figure 6.2 provides detail of different medicines licensing status and their association with MRPs.



**Figure 6:2: Medicines related problems occurrence in relation to different licensing status of medicines**



#### 6.5.4 Medicine related problems between genders with different licensing status of medicines

Among the study population, the Chi-square test showed that there was no significant difference in occurrence of MRPs between the genders,  $p= 0.24$  (42 males versus 36 females).

There was also no significant difference between genders in occurrence of MRPs due to licensed, OL and UL medicines. Table 6.2 below summarises MRPs occurrence due to different licensing status of medicines between genders.

**Table 6:2: Medicines related problems between genders with different licensing status of medicines**

Medication	MRP	Male Number (%)	Female Number (%)	P-value
<b>All medication</b>	No MRP	915 (90)	877 (91)	0.33
	MRP	102 (10)	84 (9)	
<b>Licensed</b>	No MRP	521 (90)	332 (92)	0.33
	MRP	57 (10)	46 (8)	
<b>Off-label</b>	No MRP	118 (86)	117 (84)	0.66
	MRP	20 (14)	23 (16)	
<b>Unlicensed</b>	No MRP	276 (92)	254 (94)	0.24
	MRP	25 (8)	15 (6)	

Analysis involved chi-square test

#### 6.5.5 Medicines related problems categories and associated medicines

In the previous two studies (Chapters 4 & 5) both adverse drug reactions and treatment effectiveness problems were identified; however, in this study identified MRPs were mainly ADRs. Table 6.3 below the subcategories of MRPs in the study populations.

**Table 6:3: Medicines related problems categories in study population**

<b>Primary domain</b>	<b>Code</b>	<b>Subcategory</b>	<b>Number</b>
<b>adverse drug reactions</b>	P2.1	Non-allergic adverse drug event	39
	P2.2	Allergic adverse event	38
	P2.3	Toxic adverse event	1

Analysis involved descriptive statistics (frequencies and percentages)

Morphine, paracetamol, furosemide and benzylpenicillin were the most common medicines associated with MRPs. Table 6.4 below gives examples of the identified problems with their associated medicines; a full list of all medicines prescribed to study participants, their licensing status and associated problems is provided in appendix 14.

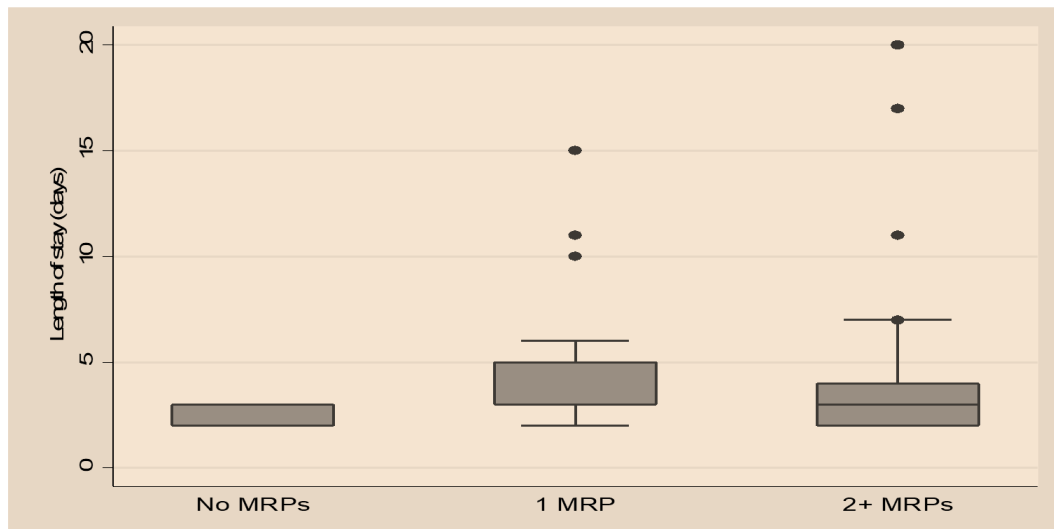
**Table 6:4: Medicines frequently associated with problems**

<b>Medicine</b>	<b>Licensing status</b>	<b>Number of times medicine prescribed</b>	<b>Number of patients</b>	<b>Number of MRPs associated with</b>	<b>Number of patients developed MRPs</b>
<b>BENZYL PENICILLIN</b>	L	92	87	45	45
<b>MORPHINE</b>	UL	92	74	36	35
<b>FUROSEMIDE</b>	OL	52	51	27	27
<b>CEFUROXIME</b>	L	47	45	13	13
<b>CO-AMOXICLAV</b>	L	18	17	16	15

Analysis involved descriptive statistics (frequencies and percentages)

### 6.5.6 Number of medicine related problems and length of stay

The association between the occurrence of MRPs and the length of stay in hospital was examined using the Kruskal-Wallis test. The results showed that there was no significant association between MRPs and LOS,  $P=0.13$ . Summary of the relationship between LOS and the number of MRPs is shown in Figure 6.3:



**Figure 6:3: Relationship between length of stay and number of medicine related problems**

### 6.5.7 Medicine related problems occurrence and number of medicines

The results of this study showed a significant association between number of medications and number of MRPs ( $p=0.006$ , coefficient of 0.29). Table 6.5 below shows the relationship between number of medicines and number of MRPs.

**Table 6:5: Relationship between number of medicines and number of medicines related problems**

Number of MRPs	Number of patients	Number of medicines per patient Mean (SD)
<b>0</b>	9	20.8 (2.3)
<b>1</b>	26	22.8 (3.0)
<b>2</b>	24	21.2 (5.5)
<b>3</b>	12	23.6 (4.9)
<b>4</b>	10	25.0 (3.6)
<b>5</b>	5	25.2 (3.3)

Analysis involved Pearson test.

### 6.5.8 Causes, interventions and outcomes

One hundred and eighty-six medicines were associated with 186 MRPs. There were 186 causes classified as others according to the PCNE V6.2 manifested medicines effects. One hundred and ninety-six interventions were required for the identified MRPs. The pharmacists in charge of the unit were responsible for 20% (n= 25/123) of interventions carried out at the prescriber level (that is, the interventions were recommended by the pharmacist and approved by the prescriber) and 10% (n= 7/73) of interventions carried out at medicines' level. All interventions resulted in a positive outcome and MRPs were resolved. Table 6.6 below shows the different MRPs interventions.

**Table 6:6: Medicines related problems interventions**

Primary domain	Code	Subcategory	Number
At prescriber level	I1.3	Intervention proposed, approved by Prescriber	123
	I13.2	Dosage changed to	1
At medicine level	I13.3	Formulation changed to	9
	I13.5	Medicine stopped	11
	I13.6	New medicine started	52

Analysis involved descriptive statistics (frequencies and percentages)

### 6.5.9 Medicines related problems severity

From experts' rating, approximately 6% (n= 11/186) of the identified MRPs were no harm, 92% (n= 171/186) were low harm, and 2% (n= 4/186) were moderate harm. An example of an MRP case study that was sent to experts is shown in Table 6.7 below.

**Table 6:7: An example of case study for medicines related problems severity**

<b>Severity of MRPs/ Case no. 13</b>			
<b>Patient details</b>		<b>Medical diagnosis &amp; Co-morbidities</b>	
Study IDP	114	Elective admission for Coarctation of the aorta surgery. Increased work of breathing since birth, suspected sepsis.	
Age	2weeks		
Weight	2.9kg		
Gender	M		
Length of stay	3days		
Allergies	NKDA		
<b>Medication history</b>			
Name of medicine	Dose (mg)	Frequency	Route of administration
Morphine 3mg/50ml	10mcg/Kg/hr	Cont	Iv
Fentanyl	6mcg	Stats	Iv
Ketamine	3mg	Stats	Iv
Cefuroxime	80mg	Stats	Iv
Clonidine	9mcg	Tds	Ngt
Paracetamol	45mg	Tds	Ngt
Furosemide	3mg	Tds	Iv
Spirolactone	3mg	Tds	Ngt
Naloxone	30mcg	Stats	Iv
Coamoxiclav	90mg	Tds	Iv
Coamoxiclav	0.75ml	Tds	Po/ngt
Lactulose	2.5ml	Bd	Po
<b>Clinical narrative</b>			
The patient was on the correct dose of morphine, the patient developed signs of seizures, respiratory depression and agitation. The patient recovered after being administered naloxone intravenously.			
<b>Medicine related problem (MRP):</b> <i>“an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”</i> . (Pharmaceutical Care Network Europe, 2010)			
<b>Please answer the following question by either YES or No</b>			
<b>Does the case include any MRP based on the attached PCNE classification tool?</b>			
<b>Please rank the harm caused by the MRP identified based on NPSA scale of harm, insert ✓</b>			
<ul style="list-style-type: none"> <li>• No harm (The incident caused no harm)</li> <li>• Low (Any patient safety incident that required extra observation or minor treatment, and caused minimal harm to the person(s) receiving NHS funded care)</li> <li>• Moderate (Any patient safety incident that resulted in a moderate increase in treatment, and which caused significant but not permanent harm to the person receiving NHS funded care) ✓</li> <li>• Severe (Any patient safety incident that resulted in permanent harm to the person(s) receiving NHS funded care)</li> </ul>			

None of the MRPs was rated as severe or death; thus only three levels were observed in the data. All experts determined that 60% of MRPs were low harm, 25% of MRPs were moderate harm and 15% at no harm. Table 6.8 summarises experts' rating.

**Table 6:8: Experts' panel severity scoring of MRPs**

Scorer	No harm Percentage (n)	Low Percentage (n)	Moderate Percentage (n)
<b>Consultant pharmacist</b>	15 (3)	60 (12)	25 (5)
<b>Consultant paediatrician</b>	15 (3)	60 (12)	25 (5)
<b>Nurse</b>	15 (3)	60 (12)	25 (5)

Analysis involved descriptive statistics (frequencies and percentages)

The agreement between panel's members is provided in Table 6.9 below. The results showed that there was agreement between the three experts in 90% of the identified MRPs. The kappa statistic was found to be 0.88, (CI 95%, 0.69- 1.0) which implies very good agreement between the three experts.

**Table 6:9: The agreement between panel's members**

Level of agreement	Number (%)
<b>All members in agreement</b>	18 (90%)
<b>Two in agreement, one disagreement</b>	2 (10%)
<b>All three members in disagreement</b>	0 (0%)

#### 6.5.10 Medicines related problems preventability

Assessment of preventability using Schumock and Thornton preventability scale showed identified MRPs were all non-preventable. Table 6.10 below shows case vignette of identified MRPs and their associated medicines in the study population.

**Table 6:10: Case vignettes of most common prescribed medicines and associated problems**

<b>Case</b>	<b>Medicines associated with MRPs</b>	<b>Licensing status</b>	<b>MRP category</b>	<b>MRP severity</b>
<b>A patient aged 1day (2kg) was admitted with seizure of epilepsy . The patient developed signs respiratory depression after administration of a correct dose of morphine. The patient recovered after being administered Naloxone intravenously.</b>	morphine	UL	ADR: toxic	Moderate harm from the three experts
<b>A patient aged 2hours admitted for a suspected sepsis. The patient developed severe allergic reactions after administration of benzylpenicillin. The patient recovered after the medicine was stopped and after administration of chlorphenarmine injection.</b>	benzylepenicillin	Licensed	ADR: allergic	Pharmacist: moderate harm Nurse: moderate harm Paediatrician: low harm
<b>A patient aged 1day was diagnosed with cardiac problem and commenced on intravenous furosemide. The potassium level dropped and required to administer potassium chloride infusion to correct it.</b>	furosemide	OL	ADR: non-allergic	No-harm from the three experts

## 6.6 Discussion

The results of the prospective study in Chapter 5 showed that OL and UL medicines were associated with more MRPs than licensed medicines. Findings of this study (NICU) showed that 90% (n= 78/87) of the total number of patients had at least one MRP and 9% (n= 186/ 1,978) of all medicines were associated with MRPs.

Findings of this study showed that MRPs associated with the use of OL medicines were higher than with licensed medicines; 9% (n=103/1,139) of licensed medicines were associated with MRPs; 15% (n=43/278) of OL were associated with MRPs, and 7% (n= 40/561) of UL medicines were associated with MRPs. These findings are consistent with the findings of PICU prospective study, which showed that MRPs associated with the use of OL medicines were higher in newborn patients than with the other age groups. This can be explained by the high use of OL medicines in this age group (Cuzzolin & Agostino, 2016).

In this study, all the identified medicines problems were classified as ADRs; there were no treatment effectiveness problems. This difference may be due to the electronic prescribing system (Medchart) that was introduced in this setting prior to the start of the study which has a number of advantages (such as, reduction in inappropriate dosing, facilitation of correct drug, provision of additional support for prescribers) over the traditional paper prescribing.

The electronic system alerts prescribers to wrong information inputted. For example, if a patient's details (such as, age, weight), the name of the medicine, and a possible wrong dose is inputted, the system alerts the prescriber to the wrong dose. The prescriber must then try to re-enter the information and that will continue until the prescriber inputs the correct dose or ignores the alert by pressing the ignore button. In the traditional paper prescribing however, the prescriber would



use a calculator and then write down the dose, where in each of these steps an error might occur. The use of electronic prescribing therefore helps to minimise MRPs caused by medication errors, especially prescribing errors. However, the electronic system has no influence on the occurrence of ADRs; this is because adverse drugs reactions are related to pharmacological effect of medicines and are sometimes non-preventable.

Among the study population both genders had MRPs, but males had more MRPs (93%) than females (86%). However, there was no statistical difference between the genders. This result is in line with the retrospective and prospective studies conducted in PICU (Chapter 4 and 5 respectively), and supported in the literature by a study of MRPs that reported there was no difference in MRPs incidence between males and females patients (Rashed et al., 2012).

With regard to the length of stay in the hospital, there was no association between the number of MRPs and the length of stay of patients. This finding was opposed to the findings from previous two studies where MRPs increased with increase in LOS. This can be explained by the fact that the identified MRPs were allergic and non-allergic ADRs, which are directly related to the commenced medicines and would have happened regardless of the length of the hospital stay because they are part of the pharmacological effect of these medicines.

The severity of the identified MRPs were of low harm (92%), 6% were of no harm and 2% were of moderate harm to patients. This is similar to the findings of the previous two studies and is supported by a study that found that 72.2% of MRPs were minor (n= 345/478) and 27% were moderate (n= 129/478) (Rashed et al., 2012).

Unlike the previous two studies and finding from literature (Easton et al., 2003; Easton et al., 2004) where some of the identified MRPs were preventable, none of the identified MRPs in this

study was preventable. These findings are supported by an MRP study conducted by Rashed et al (2012) where it was found that NICU has the lowest percentage of the preventable MRPs (8.2%). Also in this study, the nature of MRPs as well as the system currently in use can be an explanation for that. That is because of the pharmacological activity of the prescribed medicines, as well as the unexpected response of these new-born patients to the medicines.

### **6.7 Strength and limitations**

One of the major strengths of this study is that the electronic prescribing helped to minimise the challenge of poor documentation and writing mistakes. This increased the level of accuracy of data collected. The electronic prescribing system allows patient information to be accessed remotely, thus the researcher was able to access patients' charts remotely from the pharmacy department and/or nurse stations to check further information without necessarily having to be present in the ward. This helped to facilitate the study and decreased data collection time experienced in the previous two studies.

Moreover with the Medchart, the researcher was able to check for daily pharmacist re-conciliation of medicines. This helped in probing for more clarification of the patients' current situation, while in paper prescribing it was difficult to know if reconciliation had been carried out without the pharmacist signature, thus the researcher would assume reconciliation was not done. This system therefore facilitate the recording of intervention level as any updates have to be signed for. Also, the training the researcher received on the use of the software and the technology involved enhanced accurate data collection.

The major limitations of this study was that infusions were still written manually in fluids charts and the researcher had to mingle between software and paper copies for data collection of

medicines being prescribed. Another limitation of this study was the inability to access any drug chart when it was in use by other members of staff.

### **6.8 Implications of study in practice**

In this study, the identified MRPs were mainly ADRs, which, were due to pharmacological effects of the administered medicines, and they were non-preventable. Electronic prescribing should therefore be implemented in other wards to minimise treatment effectiveness problems that are due to medication errors. Monitoring and reporting of ADRs should be routine practice in healthcare settings; healthcare professionals should be encouraged to review the reported incidents as a learning process. There should also be evaluation after an intervention is implemented to prevent MRPs to assess the effectiveness of such intervention. MRPs were found to be higher with off-label and unlicensed medicines when compared to licensed medicines, thus regular education programme to increase the awareness of MRPs associated with OL and UL medicines might help to reduce the number of MRPs in the paediatric population. This will contribute to improving the practice and patients' quality of life.

### **6.9 Conclusion**

This study was carried out prospectively to investigate the prevalence of medicines related problems associated with the use of off-label and unlicensed medicines in patients admitted to neonatal intensive care unit of a paediatric hospital.

- A total of 1,978 medicines were prescribed to 87 patients.
- 90% of patients developed at least one MRP.
- 9% of the total number of medicines were associated with MRPs.

- 15% of OL medicines and 7% of UL medicines were associated with MRPs, while 9% of licensed medicines were associated with MRPs.
- All the identified medicines related problems were classified as adverse drug reactions
- Electronic prescribing had positive impact and significantly reduce treatment effectiveness problems caused by prescribing errors
- Morphine, benzylpenicillin and furosemide were found to be commonly associated with the identified MRPs.
- None of the identified MRPs was preventable; none was rated as being of severe harm to patients.

Overall discussion of the research is presented in the next chapter.

## **Chapter 7: Overall discussion**

### **7.1 Introduction**

Prior to widespread use of any medicine, pharmaceutical companies are required to provide information on the safety, efficacy and quality of the medicine to national medicines regulatory agencies. When a medicine is approved, a marketing authorisation or license is issued with a Summaries of Product Characteristics (SPC) (Silva, Ansotegui & Morais-Almeida, 2014). This usually follows from extensive clinical trials to evaluate the safety and efficacy of such medicines. These trials are mostly conducted with selected adult populations with the paediatric population grossly under-represented (Kimland et al., 2012; Magalhães et al., 2015). Thus, the majority of medicines prescribed for paediatrics have not been tested in this population and the safety and efficacy of paediatrics' medicines are reportedly supported by low quality of evidence (Silva, Ansotegui & Morais-Almeida, 2014). Therefore many medicines used in treating paediatrics in both primary and hospital care settings are used in the off-label (OL) and/or unlicensed (UL) manner (Magalhães et al., 2015; Turner, Nunn, Fielding & Choonara, 1999). UL medicines use is defined as the use of medicines without a product license or marketing authorisation. OL medicine use is the use of licensed medicines outside of the terms of their product license or marketing authorisation with regard to the dose, indication, age and route of administration as well as contraindicated drug use (Tomlin & Morris., 2009; Turner, Nunn & Choonara, 1998). UL and OL use of medicines is a common practice in paediatric population (Batchelor & Marriott, 2015; Kimland, 2012; Magalhães et al., 2015; RCPC, 2013; Richey et al., 2013; Turner, Nunn, Fielding & Choonara, 1999). The risks associated with OL and UL medicines use consist of inaccurate utilisation of formulae and calculations, opting for improper ingredients, utilising erroneous quantities, and production of unstable products (Fontan, Mille, & Brion, 2004).

Prescription of UL and/or OL has been associated with higher incidence of adverse drug reactions (ADRs), a subtype of medicine related problems (MRPs) (Fontan, Mille, & Brion, 2004; Rees et al., 2017; Turner et al., 1999; WHO, 2007). A limited number of studies have investigated MRPs in paediatric patients (Rashed et al., 2012; Ibrahim et al., 2013; Easton et al., 2003; Easton et al., 2004). Problems associated with the use of OL and UL medicines in paediatric patients have been investigated with regard to ADRs. MRPs include ADRs, treatment effectiveness problems, patients' satisfaction and cost (PCNE, 2010). To investigate MRPs associated with OL and UL medicines in paediatric patients, a literature review was carried out to determine the prevalence of use of OL and UL medicines in paediatric population as well as problems associated with their use. Findings of the literature review showed there were no studies that investigated the different types of MRPs that may result from the use of OL and UL medicines.

The aim of this research was therefore investigate MRPs associated with the use of OL and UL medicines in paediatric inpatients.

To achieve this aim, a systematic literature review was carried out in Chapter 2. Findings of the review informed the research questions, aim and objectives of this research. In Chapter 4, retrospective review of case notes of patients admitted to PICU was conducted in medical records department. In Chapters 5 and 6, prospective study was carried out in PICU and NICU respectively.

## **7.2 Key findings**

A total of 38 studies were included in the literature review of this thesis. Among the included studies, there was no unified definition of OL and UL use of medicines. Majority of the studies

defined OL and UL use based on the information from the SPCs. OL and UL medicines' use was found to be higher in intensive care units than in general paediatric wards with neonates being the most exposed (Cuzzolin & Agostino, 2016; Lass et al., 2011; Lindell-Osuagwu et al. 2014; Oguz et al., 2012). Up to 100% of patients in NICU receive at least one off-label or unlicensed medicine (Conroy et al., 1999; Kieran et al., 2014; Lass et al., 2011; O'Donnell et al., 2002). Age, indication, dosage and frequency were the main reasons for OL use of medicines in paediatrics (Ballard et al., 2013; Bellis et al., 2013; Conroy et al., 1999; Conroy et al., 2000; Di Paolo et al., 2006; Hsien et al., 2008; O'Donnell et al., 2002; Porta et al., 2010). The use of OL and UL medicines was associated with higher incidence of ADRs than licensed medicines (Turner et al., 1999). Although OL and UL use of medicines are prevalent among children, investigation of all possible problems associated with their use has not been carried out.

In Chapter 4, of 2000 medicines prescribed to 194 patients, 54.3% were licensed, 17.7% were OL and 28% were UL. Eight percent of the total number of medicines resulted in MRPs; MRPs were higher with OL and/or UL medicines than licensed medicines (57% vs 43%). The main types of problems found in this study were ADRs and treatment effectiveness (84% vs 16%). Most of the ADRs were caused by morphine and furosemide, as these two medicines were commonly used in PICU and more than 90% of patients were prescribed morphine or furosemide. Treatment effectiveness problems were mostly classified as effect of drug treatment not optimal, and wrong effect of drug treatment caused by the dose selection; medicine dose too low; medicine dose too high; treatment duration too long and prescribing errors. The literature review of this thesis did not identified studies that investigated MRPs in relation to OL and/or UL medicines use in paediatrics. However, studies of ADRs in paediatric patients have reported higher incidence of ADRs with the

use of OL and/or UL medicines when compared to licensed medicines (Neubert et al., 2004; Saiyed, Lalwani & Rana, 2015; Turner et al., 1999).

In Chapter 5, 1578 medicines were prescribed to the study population of which approximately 47% were OL and/or UL. Previous studies have reported similar prevalence. Palcevski et al. (2012) reported that 46% of medicines prescribed to paediatric patients admitted to general and surgical wards were OL or UL. Kieran et al. (2014) reported 39% of medicines used in treating neonates are prescribed in OL manner. Of the OL medicines prescribed to study population, 5.4% were associated with MRPs; 19.3% of UL medicines resulted in MRPs while 9% of licensed medicines were associated with MRPs. Identified MRPs were ADRs and treatment effectiveness; these were commonly associated with morphine, paracetamol, clonidine, furosemide and spironolactone.

In Chapter 6, 1,978 medicines were prescribed to the 87 neonates, of which 58% were licensed, 14% were OL, and 28% were UL. Nine percent of the total number of medicines was associated with MRPs and 90% of patients developed at least one MRP. MRPs associated with the use of OL medicines were found to be higher when compared to licensed medicines ( $p < 0.001$ ); 9% of licensed medicines were associated with MRPs; 15% of OL medicines were associated with MRPs; and 7% of UL medicines were associated with MRPs. The identified MRPs were classified as non-preventable ADRs; there were no treatment effectiveness problems.

Findings of the three studies are consistent with literature (Berdkan et al., 2016; Conroy et al., 1999; Kieran et al., 2014; Kimland & Odland, 2012; Magalhães et al., 2015; Pandolfini & Bonati, 2005) in establishing the fact that the use of OL and UL medicines is a common in paediatric practice. This shows that there is still lack of age-appropriate medicines and/or formulations in spite of legislations such as, Paediatric Investigation Plan (PIP) for European countries (European Parliament & EU Council, 2006) and Paediatric Study Plan (PSP) for the Americas. These



legislations encourage inclusion of children in investigation of new medicines and manufacture of age-appropriate formulations. There is therefore a need for evaluation of the effectiveness of these legislations, such as, assessment of availability of new medicines and/or formulations for the paediatric use following publication of these legislations. Furthermore, there is a need to explore alternatives to UL compounding and OL prescribing. This will help to clarify whether OL and/or UL use of medicines is a prescribers' habit or a result of the limited availability of paediatric-appropriate medicines or formulations.

Findings of the three studies are also consistent with literature (Bellis et al., 2013; Neubert et al., 2004; Saiyed, Lalwani & Rana, 2015; Turner et al., 1999) in confirming that the incidence of MRPs is higher with OL and/or UL medicines when compared to licensed medicines. In two of the studies (retrospective PICU, Chapter 4 and prospective PICU, Chapter 5) the main types of MRPs identified were ADRs and treatment effectiveness problems. However, it is difficult to relate these problems to the licensing status of medicines because the identified MRPs were seen with the most frequently used medicines (morphine, furosemide) among the study population. These problems would normally occur regardless of the licensing status, because they are part of the pharmacological effects of these medicines.

Implementation of electronic prescribing (e-prescribing) in one of the settings in this research (NICU, Chapter 6) showed that e-prescribing significantly decreased the number of MRPs, especially treatment effectiveness problems that often result from medication errors. Thus implementing e-prescribing in other hospital wards would have great impact on health care quality, by reducing mortality and morbidity-related medicine incidents. This will ultimately reduce the financial burden for the NHS. The Personalised Health and Care 2020: Using Data and Technology to Transform Outcomes for Patients and Citizens (NHS England, 2014), and the

Safer Hospitals, Safer Wards Technology Fund (NHS England, 2013) are therefore laudable government initiatives that will ensure health prosperity and quality.

### **7.3 Research contribution to knowledge**

This research is the first to investigate MRPs associated with use of OL and UL medicines in paediatric in-patients as well as determine their categories. Identified MRPs were ADRs and treatment effectiveness problems. MRPs were higher with the use of OL and UL medicines than with licensed medicines. Although previous studies have reported incidence of ADRs (non-preventable MRPs resulting from pharmacological activity of administered medicines) with use of OL and UL medicines in paediatrics, the use of PCNE classification system identified another domain of MRP: treatment effectiveness problems. Treatment effectiveness problems are preventable as they are often caused by the dose selection; medicine dose too low; medicine dose too high; treatment duration too long and prescribing errors. Implementation of electronic prescribing can prevent treatment effectiveness-related MRPs.

### **7.4 Implications for practice**

This research has successfully filled the gap in knowledge about MRPs associated with the use of OL and UL medicines in paediatric patients. MRPs associated with the use of OL and UL medicines were up to 60% in paediatric patients admitted to intensive care units, further investigation is however required to ascertain whether MRP occurrence is actually due to the licensing status of the medicines or not.

Medicines optimisation is a crucial element to ensure a safe practice for paediatric population because OL and UL medicines' use is common in this population. In light of the fact that OL and/or UL medicines' use is associated with higher incidence of MRPs when compared with

licensed medicines, effort should be geared towards optimising use of OL and UL medicines. This would include:

- double-checking of paediatric prescriptions by two or more healthcare professionals as well as reconciliation play important role in minimising treatment effectiveness problems, including prescribing errors. This is due to manipulation and adjustment of adult formulation and/or doses to meet paediatric needs.
- using standard reference sources such as, the SPCs as it stipulates the uses of medicines; this can help to avoid errors and safety incidents.
- using a unified tool such as, the PCNE classification tool for MRPs' identification in all hospital wards. This will ensure uniformity in data collection and analysis and increase the knowledge about the contributory factors to MRPs thereby eliminating them.

Pharmacovigilance of MRPs associated with OL and UL medicines should be promoted in paediatric practice. Healthcare professionals as well as parents or carers should be encouraged to report all safety incidents associated with OL/UL medicines to a central reporting system such as, the National Reporting and Learning System (NRLS). Also introducing a category of the licensing status of medicines in incidents reporting system is very important and healthcare professionals should be encouraged, when reporting a safety incident, to report whether the medicine was licensed, off-label or unlicensed. That would help to identify the medicines' license status that is most implicated with safety incidents. This would serve educational purposes, ensure safety of medicines and also improve practice.

Although pharmaceutical companies were encouraged to include paediatric patients in clinical trials for new medicinal products and to make sure that paediatric population is well represented (PIP & PSP), some companies might be exempted after a waiver application. This should be

minimised to promote the development of new medicines for paediatric population. Also introducing a category of the licensing status of medicines in incidents reporting system is very important and healthcare professionals should be encouraged, when reporting a safety incident, to report whether the medicine was licensed, off-label or unlicensed. That is might help to increase the awareness of the healthcare professionals not only with certain medicines that contributed with incidents, but also with the licensing status that are mostly implicated with safety incidents. Also a new policy to distinguish between licensed and off-label /unlicensed medicines should be introduced, such as a colour coded system which tells the professionals that this medicines is an off-label or unlicensed medicines. This will ensure that practitioners will pay more attention to the medicines that were prescribed as off-label and/or unlicensed medicines. Although pharmaceutical companies were encouraged to include paediatric patients in clinical trials for new medicinal products and to make sure that paediatric population is well represented (PIP & PSP), some companies might be exempted after a waiver application. This should be minimised to promote the development of new medicines for paediatric population.

## **7.5 Research Recommendations**

The following recommendations if implemented would improve paediatric practice with respect to OL and UL medicines:

- The research community should develop an international consensus definition for OL and UL medicines and disseminate same in peer-reviewed journal. This will allow comparison of findings of OL and UL medicines research in paediatrics from different countries and settings.

- The National Patient Safety Agency (NPSA) should increase the awareness of MRPs identification, causes, interventions and outcomes through educational programmes such as, posters, brochures, and leaflets.
- The role of the pharmacist in identifying and intervening to resolve MRPs is pivotal. Thus, NHS Trust boards should provide funding that would ensure a pharmacist is available on a 24-hour basis in the ward to review all OL and UL prescription, detect and resolve MRPs.
- Currently, hospital incident reporting is mostly performed by the nurses. The pharmacist, who is the medicines expert, should be encouraged to take the lead in identifying and documenting MRPs.
- While the hospital has its local prescribing guideline, this guideline does not have medicine manufacturers' information. Prescribers often rely on local guidelines without reference to Summary of Product Characteristics (SPCs). It is therefore crucial that healthcare professionals should be encouraged to access the information in the SPCs of medicines to identify off-label and/or unlicensed use of medicines.
- Severity scoring systems available now are designed for ADRs and MEs, which are subsets of MRPs. The research community should develop a scoring system for MRPs to minimise the confusion that might occur when using other systems.
- Findings of this research showed that there were less treatment effectiveness problems with the use of electronic prescribing. Thus, implementation of electronic prescribing in all hospital wards will help reduce MRPs and improve the quality of healthcare.
- It is recommended that a national survey be conducted to evaluate the availability of paediatric medicines. Such survey can be repeated after 10 years to evaluate the

effectiveness of the paediatric regulations (e.g., PIP) in increasing the availability of authorised and age-appropriate medicines.

## **7.6 Future Research**

- Hospital-wide studies involving all paediatric wards should be conducted to investigate MRPs associated with the use of OL and UL medicines.
- Further research should involve both quantitative and qualitative studies to explore healthcare professionals' perceptions and attitudes about OL and UL medicines' use. This should include practitioners in practice settings (secondary, primary, and community)
- Further study should be conducted to investigate hospital and A&E admissions resulting from MRPs associated with OL and UL use of medicines.

## **7.7 Research Strength and limitations**

### **7.7.1 Research Strength**

- The use of retrospective and prospective approaches provided a holistic picture of MRPs with use of OL and UL medicines in children.
- Randomisation of participants enhanced the generalisability of study results.
- The methodology adopted in the first two studies (Chapters 4 and 5), that is, intensive chart review has been recognised as the most appropriate and gold standard in pharmaco-epidemiological studies (Rashed et al., 2012).

### **7.7.2 Research Limitations**

- Major limitation is that the systematic literature review was restricted to original research papers presented in English language only and other studies published in other languages were excluded.
- There was no access to medical case-notes of patients in isolated rooms as well as deceased patients. Therefore there is no judgment about MRPs associated with the use of off-label and unlicensed medicines in those patients.
- This research did not investigate the treatment cost and patients' perspectives.

## 7.8 Conclusion

The limited availability of age-appropriate medicines for children and the consequential high rates of OL and UL use of medicines in this patient population are a worldwide concern (Nunn et al., 2014). OL and UL medicines use may hamper the effectiveness of pharmacotherapy and/or increase the risk of adverse events and problems. Findings of this research showed higher prevalence of the use of OL and UL medicines in the studied settings (PICU and NICU) and thus confirm previous studies (Conroy et al., 1999; Conroy et al., 2000). This research also showed that the use of OL and UL medicines in paediatric in-patients was associated with more MRPs than licensed medicines and between 9- 14% of OL and UL medicines were implicated in MRPs. Approximately 53% of patients admitted to PICU and 90% of patients admitted to NICU had MRPs. Although there is no study to compare these finding, higher incidence of MRPs have been reported in PICU when compared with general paediatric medical ward (Rashed et al., 2012). Findings of this research showed that the use of electronic prescribing led to reduction in occurrence of treatment effectiveness-related MRPs. Migration to electronic prescribing in all hospitals wards will help in MRPs reduction.

This research has filled a gap in knowledge in that it is the first to investigate MRPs associated with the use of OL and UL medicines in paediatric in-patients. There is a need for pharmaceutical companies to comply with the PIP regulation in order to reduce the use of OL and/or UL medicines in this population. Further research in paediatric practice is highly needed, and industry and policy makers are encouraged to work collaboratively with the healthcare research in order to assure advanced implementations of high quality of healthcare systems.



## Research Output

### Abstracts submissions:

- Elhijazi, W., Tomlin, S., Umaru, N., Liu, F., Ghaleb, M., Foulsham, R.,Kostrzewski, A. Development of a Tool to Identify Medicines Related Problems in Paediatric In-patients. LMS Research Conference 2015. School of Life and Medical Science, University of Hertfordshire, UK.
- Elhijazi, W., Ghaleb, M., Foulsham, R.,Kostrzewski, A. Medicines Related Problems Associated with the Use of Unlicensed& Off-label Medicines in Paediatric In-patients: A Systematic Literature Review. LMS Research Conference 2014. School of Life and Medical Science, University of Hertfordshire, UK.

### • Conference posters' presentations:

- Elhijazi, W., Tomlin, S., Liu, F., Ghaleb, M., Umaru, N. Medicines' Problems Associated with the Use of Unlicensed & off-label Medicines in Paediatric Population. The Clinical Pharmacy Congress Conference 2016, London, UK.
- Elhijazi, W., Tomlin, S., Liu, F., Ghaleb, M., Umaru, N. Medicines' Problems Associated with the Use of Unlicensed & off-label Medicines in Paediatric Population. PPP Research Conference 2016. School of Life and Medical Science, University of Hertfordshire, UK.

- Elhijazi, W., Tomlin, S., Umaru, N., Liu, F., Ghaleb, M., Foulsham, R.,Kostrzewski, A. Development of a Tool to Identify Medicines Related Problems in Paediatric In-patients. LMS Research Conference 2015. School of Life and Medical Science, University of Hertfordshire, UK.
- Elhijazi, W., Ghaleb, M., Foulsham, R.,Kostrzewski, A. Medicines Related Problems Associated with the Use of Unlicensed& Off-label Medicines in Paediatric In-patients: A Systematic Literature Review. LMS Research Conference 2014. School of Life and Medical Science, University of Hertfordshire, UK.
- **Seminars:**
  - Pharmacy Practice Presentation and Research Showcase Evening; University of Hertfordshire. May 2014: Medicines Related Problems Associated with the Use of Off-label & Unlicensed Medicines in Paediatric In-patients.
  - Pharmacy Practice Presentation and Research Showcase Evening; University of Hertfordshire. July 2015: Medicines Related Problems Associated with the Use of Off-label & Unlicensed Medicines in Paediatric In-patients.

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## Appendices

### Appendix 1: PCNE Classification for drug related problems

# Classification for Drug related problems

(revised 14-01-2010vm)  
V6.2

© 2003-2010 Pharmaceutical Care Network Europe Foundation  
This classification can freely be used in Pharmaceutical Care Research and practice, as long as the Foundation is informed of its use and results of validations. The classification is available both as a Word document and a PDF document.  
Contact: jwfvml@planet.nl

This classification should be referred to as 'The PCNE Classification V 6.2'  
This version is not backwards compatible with older versions.

## Introduction

During the working conference of the Pharmaceutical Care Network Europe in January 1999, a classification scheme was constructed for drug related problems (DRPs). The classification is part of a total set of instruments. The set consists of the classification scheme, reporting forms and cases for training or validation. The classification system is validated and adapted regularly. The current version is V6, which has been discussed during an expert workshop in November 2009. It is no longer compatible with previous versions because the problem and causes sections has been revised. The Intervention section has not been adapted.

The classification is for use in research into the nature, prevalence, and incidence of DRPs and also as a process indicator in experimental studies of Pharmaceutical Care outcomes. It is also meant to help health care professionals to document DRP-information in the pharmaceutical care process. Throughout the classification the word 'drug' is used, where others might use the term 'medicine'.

The hierarchical classification is based upon similar work in the field, but it differs from existing systems because it separates the problems from the causes. Quality experts will recognise that de causes are often named 'Medication Errors' by others.

The following definition is the basis for the classification:

*A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.*

The basic classification now has 4 primary domains for problems, 8 primary domains for causes and 5 primary domains for Interventions.

However, on a more detailed level there are 9 grouped sub domains for problems, 37 grouped sub domains for causes and 17 grouped sub domains for interventions. Those sub-domains can be seen as explanatory for the principal domains.

In 2003 a scale has been added to indicate if or to what extend the problem has been solved.

*Zuidlaren, November 2009 and January 2010*

## The basic classification

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

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	<i>Unclear problem/complaint. Further clarification necessary (please use as escape only)</i>

- 
- Potential Problem
  - Manifest Problem
-

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
<b>1. Drug selection</b> 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
<b>2. Drug form</b> The cause of the DRP is related to the selection of the drug form	C2.1	Inappropriate drug form
<b>3. Dose selection</b> 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
<b>4. Treatment duration</b> 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
<b>5. Drug use process</b> 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
<b>6. Logistics</b> 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)
<b>7. Patient</b> 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
<b>8. Other</b>	C8.1	Other cause; specify
	C8.2	No obvious cause

### 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, <b>approved</b> by Prescriber
	I1.4	Intervention proposed, <b>not approved</b> 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

# PCNE Classification for Drug related problems Help

(revised 09-11-2009 vm)  
V6.2

© 2003-2010 Pharmaceutical Care Network Europe Foundation  
This classification can freely be used in Pharmaceutical Care Research and practice, as long as  
the Foundation is informed of its use and results of validations. The classification is available  
both as a Word document and a PDF document.  
Contact: [info@pcne.org](mailto:info@pcne.org)

This help document is related to as 'Help to the PCNE Classification V 6.2



## Finding or selecting codes in the PCNE classification

*A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.*

For the use of the PCNE classification it is important to separate the real problem (that affects or is going to affect the outcome) from its cause. Often such problems are caused by a certain type of error e.g. prescribing errors or drug-use or administration errors. But there might be no error at all involved. Also, a medication error does not necessarily have to lead to a drug-related problem.

The cause is usually the behaviour that has caused the problem, and most often that is a medication error. A cause or a combination of causes and a problem together, will usually lead to one or more interventions.

The classification can be used in two ways, depending on the level of information needed. If only the main domains are used, there is in general enough information for research purposes.

If the system is used for documenting pharmaceutical care activities in practice, the sub domains can be used.

### Problem section

Basically, the problem is defined as 'the expected or unexpected event or circumstance that is, or might be wrong, in therapy with drugs'. (the P-codes)

There are 4 major domains in the problem section. The following descriptions could help to find the right problem domain:

The clinical effect of the treatment is not as expected or there is no treatment	See P1
The patient suffers from an ADR at normal dose or from a toxic reaction	See P2
The treatment, although leading to optimal clinical outcomes and no ADEs, is more expensive than necessary	See P3
Nothing seems wrong in the treatment, but patient is unhappy about it.	See P4

### Causes section

Each problem has a cause. The cause is the action (or lack of action) that leads up to the occurrence of a potential or real problem. There may be more causes for a problem. (The C-code)

The cause of the DRP can be related to the selection of the drug	See C1
The cause of the DRP can be related to the selection of the drug form	See C2
The cause of the DRP can be related to the selection of a dosage schedule	See C3
The cause of the DRP can be related to the duration of the therapy	See C4
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 label, leaflet or package/package insert (depending on the national custom)	See C5
The cause of the DRP can be related to the logistics of the prescribing or dispensing process	See C6
The cause of the DRP can be related to the personality or the behaviour of the patient	See C7
Other	See C8

#### Intervention section

The problem will usually lead to one or more in interventions to correct the cause of the problem. (The I-code)

There is or can be no intervention	See I0
Intervention through the prescriber	See I1
Intervention through the patient, his carers or relatives	See I2
Intervention directly by changing drug or indicating change in drug use	See I3
Other intervention	See I4

#### Outcome section

For evaluation purposes it is desirable to indicate if the problem has been solved by doing the intervention (the O-code). This scale has been added in V5 (2003)

Problem totally solved	See O1
Problem partially solved	See O2
Problem not solved	See O3

## Appendix 2: Naranjo ADR probability scale-items and score

Question	Ye s	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	-1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when drug was re-administered?	+2	-1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Scoring for Naranjo algorithm:

> 9 definite ADR

5–8 = probable ADR

1–4 = possible ADR

0 = doubtful ADR

## Appendix 3: University of Hertfordshire approval



Mrs Wijdan Elhijazi (Dr Andrzej Kostrzewski)  
Department of Pharmacy  
School of Life and Medical Sciences

University of Hertfordshire  
Hatfield  
AL10 9AB  
UK

tel +44 (0)1707 284000  
fax +44 (0)1707 284115  
herts.ac.uk

1 October 2014

Dear Wijdan,

Re: **UNIVERSITY OF HERTFORDSHIRE SPONSORSHIP IN PRINCIPLE for the following:**  
**RESEARCH STUDY TITLE:** Medicines Related Problems Associated with the Use of Unlicensed and Off-label Medicines in Paediatric In-patients.  
**NAME OF CHIEF INVESTIGATOR:** Mrs Wijdan Elhijazi  
**IF STUDENT, NAME OF SUPERVISOR:** Dr Andrzej Kostrzewski  
**UNIVERSITY OF HERTFORDSHIRE ETHICS PROTOCOL NUMBER:** LMS/PG/NHS/00290

This letter is to confirm your research study detailed above has been reviewed and accepted, and I agree to give University of Hertfordshire sponsorship in principle.

Before you commence your research you must be in full compliance with all NHS Governance requirements. You must also secure full University of Hertfordshire sponsorship, for which you will need to have supplied the following documentation:

- Final version of the submitted IRAS form (pdf)
- Approval from the relevant NRES (NHS) Research Ethics Committee (REC) as well as confirmation of favourable opinion of any possible amendments
- Evidence of relevant NHS Permissions (eg Research Passport) and NHS Trust Management Permissions (previously known as R&D Approval) as they are received
- The final version of the protocol
- The final versions of the patient information leaflet and informed consent form
- One page summary CV for the Chief Investigator (CI) and, if research student project, for the Supervisor
- Any other regulatory permissions required for your research, eg from the National Information Governance Board (NiGB), under the Human Tissue Act or the Ionising Radiation (Medical Exposure) Regulations
- If applicable, copies of any contracts/agreements with external organisations (eg funders, collaborators, co-sponsors) involved in your research study

As a condition of receiving full sponsorship, it is the responsibility of the Chief Investigator to inform the Sponsor of any changes to the duration or funding of the project, changes of investigators, changes to the protocol and any future amendments, or deviations from the protocol, which may require re-evaluation of the sponsorship arrangements. It is also the responsibility of the Chief Investigator to inform the funder, the NRES (NHS) Research Ethics Committee (REC) and the relevant University of Hertfordshire Ethics Committee with Delegated Authority (ECDA) and any other relevant authority of any of these changes.

I look forward to receiving the above documents before you commence your research. Please email these to [research-sponsorship@herts.ac.uk](mailto:research-sponsorship@herts.ac.uk) so the University can confirm sponsorship. In the meantime, we wish you well in pursuing this interesting research study.

Yours sincerely,

Professor J M Senior  
Pro Vice-Chancellor (Research and International)

Encl: Insurance certificate



A Charity Exempt from Registration under the  
Second Schedule of the Charities Act 1993

## Appendix 4: NHS Ethics application

NHS REC Form

Reference:  
15-NW-0263

IRAS Version 3.5

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)  
Medicines Related Problems In Paediatric In-patients

1. Is your project research?

Yes  No

2. Select one category from the list below:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Please answer the following question(s):

- a) Does the study involve the use of any ionising radiation?  Yes  No
- b) Will you be taking new human tissue samples (or other human biological samples)?  Yes  No
- c) Will you be using existing human tissue samples (or other human biological samples)?  Yes  No

3. In which countries of the UK will the research sites be located?(Tick all that apply)

- England
- Scotland
- Wales
- Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

Date: 16/03/2015

1

165377/754409/1/984

- England  
 Scotland  
 Wales  
 Northern Ireland  
 This study does not involve the NHS

**4. Which review bodies are you applying to?**

- NHS/HSC Research and Development offices  
 Social Care Research Ethics Committee  
 Research Ethics Committee  
 National Information Governance Board for Health and Social Care (NIGB)  
 National Offender Management Service (NOMS) (Prisons & Probation)

*For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.*

**5. Will any research sites in this study be NHS organisations?**

- Yes  No

**5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?**

- Yes  No

*If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).*

**5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see Information button for further details.**

- Yes  No

*If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.*

**6. Do you plan to include any participants who are children?**

- Yes  No

**7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?**

- Yes  No

*Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.*

**8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?**

Yes  No

8. Is the study or any part of it being undertaken as an educational project?

Yes  No

Please describe briefly the involvement of the student(s):

The student is the chief investigator who will be responsible writing the study protocol, data collection and data analysis.

8a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes  No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes  No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes  No



Integrated Research Application System  
Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study



Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)  
Medicines Related Problems In Paediatric In-patients

Please complete these details after you have booked the REC application for review.

**REC Name:**  
NRES COMMITTEE NORTH WEST-GREATER MANCHESTER SOUTH

**REC Reference Number:**  
15-NW-0263

**Submission date:**  
16/03/2015

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Medicines Related Problems Associated with The Use of Unlicensed & Off-label Medicines in Paediatric In-patients (POUMPs Study).

A2-1. Educational projects

Name and contact details of student(s):

Student 1	
<b>Title</b>	Forename/Initials Surname
	Mrs WUDAN ELHJAZI
<b>Address</b>	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
<b>Post Code</b>	AL10 9AB
<b>E-mail</b>	w.elhjaz@herts.ac.uk
<b>Telephone</b>	00441707281051
<b>Fax</b>	00441707284506



Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:  
This research project is undertaken as part of a PhD course.

Name of educational establishment:  
University of Hertfordshire

Name and contact details of academic supervisor(s):

**Academic supervisor 1**

	Title	Forename/Initials	Surname
	Dr	ANDRZEJ	KOSTRZEWSKI
Address	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield		
Post Code	AL10 9AB		
E-mail	a.kostrzewski@herts.ac.uk		
Telephone	00441707281051		
Fax	00441707284506		

Please state which academic supervisor(s) has responsibility for which student(s):  
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Mrs WIJDAN ELHIAZI	<input type="checkbox"/> Dr ANDRZEJ KOSTRZEWSKI

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- Student  
 Academic supervisor  
 Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Mrs	WIJDAN	ELHIAZI
Post	PhD Student		
Qualifications	MSc Clinical Pharmacy, International Practice & Policy School Of Pharmacy, University of London BSc Pharmacy, University of Khartoum		
Employer	University of Hertfordshire		
Work Address	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield		

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* Personal Telephone/Mobile	07765637900
Fax	00441707284506

\* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.  
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

**A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?**  
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Professor	John	Senior
Address	Pro Vice-Chancellor (Research and International)		
	University of Hertfordshire		
	Hatfield		
Post Code	AL10 9AB		
E-mail	j.m.senior@herts.ac.uk		
Telephone	01707 284000		
Fax	01707 284115		

**A5-1. Research reference numbers.** Please give any relevant references for your study:

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number: LMS/PG/NHS/00290

Protocol Version: 3rd ver

Protocol Date: 29/07/2014

Funder's reference number:

Project website:

**Additional reference number(s):**

Ref.Number	Description	Reference Number

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

**A5-2. Is this application linked to a previous study or another current application?**

Yes  No

Please give brief details and reference numbers.

## 2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and

members of the public. Please read the guidance notes for advice on this section.

**A6-1. Summary of the study.** Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.

This research project aims to identify problems that might occur as a result of using medicines in children while they are in paediatric intensive care unit or neonatal intensive care unit at Evelina London Children Hospital, from the admission day and until discharge. All patients who are under 18 years will be included, however patients who are not receiving medicines and they are only on nutritional products will be excluded from this study. This research project is designed as a case-note review which will be carried out by a qualified pharmacist. Information will be collected through a review of children's medical notes and drug charts by using a data collection form. All data will be anonymised and stored electronically for analysis. Findings will include type and nature of any medicines related problems, percentage of the occurrence of these problems, and the severity of these problems.

**A6-2. Summary of main issues.** Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

This research project doesn't require explicit patients' consents because it is a non-interventional project, and there will not be any direct contact with patients or their carers. All the information to be reviewed is already screened by a ward pharmacist, nurses, and other healthcare professionals, as part of their clinical routine procedure.

All patients' identifiable information will be viewed only in the hospital setting through the hospital electronic resources and will be recorded anonymously, to ensure patients' confidentiality.

All data will be stored anonymously, and will not be shared in public places or with people who are not members of the research team. Data will be stored electronically in a password protected computer.

In case of any identified problem, the researcher will report that to the ward pharmacist and will not initiate any further action without consulting the pharmacist in-charge.

There is no expected risk for participants including the patients, healthcare professionals and the researcher.

**A6-3. Proportionate review of REC application.** The initial project filter has identified that your study may be suitable for proportionate review by a REC sub-committee. Please consult the current guidance notes from NRES and indicate whether you wish to apply through the proportionate review service or, taking into account your answer to A6-2, you consider there are ethical issues that require consideration at a full REC meeting.

Yes - proportionate review  No - review by full REC meeting

Further comments (optional):

Note: This question only applies to the REC application.

### 3. PURPOSE AND DESIGN OF THE RESEARCH

**A7. Select the appropriate methodology description for this research.** Please tick all that apply:

Case series/ case note review

Case control

- Cohort observation
- Controlled trial without randomisation
- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study
- Laboratory study
- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

**A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.**

What are the medicines related problems experienced by paediatric patients admitted to Paediatric/Neonatal Intensive Care unit at Evelina London Children's Hospital?

**A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.**

1. What is the prevalence of medicines related problems associated with unlicensed and off-label medicines in paediatrics in-patients?
2. What is the clinical significance of these medicines related problems?
3. What are the possible intervention strategies that might help to prevent medicines related problems associated with the use of unlicensed and off-label medicines in paediatric in-patients?

**A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.**

Although most research projects focus on the adult population, the paediatric population are at much higher risk of suffering from medicines related problems due to the difference in pharmacokinetics and pharmacodynamics features when compared to adults (Keams GL, 2003). Medicines related problem include adverse drug reactions, medication errors and drug drug interactions. Dose calculation for paediatric patients are based on many factors such as weight, surface area and height, which are variable among children. Thus the paediatric populations at a much higher risk of developing medicines related problems.

In England, approximately 5% of the total medicines prescribed are received by the paediatric population (Anon., 2008). Most of the medicines that are used in paediatrics are either off-label (OL) or unlicensed (UL). (Choonara & McIntyre, 2001). For this reason, there is a high risk of paediatric patients suffering from medicine related problems.

A number of studies have been conducted globally to identify the prevalence of off-label and unlicensed medicines as well as some of the problems associated with them. For more than a decade, off-label and unlicensed medicines prescribing and their associated problems were major issues and had been investigated by a number of researchers such as Turner S in 1999 who had investigated this area in the UK and found that adverse drug reactions are more frequent with unlicensed and off-label medicines than with licensed medicines representing 6% and 3.9% respectively. (Turner S, 1999), but what missing is a study that investigated all aspects of off-label and unlicensed medicines' related problems including adverse drug reactions, medication errors and adverse drug events. A recent study conducted in the UK revealed that off-label and unlicensed medicines are more likely to be implicated with adverse drug reactions than authorised medicines (Bellis, 2013). Another study conducted in 2013 in the UK illustrated that adverse drug reactions are frequent between hospitalised children reaches 17.7% of 6,601 total admissions (Thelsen, 2013).

Although there are different intervention strategies have been implemented into practice in adults, a limited number have found to be used in the paediatric population and there is no such strategy to highlight the risk associated with off-label and unlicensed medicines and their associated problems. Therefore conducting a research study to explore all the concepts and issues of medicines related problems-with a main focus on medication errors and adverse drug reactions-associated with the use of unlicensed and off-label medicines in order to recommend different ways of intervention for improving paediatrics' practice, is clearly justifiable.

The research team have a previous experience with such a research project in the ADVISE study (Rashed AN et al,

2012) which conducted in the same setting with other collaborating centres. The ADVISE study has contributed to improving the healthcare quality for paediatric population but more studies are needed.

## References:

- Anon., 2008. ONS. [Online] <http://www.ons.gov.uk/ons/index.html> (accessed on 13/03/2014)
- Choonara, I. & McIntyre, J., 2001. Training in clinical pharmacology. Paediatric and perinatal drug therapy [PDF document], 4(3), pp. 124-127.
- Turner, S. E. A. N., Nunn, A. J., Fielding, K., & Choonara, I. M. T. I. (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica*, 88(9), 965-968.
- Thiesen, S., Conroy, E. J., Bells, J. R., Bracken, L. E., Mannix, H. L., Bird, K. A., ... & Smyth, R. L. (2013). Incidence, characteristics and risk factors of adverse drug reactions in hospitalized children? A prospective observational cohort study of 5,601 admissions. *BMC medicine*, 11(1), 237.
- Gregory L. Keams., Susan M. Abdel-Rahman., Sarah W. Alander., Douglas L. Blowey., J. Steven Leeder., and Ralph E. Kauffman. (2003). Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. *N Engl J Med* 2003; 349:1157-1167.
- Rashed AN, Wong IC, Cranswick N, Hefele B, Tomlin S, et al. (2012) Adverse Drug Reactions in Children—International Surveillance and Evaluation (ADVISE): a multicentre cohort study. *Drug Saf* 35: 481–494. doi: 10.2165/11597920

**A13. Please summarise your design and methodology.** It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

A mixed-method approach (qualitative and quantitative) will be used. The study will be divided into three different Phases. The first Phase will be a retrospective identification of the prevalence of medicines related problems (MRPs) associated with the use of unlicensed medicines (medicines with no license) and off-label medicines (medicines have a license to be prescribed to a different age group) and the severity of these problems. Data retrieved from this Phase will be analysed to identify type and nature of medicines related problems. Phase 2 will be a prospective identification of MRPs and their clinical significance to measure the current situation with comparison of the results from the previous Phase (Phase 1) and identify errors and areas with high need of improvement. The last Phase (Phase 3) will produce a list of recommendations and ways of intervention to improve practice. A panel of experts will be asked for their opinion of the recommendations and how to implement them into practice.

Patients aged 0-18 years old who will be admitted to the Paediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at Evelina London Children's Hospital at the time of the study will be included. Patients who are in isolated rooms or there are no access to their medical notes will be excluded. Also patients admitted to the PICU but are on only nutritional products and no medications, will be excluded.

Sample size that has to be investigated for Phase 1 and Phase 2 is 121 medical notes of patients from neonatal intensive care unit and 268 medical notes of patients from paediatrics intensive care unit.

## Phase 1:

Retrospective study to identify prevalence of Medicines Related Problems and their clinical significance

This is a retrospective study which will be about information that happened in the previous period during 2014. It will be conducted at the hospital for the purpose of identification of medicines related problems in terms of prevalence and their clinical significance. It will use a case-note review. Patients' information will be retrieved from drug charts and medical notes by using a data collection form to identify medicines related problems associated with unlicensed and off-label medicines' use in paediatric in-patients. Differences in the use of medicines will also be evaluated against the standard hospital guideline and the British National Formulary for Children (BNF for Children).

## Phase 2:

Prospective study to detect MRPs & categorise their clinical significance

This is a prospective study which will be for the current time in the ward. It will be conducted in the Paediatrics Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at Evelina London Children's Hospital to identify medicines related problems associated with the use of unlicensed and off-label medicines and their clinical significance. It will also include an investigation of patients' pathways to detect the area with higher rate of errors. A panel of experts, (of the research team), will be asked to assess the clinical significance rating. The finding from this study will be evaluated to produce a list of recommendations to improve paediatric practice.

## Phase 3:

Proposed Recommendations & Ways of Intervention to reduce MRPs:

This is a prospective study to use the findings from Phase 2 to develop a list of recommendation in order to prevent medicines related problems associated with the use of off-label and/or unlicensed medicines in paediatrics inpatients. A number of focus group sessions will be used in order to engage the healthcare professionals in the



setting to discuss the produced recommendations and how they can work collaboratively to implement these recommendations into practice. The focus groups will be organised, led and recorded by the moderator (researcher). The data collected from these focus groups will be analysed to be taken into consideration for improving the practice.

**A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?**

- Design of the research  
 Management of the research  
 Undertaking the research  
 Analysis of results  
 Dissemination of findings  
 None of the above

Give details of involvement, or if none please justify the absence of involvement.

This project designed as a case-note review where only medical records and drug charts will be reviewed for information. There is no intended contact with patients or their guardians at any point of the study. Members of the public who are out of the research team will not be involved in this project.

#### 4. RISKS AND ETHICAL ISSUES

##### RESEARCH PARTICIPANTS

**A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).**

Patients who are under 18 years old and who were admitted to the Paediatric Intensive Care Unit and/or Neonatal Intensive Care Unit within the study duration and on medications will be included.

**A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).**

Patients who are in isolated rooms or there are no access to their medical notes will be excluded. Also patients who admitted to the Paediatric/Neonatal Intensive Care Units but they are on only nutritional products but not medications will be excluded.

##### RESEARCH PROCEDURES, RISKS AND BENEFITS

**A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.**

Please complete the columns for each intervention/procedure as follows:

- Total number of interventions/procedures to be received by each participant as part of the research protocol.
- If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
- Average time taken per intervention/procedure (minutes, hours or days)
- Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Daily review of	2	2	1	The researcher will review the medical notes in the paediatric intensive care

patients' case-notes for Phase 2	hours	units.
Focus groups for healthcare professionals for Phase 3	1 0 1	hour The researcher will design and invite healthcare professionals to focus group to ask about their opinion of the list of recommendations
Obtaining Consents for focus groups for Phase 3	1 0 48	hours The researcher will send an email with the consent form attached for the healthcare professionals who will be invited for the focus groups, and will allow them 48 hours to respond. Then the researcher will contact them physically to sign the form. All the signed forms will kept with the research documents in a locked drawer.

## A21. How long do you expect each participant to be in the study in total?

For the whole period of the study programme (2years from January 2015- December 2016) divided as following:  
Phase 1 will take up to 8months  
Phase 2 will take up to 8months  
Phase 3 will take up to 8months

## A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

There is no expected risks for participants, researcher and healthcare providers in the setting at the time of the study. There is no burden on nurses. The researcher will only view the medical notes and drug charts of patients. The researcher will ask the hospital supervisor (Stephen Tomlin) in case of unclear information on the patients' notes.

## A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

Yes  No

## A24. What is the potential for benefit to research participants?

Findings of the study will improve the healthcare quality provided for the study participants by providing a list of recommendations to reduce medicines related problems associated with the use of off-label and unlicensed medicines.

The hospital setting is hosting a medicines' safety campaign, and findings from this study will participate in improving this campaign.

## A26. What are the potential risks for the researchers themselves? (if any)

There is no expected risks for participants, researcher and healthcare providers in the setting at the time of the study.

## RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

## A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Phase 1:

A list of patients who admitted to PICU and NICU in the last six months will be retrieved from the medical records department by the hospital supervisor (ST). Then the researcher will apply a computer randomisation to retrieve the required sample size. Patients' records, medical notes and drug charts will be reviewed by the researcher under arrangement with the hospital supervisor. The hospital supervisor will be contacted in case of ambiguity or unclear information which needed for the researcher to complete the data collection form.

## Phase 2:

All patients are admitted to paediatric/neonatal intensive care units at the time of the study will be included and their medical records and drug charts will be reviewed by the researcher. Information collected by the researcher will be further evaluated by panel of experts from the research team.

## Phase 3:

Healthcare professionals will be invited to participate in focus groups. This will be organised by the researcher and the supervisory team. Selecting these participants will be according to the job description of the professionals as nurses, prescribers, or pharmacists.

**A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?**

Yes  No

Please give details below:

**A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?**

Yes  No

**A28. How and by whom will potential participants first be approached?**

## Phase 1:

The researcher will be introduced by the hospital supervisor to the staff of the paediatric and neonatal intensive care units. A list of patients who admitted to PICU and NICU in the last six months will be retrieved from the medical records department by the hospital supervisor (ST). Then the researcher will apply a computer randomisation to retrieve the required sample size. Patients' records, medical notes and drug charts will be reviewed by the researcher under arrangement with the hospital supervisor. The hospital supervisor will be contacted in case of ambiguity or unclear information which needed for the researcher to complete the data collection form.

## Phase 2:

The hospital supervisor (the clinical pharmacist) will introduce the researcher to the staff who are working at the pharmacy department, PICU and NICU to facilitate the process of the data collection. The researcher will have an honorary contract and will be counted as a member of the staff.

Healthcare professionals will be invited, by the researcher under arrangement with the hospital supervisor, to participate into focus groups. Selecting these participants will be according to the job description of the professionals as nurses, prescribers, or pharmacists.

**A30-1. Will you obtain informed consent from or on behalf of research participants?**

Yes  No

*If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.*

*If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.*

*If you are not obtaining consent, please explain why not.*

## For Phase 1:

Explicit patients' consents are not required as this project is a non-interventional project and will not affect the clinical



care of these patients, or cause any changes in the practice by any measure. Furthermore, this study is based on case note review and review of medical records whether prospectively or retrospectively does not require any contact with patients and/or their carers.

## Phase 2:

Explicit patients' consents are not required and data will be collected from medical notes and drug charts.

## Phase 3:

Healthcare professionals who will be invited for focus groups, will be asked to sign consent forms before they join the group discussion. This consent form will be sent via emails.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

Yes  No

A31. How long will you allow potential participants to decide whether or not to take part?

48 hours will be given for all healthcare professionals who will be invited to take part for focus groups, in order to respond and sign the consent form.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters)

All the healthcare professionals are expected to have a good level of communication skills.

## CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

## Storage and use of personal data during the study

A38. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
  - Manual files including X-rays
  - NHS computers
  - Home or other personal computers
  - University computers
  - Private company computers
  - Laptop computers

Further details:

**A38. How will you ensure the confidentiality of personal data?** Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

All patients' relevant information will be protected through different numbers of measures: Confidentiality agreement will be signed by the researcher, Patients' information will not be discussed in public, and electronic devices, where the data will be stored, will be password protected. Data collected will not include any identifiers or patients' identifiable information and all the collected parameters will be presented anonymously. All the collected data will be destroyed after three years after the completion of the project.

**A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.**

The chief investigator and the local collaborator.

#### Storage and use of data after the end of the study

**A43. How long will personal data be stored or accessed after the study has ended?**

- Less than 3 months  
 3 – 6 months  
 6 – 12 months  
 12 months – 3 years  
 Over 3 years

*If longer than 12 months, please justify:*

The data will be used for production of list of recommendations. Focus groups will be designed in order to discuss these recommendations. Further updates and improvements might require reviewing the data again.

#### INCENTIVES AND PAYMENTS

**A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?**

- Yes  No

**A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?**

- Yes  No

**A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?**

- Yes  No

#### NOTIFICATION OF OTHER PROFESSIONALS

**A48-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?**

Yes  No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

#### PUBLICATION AND DISSEMINATION

**A60. Will the research be registered on a public database?**

Yes  No

Please give details, or justify if not registering the research.

The research might be registered through the Evelina London Children's Hospital where this project will be conducted (NHS organisation), and through the university website (University of Hertfordshire).

Registration of research studies is encouraged wherever possible.

You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A6-1.

**A61. How do you intend to report and disseminate the results of the study? Tick as appropriate:**

- Peer reviewed scientific journals  
 Internal report  
 Conference presentation  
 Publication on website  
 Other publication  
 Submission to regulatory authorities  
 Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators  
 No plans to report or disseminate the results  
 Other (please specify)

**A63. Will you inform participants of the results?**

Yes  No

Please give details of how you will inform participants or justify if not doing so.

The findings will be evaluate the medicines related problems in general and will not identify an exact patient's problem. However healthcare professionals of the setting will be informed of the results, and involved in the proposed focus groups and their opinions will be evaluated for further improvement of the recommendation.

#### 6. Scientific and Statistical Review

**A64. How has the scientific quality of the research been assessed? Tick as appropriate:**

- Independent external review  
 Review within a company  
 Review within a multi-centre research group  
 Review within the Chief Investigator's institution or host organisation  
 Review within the research team  
 Review by educational supervisor  
 Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:  
The research team have done the initial review for the project protocol. A second review has been done by an independent body who is the Research associate dean of the department of Pharmacy in University of Hertfordshire. By the end of the reviewing process, the university has agreed to sponsor the research project.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A66. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- Review by independent statistician commissioned by funder or sponsor  
 Other review by independent statistician  
 Review by company statistician  
 Review by a statistician within the Chief Investigator's Institution  
 Review by a statistician within the research team or multi-centre group  
 Review by educational supervisor  
 Other review by individual with relevant statistical expertise  
 No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Mrs	SUSAN	BAKER
Department	Statistical Services and Consultancy Unit		
Institution	University of Hertfordshire		
Work Address	DeHavillandCampus University of Hertfordshire Hatfield		
Post Code	AL10 9AB		
Telephone	01707285529		
Fax			
Mobile			
E-mail	s.m.1.baker@herts.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A67. What is the primary outcome measure for the study?

Prevalence, type and nature of medicines related problems associated with the use of unlicensed and off-label medicines in paediatrics in-patients, and the level of severity of these problems.

A68. What are the secondary outcome measures? (if any)

The research secondary outcome aims:

- \* To identify prescribing errors.
- \* To identify preparation and administration errors.
- \* To identify monitoring errors.
- \* To identify adverse drug reactions.
- \* To identify where more errors occur during patients' pathways.

\* To categorise those medicines related problems according to their clinical significance.  
\* To recommend ways of intervention to prevent medicines related problems associated with unlicensed and off-label medicines' use in paediatrics.

**A88. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.**

Total UK sample size: 194

Total international sample size (including UK):

Total in European Economic Area:

Further details:

Phase 1 & 2:

Sample size that has to be investigated for Phase 1 is 194 case-notes for patients who were admitted to intensive care unit at Evelina Children Hospital.

**A89. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.**

The sample size for this Phase has been calculated following sample size by proportion calculation equation (<http://www.select-statistics.co.uk/sample-size-calculator-proportion>), taking into account a 95% confidence level, and 5% margin of error. The percentages were taken from the literature depending on the setting.

**Neonatal Intensive Care Unit:**

A study conducted by Sharon Conroy stated that 90% of patients were administered an unlicensed or off-label medicines in a neonatal population (Conroy S, 1999). Taking in account that the same percent might be found in the NICU at Evelina Hospital, the proper sample size that has to be investigated is 12 neonates as there was 952 neonates were admitted to the setting during the previous year. Thus Phase 1 sample size will be 60 patients' case-notes because Phase 1 will investigate six months admission.

**Paediatric Intensive Care Unit:**

The number of patients that were admitted to PICU at Evelina Hospital in 2013 was 1249 patients, so the sample size required to complete the first Phase of the project is 134 patients' case-notes (268 patients' case-notes for 12 months). That was counted according to the information retrieved from the literature that 67% of patients in paediatric intensive care unit received either off-label and/or unlicensed medicines (Conroy S, 2000).

**A81. Will participants be allocated to groups at random?**

Yes  No

**A82. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.**

Advanced computer programmes such as Statistical Package for the Social Sciences (SPSS) and Excel will be applied in order to obtain a proper data management and statistical analysis, and to relate different variables with each other in regard to the findings from the studies.

#### 6. MANAGEMENT OF THE RESEARCH

**A83. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief investigator's team, including non-doctoral student researchers.**

Title Forename/Initials Surname  
MR. STEPHEN TOMLIN

Post	Consultant Pharmacist – Children's Services, Pharmacy Department, Guy's & St Thomas' NHS Foundation Trust
Qualifications	BPharm (Hons) - 1990 FRPharmS – 2011 FFRPS - 2013
Employer	EVELINA LONDON CHILDREN'S HOSPITAL
Work Address	PHARMACY DEPARTMENT, EVELINA LONDON CHILDREN'S HOSPITAL ST THOMAS'S HOSPITAL, WESTMINSTER BRIDGE RD LONDON, ENGLAND
Post Code	SE1 7EH
Telephone	0044207 1889202
Fax	0044207 1889155
Mobile	07766603154
Work Email	Stephen.Tomlin@gstf.nhs.uk

## A84. Details of research sponsor(s)

## A84-1. Sponsor

<b>Lead sponsor</b>	
Status:	Commercial status:
<input type="radio"/> NHS or HSC care organisation	
<input checked="" type="radio"/> Academic	
<input type="radio"/> Pharmaceutical industry	
<input type="radio"/> Medical device industry	
<input type="radio"/> Local Authority	
<input type="radio"/> Other social care provider (Including voluntary sector or private organisation)	
<input type="radio"/> Other	
If Other, please specify:	
<b>Contact person</b>	
Name of organisation	University of Hertfordshire
Given name	Professor John
Family name	Senior
Address	University of Hertfordshire, Department of Pharmacy
Town/city	Hatfield
Post code	AL10 9AB
Country	UNITED KINGDOM
Telephone	+441707 284000
Fax	+441707 284115
E-mail	research-sponsorship@herts.ac.uk
<b>Is the sponsor based outside the UK?</b>	
<input type="radio"/> Yes	<input checked="" type="radio"/> No
Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.	

A85. Has external funding for the research been secured?

Funding secured from one or more funders  
 External funding application to one or more funders in progress  
 No application for external funding will be made

What type of research project is this?

Standalone project  
 Project that is part of a programme grant  
 Project that is part of a Centre grant  
 Project that is part of a fellowship/ personal award/ research training award  
 Other

Other – please state:  
self-funded PhD

A87. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

Yes  No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A88-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Ms	Elizabeth	Smith
Organisation	NIHR GSTFT/KCL Biomedical Research Centre		
Address	16th floor, Tower Wing, Guy's Hospital Great Maze Pond, London		
Post Code	SE1 9RT		
Work Email	liz.smith@gstt.nhs.uk		
Telephone	+44 (0)20 7188 7188 Ext: 54426		
Fax	0044207 188 8330		
Mobile			

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A88-1. How long do you expect the study to last in the UK?

Planned start date: 01/01/2015  
 Planned end date: 31/12/2016  
 Total duration:  
 Years: 1 Months: 11 Days: 31

A71-2. Where will the research take place? (Tick as appropriate)



- England  
 Scotland  
 Wales  
 Northern Ireland  
 Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

- Yes  No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:

- NHS organisations in England 1  
 NHS organisations in Wales  
 NHS organisations in Scotland  
 HSC organisations in Northern Ireland  
 GP practices in England  
 GP practices in Wales  
 GP practices in Scotland  
 GP practices in Northern Ireland  
 Social care organisations  
 Phase 1 trial units  
 Prison establishments  
 Probation areas  
 Independent hospitals  
 Educational establishments  
 Independent research units  
 Other (give details)

Total UK sites in study: 1

A78. Insurance/ Indemnity to meet potential legal liabilities

*Note: In this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A78-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (NHS sponsors only)  
 Other insurance or indemnity arrangements will apply (give details below)

University of Hertfordshire

Please enclose a copy of relevant documents.



**A78-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.**

*Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.*

NHS indemnity scheme will apply (protocol authors with NHS contracts only)

Other insurance or indemnity arrangements will apply (give details below)

University of Hertfordshire

Please enclose a copy of relevant documents.

**A78-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?**

*Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.*

NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

University of Hertfordshire

Please enclose a copy of relevant documents.

## PART B: Section 7 - Children

**1. Please specify the potential age range of children under 18 who will be included and give reasons for carrying out the research in this age group.**

Medical notes and drug charts for children between 0-18 years will be reviewed. Paediatric patients who received unlicensed and off-label medicines might be at risk of developing medicines related problems as these medicines have no safety studies into this population.

**2. Indicate whether any children under 18 will be recruited as controls and give further details.**

No, this is a case-note review.

**3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.**

Not applicable.

**4. If you intend to provide children under 18 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.**

Not applicable

Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.

**PART C: Overview of research sites**

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

Research site		Investigator/ Collaborator/ Contact	
Institution name	EVELINA LONDON CHILDREN'S HOSPITAL	Title	MR
Department name	DEPARTMENT OF PHARMACY	First name/	STEPHEN
Street address	Westminster Bridge Rd	Initials	
Town/city	LONDON	Surname	TOMLIN
Post Code	SE1 7EH		

**PART D: Declarations****D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
  - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
  - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
  - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
  - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
  - May be sent by email to REC members.
10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

**Contact point for publication (Not applicable for R&D Forms)**

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator  
 Sponsor

- Study co-ordinator
- Student
- Other – please give details
- None

**Access to application for training purposes** (Not applicable for R&D Forms)

Optional – please tick as appropriate:

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Mrs WIJDAN ELHIJAZI on 13/03/2015 09:01.

Job Title/Post:        PhD Student  
Organisation:        University of Hertfordshire  
Email:                w.ehjaz@herts.ac.uk

**D2. Declaration by the sponsor's representative**

*If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.*

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publicly accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Professor John Senior on 13/03/2015 09:36.

Job Title/Post: Pro Vice-Chancellor (Research & International)  
Organisation: University of Hertfordshire  
Email: j.m.senior@herts.ac.uk

**D8. Declaration for student projects by academic supervisor(s)**

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.
2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.
3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.
4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

**Academic supervisor 1**

This section was signed electronically by Dr Andrzej Kostrzewski on 13/03/2015 17:50.

Job Title/Post: Academic Lead Clinical  
Organisation: University of Hertfordshire  
Email:

## Appendix 5: NHS REC approval



### NRES Committee North West - Greater Manchester South

3rd Floor, Barlow House  
4 Minshull Street  
Manchester  
M1 3DZ

17 April 2015

Mrs Wijdan Elhijazi  
PhD Student  
University of Hertfordshire  
School of Life & Medical Science, Department of Pharmacy  
University of Hertfordshire  
Hatfield  
AL10 9AB

Dear Mrs Elhijazi

**Study title:** Medicines Related Problems Associated with The Use of Unlicensed & Off-label Medicines in Paediatric In-patients (POUMPs Study).  
**REC reference:** 15/NW/0263  
**Protocol number:** LMS/PG/NHS/00290  
**IRAS project ID:** 165377

Thank you for your submission, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Helen Penlstone, [nrescommittee.northwest-qmsouth@nhs.net](mailto:nrescommittee.northwest-qmsouth@nhs.net). Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

#### Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

#### Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.



Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

#### Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact [hra\\_studyregistration@nhs.net](mailto:hra_studyregistration@nhs.net). The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

#### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

#### **Approved documents**

The documents reviewed and approved by the Committee are:

Document	Version	Date
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only) [Indemnity letter]	1	30 July 2014
Interview schedules or topic guides for participants [topic guide]	1	05 March 2015
Letter from sponsor [Sponsorship letter]	1	01 October 2014
Letters of invitation to participant [invitation Letter]	2.0- Tracked	09 April 2015
Other [Email Confirming researcher is part of the direct care team]		19 March 2015
Other [Ethics - approval letter]		07 April 2015

A Research Ethics Committee established by the Health Research Authority



Participant consent form [Consent form]	1	05 March 2015
Participant Information sheet (PIS) [Participant Information Sheet ]	2.0- Tracked	09 April 2015
REC Application Form [REC_Form_16032015]		16 March 2015
Research protocol or project proposal [research protocol]	3	30 July 2014
Summary CV for Chief Investigator (CI) [W ELHIJAZI CV]	1	05 March 2015
Summary CV for supervisor (student research) [A KOSTRZEWSKI CV]	1	05 March 2015

#### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

#### After ethical review

##### Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

##### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance>

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

15/NW/0263	Please quote this number on all correspondence
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With the Committee's best wishes for the success of this project.

Yours sincerely



On behalf of Professor Sobhan Vinjamuri  
Chair

Email: [nrescommittee.northwest-qmsouth@nhs.net](mailto:nrescommittee.northwest-qmsouth@nhs.net)

Enclosures: *After ethical review – guidance for researchers*

## Appendix 6: R & D application

NHS R&D Form

IRAS Version 4.0.0

Welcome to the Integrated Research Application System
IRAS Project Filter
<p>The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.</p> <p>Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.</p>
<p><b>Please enter a short title for this project (maximum 70 characters)</b> Medicines Related Problems In Paediatric In-patients</p>
<p><b>1. Is your project research?</b></p> <p><input checked="" type="radio"/> Yes <input type="radio"/> No</p>
<p><b>2. Select one category from the list below:</b></p> <p><input type="radio"/> Clinical trial of an investigational medicinal product <input type="radio"/> Clinical investigation or other study of a medical device <input type="radio"/> Combined trial of an investigational medicinal product and an investigational medical device <input type="radio"/> Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice <input type="radio"/> Basic science study involving procedures with human participants <input checked="" type="radio"/> Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology <input type="radio"/> Study involving qualitative methods only <input type="radio"/> Study limited to working with human tissue samples (or other human biological samples) and data (specific project only) <input type="radio"/> Study limited to working with data (specific project only) <input type="radio"/> Research tissue bank <input type="radio"/> Research database</p> <p>If your work does not fit any of these categories, select the option below:</p> <p><input type="radio"/> Other study</p>
<p><b>2a. Please answer the following question(s):</b></p> <p>a) Does the study involve the use of any ionising radiation? <input type="radio"/> Yes <input checked="" type="radio"/> No b) Will you be taking new human tissue samples (or other human biological samples)? <input type="radio"/> Yes <input checked="" type="radio"/> No c) Will you be using existing human tissue samples (or other human biological samples)? <input type="radio"/> Yes <input checked="" type="radio"/> No</p>
<p><b>3. In which countries of the UK will the research sites be located? (Tick all that apply)</b></p> <p><input checked="" type="checkbox"/> England <input type="checkbox"/> Scotland <input type="checkbox"/> Wales <input type="checkbox"/> Northern Ireland</p>

3a. In which country of the UK will the lead NHS R&D office be located:

- England  
 Scotland  
 Wales  
 Northern Ireland  
 This study does not involve the NHS

4. Which review bodies are you applying to?

- NHS/HSC Research and Development offices  
 Social Care Research Ethics Committee  
 Research Ethics Committee  
 Confidentiality Advisory Group (CAG)  
 National Offender Management Service (NOMS) (Prisons & Probation)

*For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.*

5. Will any research sites in this study be NHS organisations?

- Yes  No

6a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

- Yes  No

*If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).*

6b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see Information button for further details.

- Yes  No

*If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.*

8. Do you plan to include any participants who are children?

- Yes  No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

- Yes  No

*Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.*

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

Yes  No

9. Is the study or any part of it being undertaken as an educational project?

Yes  No

Please describe briefly the involvement of the student(s):

The student is the chief investigator who will be responsible writing the study protocol, data collection and data analysis.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes  No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes  No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes  No

**Integrated Research Application System  
Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study**

**NHS/HSC R&D Form (project information)**

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)  
Medicines Related Problems In Paediatric In-patients

**PART A: Core study information**

**1. ADMINISTRATIVE DETAILS**

**A1. Full title of the research:**

Medicines Related Problems Associated with The Use of Unlicensed & Off-label Medicines in Paediatric In-patients (POUMPs Study).

**A2-1. Educational projects**

**Name and contact details of student(s):**

**Student 1**

<b>Title:</b>	Forename/Initials Surname
	Mrs WUDAN ELHJAZI
<b>Address:</b>	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
<b>Post Code:</b>	AL10 9AB
<b>E-mail:</b>	w.elh@herts.ac.uk
<b>Telephone:</b>	00441707281051
<b>Fax:</b>	00441707284506

Give details of the educational course or degree for which this research is being undertaken:

**Name and level of course/ degree:**  
This research project is undertaken as part of a PhD course.

**Name of educational establishment:**  
University of Hertfordshire

**Name and contact details of academic supervisor(s):**

Academic supervisor 1	
	Title Forename/Initials Surname Dr ANDRZEJ KOSTRZEWSKI
Address	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
Post Code	AL10 9AB
E-mail	a.kostrzewski@herts.ac.uk
Telephone	00441707281051
Fax	00441707284506

Please state which academic supervisor(s) has responsibility for which student(s):  
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Mrs WIJDAN ELHJAZI	<input type="checkbox"/> Dr ANDRZEJ KOSTRZEWSKI

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

**A2-2. Who will act as Chief Investigator for this study?**

Student  
 Academic supervisor  
 Other

**A3-1. Chief Investigator:**

	Title Forename/Initials Surname Mrs WIJDAN ELHJAZI
Post	PhD Student
Qualifications	MSc Clinical Pharmacy, International Practice & Policy School Of Pharmacy, University of London BSc Pharmacy, University of Khartoum
Employer	University of Hertfordshire
Work Address	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
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Work E-mail	w.elhjaz@herts.ac.uk
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\* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.  
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

**A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?**  
*This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.*

	<b>Title</b>	<b>Forename/Initials</b>	<b>Surname</b>
	Professor	John	Senior
<b>Address</b>	Pro Vice-Chancellor (Research and International)		
	University of Hertfordshire		
	Hatfield		
<b>Post Code</b>	AL10 9AB		
<b>E-mail</b>	j.m.senior@herts.ac.uk		
<b>Telephone</b>	01707 284000		
<b>Fax</b>	01707 284115		

**A6-1. Research reference numbers. Please give any relevant references for your study:**

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number: LMS/PG/NHS/00290

Protocol Version: 3rd ver

Protocol Date: 29/07/2014

Funder's reference number:

Project website:

**Additional reference number(s):**

Ref.Number	Description	Reference Number

*Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.*

**A6-2. Is this application linked to a previous study or another current application?**

Yes  No

Please give brief details and reference numbers.

## 2. OVERVIEW OF THE RESEARCH

*To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.*

**A8-1. Summary of the study.** Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.

This research project aims to identify problems that might occur as a result of using medicines in children while they are in paediatric intensive care unit or neonatal intensive care unit at Evelina London Children Hospital, from the admission day and until discharge. All patients who are under 18 years will be included, however patients who are not receiving medicines and they are only on nutritional products will be excluded from this study. This research project is designed as a case-note review which will be carried out by a qualified pharmacist. Information will be collected



through a review of children's medical notes and drug charts by using a data collection form. The hospital supervisor will anonymise the data before give it to the researcher to ensure confidentiality. All data will be anonymised and stored electronically for analysis. Findings will include type and nature of any medicines related problems, percentage of the occurrence of these problems, and the severity of these problems.

**A8-2. Summary of main issues.** Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

*Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.*

This research project doesn't require explicit patients' consents because it is a non-interventional project, and there will not be any direct contact with patients or their carers. All the information to be reviewed is already screened by a ward pharmacist, nurses, and other healthcare professionals, as part of their clinical routine procedure.

All patients' identifiable information will be viewed only in the hospital setting through the hospital electronic resources and will be recorded anonymously, to ensure patients' confidentiality.

All data will be stored anonymously, and will not be shared in public places or with people who are not members of the research team. Data will be stored electronically in a password protected computer.

In case of any identified problem, the researcher will report that to the ward pharmacist and will not initiate any further action without consulting the pharmacist in-charge.

There is no expected risk for participants including the patients, healthcare professionals and the researcher.

### 3. PURPOSE AND DESIGN OF THE RESEARCH

**A7. Select the appropriate methodology description for this research. Please tick all that apply:**

- Case series/ case note review
- Case control
- Cohort observation
- Controlled trial without randomisation
- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study
- Laboratory study
- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

**A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.**

What are the medicines related problems experienced by paediatric patients admitted to Paediatric/Neonatal Intensive Care unit at Evelina London Children's Hospital?



**A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.**

1. What is the prevalence of medicines related problems associated with unlicensed and off-label medicines in paediatrics in-patients?
2. What is the clinical significance of these medicines related problems?
3. What are the possible intervention strategies that might help to prevent medicines related problems associated with the use of unlicensed and off-label medicines in paediatric in-patients?

**A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.**

Although most research projects focus on the adult population, the paediatric population are at much higher risk of suffering from medicines related problems due to the difference in pharmacokinetics and pharmacodynamics features when compared to adults (Keams GL, 2003). Medicines related problem include adverse drug reactions, medication errors and drug drug interactions. Dose calculation for paediatric patients are based on many factors such as weight, surface area and height, which are variable among children. Thus the paediatric populations at a much higher risk of developing medicines related problems.

In England, approximately 5% of the total medicines prescribed are received by the paediatric population (Anon., 2008). Most of the medicines that are used in paediatrics are either off-label (OL) or unlicensed (UL). (Choonara & McIntyre, 2001). For this reason, there is a high risk of paediatric patients suffering from medicine related problems.

A number of studies have been conducted globally to identify the prevalence of off-label and unlicensed medicines as well as some of the problems associated with them. For more than a decade, off-label and unlicensed medicines prescribing and their associated problems were major issues and had been investigated by a number of researchers such as Turner S in 1999 who had investigated this area in the UK and found that adverse drug reactions are more frequent with unlicensed and off-label medicines than with licensed medicines representing 6% and 3.9% respectively. (Turner S, 1999), but what missing is a study that investigated all aspects of off-label and unlicensed medicines' related problems including adverse drug reactions, medication errors and adverse drug events. A recent study conducted in the UK revealed that off-label and unlicensed medicines are more likely to be implicated with adverse drug reactions than authorised medicines (Bellis, 2013). Another study conducted in 2013 in the UK illustrated that adverse drug reactions are frequent between hospitalised children reaches 17.7% of 6,601 total admissions (Thlesen, 2013).

Although there are different intervention strategies have been implemented into practice in adults, a limited number have found to be used in the paediatric population and there is no such strategy to highlight the risk associated with off-label and unlicensed medicines and their associated problems. Therefore conducting a research study to explore all the concepts and issues of medicines related problems-with a main focus on medication errors and adverse drug reactions- associated with the use of unlicensed and off-label medicines in order to recommend different ways of intervention for improving paediatrics' practice, is clearly justifiable.

The research team have a previous experience with such a research project in the ADVISE study (Rashed AN et al, 2012) which conducted in the same setting with other collaborating centres. The ADVISE study has contributed to improving the healthcare quality for paediatric population but more studies are needed.

**References:**

- Anon., 2008. ONS. [Online] <http://www.ons.gov.uk/ons/index.html> (accessed on 13/03/2014)
- Choonara, I. & McIntyre, J., 2001. Training in clinical pharmacology. Paediatric and perinatal drug therapy [PDF document], 4(3), pp. 124-127.
- Turner, S. E. A. N., Nunn, A. J., Fielding, K., & Choonara, I. M. T. I. (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica*, 88(9), 965-968.
- Thlesen, S., Conroy, E. J., Bellis, J. R., Bracken, L. E., Mannix, H. L., Bird, K. A., ... & Smyth, R. L. (2013). Incidence, characteristics and risk factors of adverse drug reactions in hospitalized children? A prospective observational cohort study of 6,601 admissions. *BMC medicine*, 11(1), 237.
- Gregory L. Keams., Susan M. Abdel-Rahman., Sarah W. Alander., Douglas L. Blowey., J. Steven Leeder., and Ralph E. Kauffman. (2003). Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. *N Engl J Med* 2003; 349:1157-1167.
- Rashed AN, Wong IC, Cranswick N, Hefele B, Tomlin S, et al. (2012) Adverse Drug Reactions in Children—International Surveillance and Evaluation (ADVISE): a multicentre cohort study. *Drug Saf* 35: 481–494. doi: 10.2165/11597920

**A13. Please summarise your design and methodology. It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.**

A mixed-method approach (qualitative and quantitative) will be used. The study will be divided into three different Phases. The first Phase will be a retrospective identification of the prevalence of medicines related problems (MRPs) associated with the use of unlicensed medicines (medicines with no license) and off-label medicines (medicines have a license to be prescribed to a different age group) and the severity of these problems. Data retrieved from this Phase will be analysed to identify type and nature of medicines related problems. Phase 2 will be a prospective identification of MRPs and their clinical significance to measure the current situation with comparison of the results from the previous Phase (Phase 1) and identify errors and areas with high need of improvement. The last Phase (Phase 3) will produce a list of recommendations and ways of intervention to improve practice. A panel of experts will be asked for their opinion of the recommendations and how to implement them into practice. Patients aged 0-18 years old who will be admitted to the Paediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at Evelina London Children's Hospital at the time of the study will be included. Patients who are in isolated rooms or there are no access to their medical notes will be excluded. Also patients admitted to the PICU but are on only nutritional products and no medications, will be excluded. Sample size that has to be investigated for Phase 1 and Phase 2 is 121 medical notes of patients from neonatal intensive care unit and 268 medical notes of patients from paediatrics intensive care unit.

**Phase 1:**

**Retrospective study to identify prevalence of Medicines Related Problems and their clinical significance**  
This is a retrospective study which will be about information that happened in the previous period during 2014. It will be conducted at the hospital for the purpose of identification of medicines related problems in terms of prevalence and their clinical significance. It will use a case-note review. Patients' information will be retrieved from drug charts and medical notes by using a data collection form to identify medicines related problems associated with unlicensed and off-label medicines' use in paediatric in-patients. Differences in the use of medicines will also be evaluated against the standard hospital guideline and the British National Formulary for Children (BNF for Children).

**Phase 2:**

**Prospective study to detect MRPs & categorise their clinical significance**  
This is a prospective study which will be for the current time in the ward. It will be conducted in the Paediatrics Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at Evelina London Children's Hospital to identify medicines related problems associated with the use of unlicensed and off-label medicines and their clinical significance. It will also include an investigation of patients' pathways to detect the area with higher rate of errors. A panel of experts, (of the research team), will be asked to assess the clinical significance rating. The finding from this study will be evaluated to produce a list of recommendations to improve paediatric practice.

**Phase 3:**

**Proposed Recommendations & Ways of Intervention to reduce MRPs:**  
This is a prospective study to use the findings from Phase 2 to develop a list of recommendation in order to prevent medicines related problems associated with the use of off-label and/or unlicensed medicines in paediatrics inpatients. A number of focus group sessions will be used in order to engage the healthcare professionals in the setting to discuss the produced recommendations and how they can work collaboratively to implement these recommendations into practice. The focus groups will be organised, led and recorded by the moderator (researcher). The data collected from these focus groups will be analysed to be taken into consideration for improving the practice.

**A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?**

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

*Give details of involvement, or if none please justify the absence of involvement.*

This project designed as a case-note review where only medical records and drug charts will be reviewed for information. There is no intended contact with patients or their guardians at any point of the study. Members of the public who are out of the research team will not be involved in this project.

#### 4. RISKS AND ETHICAL ISSUES

##### RESEARCH PARTICIPANTS

#### A16. What is the sample group or cohort to be studied in this research?

Select all that apply:

- Blood
- Cancer
- Cardiovascular
- Congenital Disorders
- Dementias and Neurodegenerative Diseases
- Diabetes
- Ear
- Eye
- Generic Health Relevance
- Infection
- Inflammatory and Immune System
- Injuries and Accidents
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Oral and Gastrointestinal
- Paediatrics
- Renal and Urogenital
- Reproductive Health and Childbirth
- Respiratory
- Skin
- Stroke

Gender:  Male and female participants

Lower age limit: 0 Days

Upper age limit: 18 Years

#### A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Patients who are under 18 years old and who were admitted to the Paediatric Intensive Care Unit and/or Neonatal Intensive Care Unit within the study duration and on medications will be included.

#### A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Patients who are in isolated rooms or there are no access to their medical notes will be excluded. Also patients who admitted to the Paediatric/Neonatal Intensive Care Units but they are on only nutritional products but not medications

will be excluded.

#### RESEARCH PROCEDURES, RISKS AND BENEFITS

**A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.**

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Daily review of patients' case-notes for Phase 2	2	2	1	The researcher will review the medical notes in the paediatric intensive care units.
Focus groups for healthcare professionals for Phase 3	1	0	1	hour The researcher will design and invite healthcare professionals to focus group to ask about their opinion of the list of recommendations
Obtaining Consents for focus groups for Phase 3	1	0	48	hours The researcher will send an email with the consent form attached for the healthcare professionals who will be invited for the focus groups, and will allow them 48 hours to respond. Then the researcher will contact them physically to sign the form. All the signed forms will kept with the research documents in a locked drawer.

**A21. How long do you expect each participant to be in the study in total?**

For the whole period of the study programme (2years from January 2015- December 2016) divided as following:  
Phase 1 will take up to 8months  
Phase 2 will take up to 8months  
Phase 3 will take up to 8months

**A22. What are the potential risks and burdens for research participants and how will you minimise them?**

*For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.*

There is no expected risks for participants, researcher and healthcare providers in the setting at the time of the study. There is no burden on nurses. The researcher will only view the medical notes and drug charts of patients. The researcher will ask the hospital supervisor (Stephen Tomlin) in case of unclear information on the patients' notes.

**A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?**

Yes  No

**A24. What is the potential for benefit to research participants?**

Findings of the study will improve the healthcare quality provided for the study participants by providing a list of recommendations to reduce medicines related problems associated with the use of off-label and unlicensed medicines.



A26. What are the potential risks for the researchers themselves? (if any)

There is no expected risks for participants, researcher and healthcare providers in the setting at the time of the study.

#### RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Phase 1:

A list of patients who admitted to PICU and NICU in the last six months will be retrieved from the medical records department by the hospital supervisor (ST). Then the researcher will apply a computer randomisation to retrieve the required sample size. Patients' records, medical notes and drug charts will be reviewed by the researcher under arrangement with the hospital supervisor. The hospital supervisor will be contacted in case of ambiguity or unclear information which needed for the researcher to complete the data collection form.

Phase 2:

All patients are admitted to paediatric/neonatal intensive care units at the time of the study will be included and their medical records and drug charts will be reviewed by the researcher. Information collected by the researcher will be further evaluated by panel of experts from the research team.

Phase 3:

Healthcare professionals will be invited to participate in focus groups. This will be organised by the researcher and the supervisory team. Selecting these participants will be according to the job description of the professionals as nurses, prescribers, or pharmacists.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

Yes  No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

Yes  No

A29. How and by whom will potential participants first be approached?

Phase 1:

The researcher will be introduced by the hospital supervisor to the staff of the paediatric and neonatal intensive care units. A list of patients who admitted to PICU and NICU in the last six months will be retrieved from the medical records department by the hospital supervisor (ST). Then the researcher will apply a computer randomisation to retrieve the required sample size. Patients' records, medical notes and drug charts will be reviewed by the researcher under arrangement with the hospital supervisor. The hospital supervisor will be contacted in case of ambiguity or unclear information which needed for the researcher to complete the data collection form.

Phase 2:

The hospital supervisor (the clinical pharmacist) will introduce the researcher to the staff who are working at the pharmacy department, PICU and NICU to facilitate the process of the data collection. The researcher will have an honorary contract and will be counted as a member of the staff.

Healthcare professionals will be invited, by the researcher under arrangement with the hospital supervisor, to participate into focus groups. Selecting these participants will be according to the job description of the professionals as nurses, prescribers, or pharmacists.

**A30-1. Will you obtain Informed consent from or on behalf of research participants?**

Yes  No

*If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.*

*If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.*

*If you are not obtaining consent, please explain why not.*

For Phase 1:

Explicit patients' consents are not required as this project is a non-interventional project and will not affect the clinical care of these patients, or cause any changes in the practice by any measure. Furthermore, this study is based on case note review and review of medical records whether prospectively or retrospectively does not require any contact with patients and/or their carers.

Phase 2:

Explicit patients' consents are not required and data will be collected from medical notes and drug charts.

Phase 3:

Healthcare professionals who will be invited for focus groups, will be asked to sign consent forms before they join the group discussion. This consent form will be sent via emails.

Please enclose a copy of the information sheet(s) and consent form(s).

**A30-2. Will you record informed consent (or advice from consultees) in writing?**

Yes  No

**A31. How long will you allow potential participants to decide whether or not to take part?**

48 hours will be given for all healthcare professionals who will be invited to take part for focus groups, in order to respond and sign the consent form.

**A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters)**

All the healthcare professionals are expected to have a good level of communication skills.

**CONFIDENTIALITY**

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

**Storage and use of personal data during the study**

**A38. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)**

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations

- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
  - Manual files including X-rays
  - NHS computers
  - Home or other personal computers
  - University computers
  - Private company computers
  - Laptop computers

Further details:

**A37. Please describe the physical security arrangements for storage of personal data during the study?**

University of Hertfordshire's computers will be used for data storage. All computers used in the study will be password-protected. During data collection at the study site (Evelina Hospital), data collection forms will always be in the possession of the researcher or in a lockable cupboard with keys on the researchers. Research team members will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The research team will only collect the minimum required information for the purposes of the study. Data will be held securely, in a locked room, or locked cupboard or filing cabinet. Access to the information will be limited to the chief investigator and the research team. Access will be restricted by user identifiers and passwords. Data will be stored on encrypted sticks.

**A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.**

All patients' relevant information will be protected through different numbers of measures: Confidentiality agreement will be signed by the researcher, Patients' information will not be discussed in public, and electronic devices, where the data will be stored, will be password protected. Data collected will not include any identifiers or patients' identifiable information and all the collected parameters will be presented anonymously. All the collected data will be destroyed after three years after the completion of the project.

**A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.**

The chief investigator and the local collaborator.

#### Storage and use of data after the end of the study

**A41. Where will the data generated by the study be analysed and by whom?**

It will be analysed by the researcher using University of Hertfordshire computers, department of pharmacy.

**A42. Who will have control of and act as the custodian for the data generated by the study?**

Title Forename/Initials Surname  
Mrs WUDAN ELHIJAZI

Post	PhD student
Qualifications	MSc in Clinical Pharmacy, International Practice & Policy,
Work Address	School of Life & Medical Sciences, Department of Pharmacy University of Hertfordshire Hatfield
Post Code	AL10 9AB
Work Email	w.eh szl herts.ac.uk
Work Telephone	00441707281051
Fax	00441707284506

A43. How long will personal data be stored or accessed after the study has ended?

- Less than 3 months  
 3 – 5 months  
 6 – 12 months  
 12 months – 3 years  
 Over 3 years

*If longer than 12 months, please justify:*

The data will be used for production of list of recommendations. Focus groups will be designed in order to discuss these recommendations. Further updates and improvements might require reviewing the data again.

A44. For how long will you store research data generated by the study?

Years: 3  
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

The collected data will be stored in the university computer and can be accessed only by the research team. The data will be destroyed immediately after the PhD programme completion.

#### INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

- Yes     No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- Yes     No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- Yes     No



## NOTIFICATION OF OTHER PROFESSIONALS

**A48-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?**

Yes  No

*If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.*

## PUBLICATION AND DISSEMINATION

**A60. Will the research be registered on a public database?**

Yes  No

*Please give details, or justify if not registering the research.*

The research might be registered through the Evelina London Children's Hospital where this project will be conducted (NHS organisation), and through the university website (University of Hertfordshire).

*Registration of research studies is encouraged wherever possible.*

*You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A6-1.*

**A61. How do you intend to report and disseminate the results of the study? Tick as appropriate:**

- Peer reviewed scientific journals  
 Internal report  
 Conference presentation  
 Publication on website  
 Other publication  
 Submission to regulatory authorities  
 Access to raw data and right to publish freely by all Investigators in study or by Independent Steering Committee on behalf of all Investigators  
 No plans to report or disseminate the results  
 Other (please specify)

**A62. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?**

The results will be published in an anonymous way and will not include any individual participant or any identifiers. All identifiable information will be presented anonymously and will not be able to identify patients through these information.

**A63. Will you inform participants of the results?**

Yes  No

*Please give details of how you will inform participants or justify if not doing so.*

The findings will be evaluate the medicines related problems in general and will not identify an exact patient's problem. However healthcare professionals of the setting will be informed of the results, and involved in the proposed focus groups and their opinions will be evaluated for further improvement of the recommendation.

**A64. How has the scientific quality of the research been assessed? Tick as appropriate:**

Independent external review  
 Review within a company  
 Review within a multi-centre research group  
 Review within the Chief Investigator's Institution or host organisation  
 Review within the research team  
 Review by educational supervisor  
 Other

*Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:*  
The research team have done the initial review for the project protocol. A second review has been done by an independent body who is the Research associate dean of the department of Pharmacy in University of Hertfordshire. By the end of the reviewing process, the university has agreed to sponsor the research project.

*For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.*

*For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.*

**A68. How have the statistical aspects of the research been reviewed? Tick as appropriate:**

Review by independent statistician commissioned by funder or sponsor  
 Other review by independent statistician  
 Review by company statistician  
 Review by a statistician within the Chief Investigator's Institution  
 Review by a statistician within the research team or multi-centre group  
 Review by educational supervisor  
 Other review by individual with relevant statistical expertise  
 No review necessary as only frequencies and associations will be assessed – details of statistical input not required

*In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.*

	Title	Forename/Initials	Surname
	Mrs	SUSAN	BAKER
Department	Statistical Services and Consultancy Unit		
Institution	University of Hertfordshire		
Work Address	DeHavilland Campus University of Hertfordshire Hatfield		
Post Code	AL10 9AB		
Telephone	01707285529		
Fax			
Mobile			
E-mail	s.m.1.baker@herts.ac.uk		

*Please enclose a copy of any available comments or reports from a statistician.*

**A67. What is the primary outcome measure for the study?**

Prevalence, type and nature of medicines related problems associated with the use of unlicensed and off-label medicines in paediatrics in-patients, and the level of severity of these problems.

**A68. What are the secondary outcome measures? (if any)**

The research secondary outcome aims:

- To identify prescribing errors.
- To identify preparation and administration errors.
- To identify monitoring errors.
- To identify adverse drug reactions.
- To identify where more errors occur during patients' pathways.
- To categorise those medicines related problems according to their clinical significance.
- To recommend ways of intervention to prevent medicines related problems associated with unlicensed and off-label medicines' use in paediatrics.

**A69. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.**

Total UK sample size: 194

Total international sample size (including UK):

Total in European Economic Area:

Further details:

Phase 1 & 2:

Sample size that has to be investigated for Phase 1 is 194 case-notes for patients who were admitted to intensive care unit at Evelina Children Hospital.

**A80. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.**

The sample size for this Phase has been calculated following sample size by proportion calculation equation (<http://www.select-statistics.co.uk/sample-size-calculator-proportion>), taking into account a 95% confidence level, and 5% margin of error. The percentages were taken from the literature depending on the setting.

Neonatal Intensive Care Unit:

A study conducted by Sharon Conroy stated that 90% of patients were administered an unlicensed or off-label medicines in a neonatal population (Conroy S, 1999). Taking into account that the same percent might be found in the NICU at Evelina Hospital, the proper sample size that has to be investigated is 12 neonates as there was 952 neonates were admitted to the setting during the previous year. Thus Phase 1 sample size will be 60 patients' case-notes because Phase 1 will investigate six months admission.

Paediatric Intensive Care Unit:

The number of patients that were admitted to PICU at Evelina Hospital in 2013 was 1249 patients, so the sample size required to complete the first Phase of the project is 134 patients' case-notes (268 patients' case-notes for 12 months). That was counted according to the information retrieved from the literature that 67% of patients in paediatric intensive care unit received either off-label and/or unlicensed medicines (Conroy S, 2000).

**A81. Will participants be allocated to groups at random?**

Yes  No

**A82. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.**

Advanced computer programmes such as Statistical Package for the Social Sciences (SPSS) and Excel will be applied

In order to obtain a proper data management and statistical analysis, and to relate different variables with each other in regard to the findings from the studies.

#### 8. MANAGEMENT OF THE RESEARCH

**A83. Other key investigators/collaborators.** Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

	Title	Forename/Initials	Surname
	MR	STEPHEN	TOMLIN
Post	Consultant Pharmacist – Children's Services, Pharmacy Department, Guy's & St Thomas' NHS Foundation Trust		
Qualifications	BPharm (Hons) - 1990 FRPharmS – 2011 FFRPS - 2013		
Employer	EVELINA LONDON CHILDREN'S HOSPITAL		
Work Address	PHARMACY DEPARTMENT, EVELINA LONDON CHILDREN'S HOSPITAL ST THOMAS'S HOSPITAL, WESTMINSTER BRIDGE RD LONDON, ENGLAND		
Post Code	SE1 7EH		
Telephone	0044207 1889202		
Fax	0044207 1889155		
Mobile	07766603154		
Work Email	Stephen.Tomlin@gstf.nhs.uk		

#### A84. Details of research sponsor(s)

##### A84-1. Sponsor

###### Lead sponsor

Status:  NHS or HSC care organisation Commercial status:  
 Academic  
 Pharmaceutical industry  
 Medical device industry  
 Local Authority  
 Other social care provider (including voluntary sector or private organisation)  
 Other

If Other, please specify:

###### Contact person

Name of organisation University of Hertfordshire  
 Given name Professor John  
 Family name Senior  
 Address University of Hertfordshire, Department of Pharmacy  
 Town/city Hatfield  
 Post code AL10 9AB

Country	UNITED KINGDOM
Telephone	+441707 284000
Fax	+441707 284115
E-mail	research-sponsorship@herts.ac.uk

**Is the sponsor based outside the UK?**  
 Yes  No

*Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.*

**A85. Has external funding for the research been secured?**

Funding secured from one or more funders  
 External funding application to one or more funders in progress  
 No application for external funding will be made

What type of research project is this?

Standalone project  
 Project that is part of a programme grant  
 Project that is part of a Centre grant  
 Project that is part of a fellowship/ personal award/ research training award  
 Other

Other – please state:  
 self-funded PhD

**A86. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A84-1)? Please give details of subcontractors if applicable.**

Yes  No

**A87. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?**

Yes  No

*Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.*

**A88-1. Give details of the lead NHS R&D contact for this research:**

Title	Forename/Initials	Surname
	Ms Elizabeth	Smith
Organisation	NIHR GSTFT/KCL Biomedical Research Centre	
Address	16th floor, Tower Wing, Guy's Hospital Great Maze Pond, London	

Post Code SE1 9RT  
 Work Email liz.smith@gstt.nhs.uk  
 Telephone +44 (0)20 7188 7188 Ext: 54426  
 Fax 0044207 188 8330  
 Mobile

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

**A68-1. How long do you expect the study to last in the UK?**

Planned start date: 01/01/2015  
 Planned end date: 31/12/2015  
 Total duration:  
 Years: 1 Months: 11 Days: 31

**A71-1. Is this study?**

- Single centre  
 Multicentre

**A71-2. Where will the research take place? (Tick as appropriate)**

- England  
 Scotland  
 Wales  
 Northern Ireland  
 Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

- Yes  No

**A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:**

- NHS organisations in England 1  
 NHS organisations in Wales  
 NHS organisations in Scotland  
 HSC organisations in Northern Ireland  
 GP practices in England  
 GP practices in Wales  
 GP practices in Scotland  
 GP practices in Northern Ireland  
 Social care organisations  
 Phase 1 trial units  
 Prison establishments  
 Probation areas  
 Independent hospitals  
 Educational establishments

- Independent research units  
 Other (give details)

Total UK sites in study: 1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

- Yes  No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Regular meetings every two weeks will be carried out with the chief investigator and the supervisory team to ensure a good level of monitoring.

A76. Insurance/ indemnity to meet potential legal liabilities

*Note: In this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (NHS sponsors only)  
 Other insurance or indemnity arrangements will apply (give details below)

University of Hertfordshire

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

*Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (protocol authors with NHS contracts only)  
 Other insurance or indemnity arrangements will apply (give details below)

University of Hertfordshire

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

*Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.*



- NHS Indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)  
 Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

University of Hertfordshire

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

- Yes  No  Not sure

### PART B: Section 7 - Children

1. Please specify the potential age range of children under 18 who will be included and give reasons for carrying out the research in this age group.

Medical notes and drug charts for children between 0-18 years will be reviewed. Paediatric patients who received unlicensed and off-label medicines might be at risk of developing medicines related problems as these medicines have no safety studies into this population.

2. Indicate whether any children under 18 will be recruited as controls and give further details.

No, this is a case-note review.

3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.

Not applicable.

4. If you intend to provide children under 18 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.

Not applicable

Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.



## PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

Research site		Investigator/ Collaborator/ Contact	
Institution name	EVELINA LONDON CHILDREN'S HOSPITAL	Title	MR
Department name	DEPARTMENT OF PHARMACY	First name/ Initials	STEPHEN
Street address	Westminster Bridge Rd	Surname	TOMLIN
Town/city	LONDON		
Post Code	SE1 7EH		

## PART D: Declarations

## D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
  - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
  - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
  - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
  - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
  - May be sent by email to REC members.
10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

**Contact point for publication (Not applicable for R&D Forms)**

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator  
 Sponsor

- Study co-ordinator
- Student
- Other – please give details
- None

**Access to application for training purposes** (Not applicable for R&D Forms)

Optional – please tick as appropriate:

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Mrs WIJDAN ELHIJAZI on 20/04/2015 11:11.

Job Title/Post: PhD student  
Organisation: University of Hertfordshire  
Email: w.eh|zi|herts.ac.uk

**D2. Declaration by the sponsor's representative**

*If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.*

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publicly accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Professor John Senior on 20/04/2015 12:23.

Job Title/Post: Pro Vice-Chancellor (Research & International)  
Organisation: University of Hertfordshire  
Email: j.m.senior@herts.ac.uk

**D3. Declaration for student projects by academic supervisor(s)**

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.
2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.
3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.
4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

**Academic supervisor 1**

This section was signed electronically by Dr Andrzej Kostrzewski on 20/04/2015 14:20.

Job Title/Post: Academic Lead Clinical Development  
Organisation: University of Hertfordshire  
Email: a.kostrzewski@herts.ac.uk

Welcome to the Integrated Research Application System

IRAS Project Filter

The Integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)  
Medicines Related Problems in Paediatric In-patients

1. Is your project research?

Yes  No

2. Select one category from the list below:

- Clinical trial of an Investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an Investigational medicinal product and an Investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Please answer the following question(s):

- a) Does the study involve the use of any ionising radiation?  Yes  No
- b) Will you be taking new human tissue samples (or other human biological samples)?  Yes  No
- c) Will you be using existing human tissue samples (or other human biological samples)?  Yes  No

3. In which countries of the UK will the research sites be located? (Tick all that apply)

- England
- Scotland
- Wales
- Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- England  
 Scotland  
 Wales  
 Northern Ireland  
 This study does not involve the NHS

4. Which review bodies are you applying to?

- NHS/HSC Research and Development offices  
 Social Care Research Ethics Committee  
 Research Ethics Committee  
 Confidentiality Advisory Group (CAG)  
 National Offender Management Service (NOMS) (Prisons & Probation)

*For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.*

5. Will any research sites in this study be NHS organisations?

- Yes  No

5a. Are all the research sites and infrastructure sites for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

- Yes  No

*If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).*

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see Information button for further details.

- Yes  No

*If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.*

6. Do you plan to include any participants who are children?

- Yes  No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

- Yes  No

*Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.*

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

Yes  No

9. Is the study or any part of it being undertaken as an educational project?

Yes  No

Please describe briefly the involvement of the student(s):

The student is the chief investigator who will be responsible writing the study protocol, data collection and data analysis.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes  No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes  No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes  No



**Integrated Research Application System  
Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study**

**NHS/HSC R&D Form (project information)**

Please refer to the *Submission and Checklist* tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)  
Medicines Related Problems In Paediatric In-patients

**PART A: Core study information**

**1. ADMINISTRATIVE DETAILS**

**A1. Full title of the research:**

Medicines Related Problems Associated with The Use of Unlicensed & Off-label Medicines in Paediatric In-patients (POUMPs Study).

**A2-1. Educational projects**

**Name and contact details of student(s):**

**Student 1**

<b>Title:</b>	Forename/Initials Surname
	Mrs WUDAN ELHJAZI
<b>Address:</b>	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
<b>Post Code:</b>	AL10 9AB
<b>E-mail:</b>	w.elh@herts.ac.uk
<b>Telephone:</b>	00441707281051
<b>Fax:</b>	00441707284506

Give details of the educational course or degree for which this research is being undertaken:

**Name and level of course/ degree:**

This research project is undertaken as part of a PhD course.

**Name of educational establishment:**

University of Hertfordshire

**Name and contact details of academic supervisor(s):**

Academic supervisor 1	
	Title Forename/Initials Surname Dr ANDRZEJ KOSTRZEWSKI
Address	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
Post Code	AL10 9AB
E-mail	a.kostrzewski@herts.ac.uk
Telephone	00441707281051
Fax	00441707284506

Please state which academic supervisor(s) has responsibility for which student(s):  
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Mrs WIJDAN ELHJAZI	<input type="checkbox"/> Dr ANDRZEJ KOSTRZEWSKI

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

**A2-2. Who will act as Chief Investigator for this study?**

Student  
 Academic supervisor  
 Other

**A3-1. Chief Investigator:**

	Title Forename/Initials Surname Mrs WIJDAN ELHJAZI
Post	PhD Student
Qualifications	MSC Clinical Pharmacy, International Practice & Policy School Of Pharmacy, University of London BSc Pharmacy, University of Khartoum
Employer	University of Hertfordshire
Work Address	School of Life & Medical Science, Department of Pharmacy University of Hertfordshire Hatfield
Post Code	AL10 9AB
Work E-mail	w.elhjaz@herts.ac.uk
* Personal E-mail	wijdanehjaz@yaho.com
Work Telephone	00441707281051
* Personal Telephone/Mobile	07765637900
Fax	00441707284506

\* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.  
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

**A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?**  
*This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.*

	<b>Title</b>	<b>Forename/Initials</b>	<b>Surname</b>
	Professor	John	Senior
<b>Address</b>	Pro Vice-Chancellor (Research and International)		
	University of Hertfordshire		
	Hatfield		
<b>Post Code</b>	AL10 9AB		
<b>E-mail</b>	j.m.senior@herts.ac.uk		
<b>Telephone</b>	01707 284000		
<b>Fax</b>	01707 284115		

**A6-1. Research reference numbers. Please give any relevant references for your study:**

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number:	LMS/PG/NHS/00290
Protocol Version:	3rd ver
Protocol Date:	29/07/2014
Funder's reference number:	
Project website:	

**Additional reference number(s):**

Ref.Number	Description	Reference Number

*Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.*

**A6-2. Is this application linked to a previous study or another current application?**

Yes  No

Please give brief details and reference numbers.

## 2. OVERVIEW OF THE RESEARCH

*To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.*

**A6-1. Summary of the study. Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.**

This research project aims to identify problems that might occur as a result of using medicines in children while they are in paediatric intensive care unit or neonatal intensive care unit at Evelina London Children Hospital, from the admission day and until discharge. All patients who are under 18 years will be included, however patients who are not receiving medicines and they are only on nutritional products will be excluded from this study. This research project is designed as a case-note review which will be carried out by a qualified pharmacist. Information will be collected

through a review of children's medical notes and drug charts by using a data collection form. The hospital supervisor will anonymise the data before give it to the researcher to ensure confidentiality. All data will be anonymised and stored electronically for analysis. Findings will include type and nature of any medicines related problems, percentage of the occurrence of these problems, and the severity of these problems.

**A8-2. Summary of main issues.** Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.

*Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.*

This research project doesn't require explicit patients' consents because it is a non-interventional project, and there will not be any direct contact with patients or their carers. All the information to be reviewed is already screened by a ward pharmacist, nurses, and other healthcare professionals, as part of their clinical routine procedure.

All patients' identifiable information will be viewed only in the hospital setting through the hospital electronic resources and will be recorded anonymously, to ensure patients' confidentiality.

All data will be stored anonymously, and will not be shared in public places or with people who are not members of the research team. Data will be stored electronically in a password protected computer.

In case of any identified problem, the researcher will report that to the ward pharmacist and will not initiate any further action without consulting the pharmacist in-charge.

There is no expected risk for participants including the patients, healthcare professionals and the researcher.

### 3. PURPOSE AND DESIGN OF THE RESEARCH

**A7. Select the appropriate methodology description for this research. Please tick all that apply:**

- Case series/ case note review
- Case control
- Cohort observation
- Controlled trial without randomisation
- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study
- Laboratory study
- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

**A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.**

What are the medicines related problems experienced by paediatric patients admitted to Paediatric/Neonatal Intensive Care unit at Evelina London Children's Hospital?

**A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.**

1. What is the prevalence of medicines related problems associated with unlicensed and off-label medicines in paediatrics in-patients?
2. What is the clinical significance of these medicines related problems?
3. What are the possible intervention strategies that might help to prevent medicines related problems associated with the use of unlicensed and off-label medicines in paediatric in-patients?

**A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.**

Although most research projects focus on the adult population, the paediatric population are at much higher risk of suffering from medicines related problems due to the difference in pharmacokinetics and pharmacodynamics features when compared to adults (Keams GL, 2003). Medicines related problem include adverse drug reactions, medication errors and drug drug interactions. Dose calculation for paediatric patients are based on many factors such as weight, surface area and height, which are variable among children. Thus the paediatric populations at a much higher risk of developing medicines related problems.

In England, approximately 5% of the total medicines prescribed are received by the paediatric population (Anon., 2008). Most of the medicines that are used in paediatrics are either off-label (OL) or unlicensed (UL). (Choonara & McIntyre, 2001). For this reason, there is a high risk of paediatric patients suffering from medicine related problems.

A number of studies have been conducted globally to identify the prevalence of off-label and unlicensed medicines as well as some of the problems associated with them. For more than a decade, off-label and unlicensed medicines prescribing and their associated problems were major issues and had been investigated by a number of researchers such as Turner S in 1999 who had investigated this area in the UK and found that adverse drug reactions are more frequent with unlicensed and off-label medicines than with licensed medicines representing 6% and 3.9% respectively. (Turner S, 1999), but what missing is a study that investigated all aspects of off-label and unlicensed medicines' related problems including adverse drug reactions, medication errors and adverse drug events. A recent study conducted in the UK revealed that off-label and unlicensed medicines are more likely to be implicated with adverse drug reactions than authorised medicines (Bellis, 2013). Another study conducted in 2013 in the UK illustrated that adverse drug reactions are frequent between hospitalised children reaches 17.7% of 6,601 total admissions (Thlesen, 2013).

Although there are different intervention strategies have been implemented into practice in adults, a limited number have found to be used in the paediatric population and there is no such strategy to highlight the risk associated with off-label and unlicensed medicines and their associated problems. Therefore conducting a research study to explore all the concepts and issues of medicines related problems-with a main focus on medication errors and adverse drug reactions- associated with the use of unlicensed and off-label medicines in order to recommend different ways of intervention for improving paediatrics' practice, is clearly justifiable.

The research team have a previous experience with such a research project in the ADVISE study (Rashed AN et al, 2012) which conducted in the same setting with other collaborating centres. The ADVISE study has contributed to improving the healthcare quality for paediatric population but more studies are needed.

**References:**

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- Choonara, I. & McIntyre, J., 2001. Training in clinical pharmacology. Paediatric and perinatal drug therapy [PDF document], 4(3), pp. 124-127.
- Turner, S. E. A. N., Nunn, A. J., Fielding, K., & Choonara, I. M. T. I. (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica*, 88(9), 965-968.
- Thlesen, S., Conroy, E. J., Bellis, J. R., Bracken, L. E., Mannix, H. L., Bird, K. A., ... & Smyth, R. L. (2013). Incidence, characteristics and risk factors of adverse drug reactions in hospitalized children? A prospective observational cohort study of 6,601 admissions. *BMC medicine*, 11(1), 237.
- Gregory L. Keams., Susan M. Abdel-Rahman., Sarah W. Alander., Douglas L. Blowey., J. Steven Leeder., and Ralph E. Kaufman. (2003). Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. *N Engl J Med* 2003; 349:1157-1167.
- Rashed AN, Wong IC, Cranswick N, Hefele B, Tomlin S, et al. (2012) Adverse Drug Reactions in Children—International Surveillance and Evaluation (ADVISE): a multicentre cohort study. *Drug Saf* 35: 481–494. doi: 10.2165/11597920



**A13. Please summarise your design and methodology.** It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

A mixed-method approach (qualitative and quantitative) will be used. The study will be divided into three different Phases. The first Phase will be a retrospective identification of the prevalence of medicines related problems (MRPs) associated with the use of unlicensed medicines (medicines with no license) and off-label medicines (medicines have a license to be prescribed to a different age group) and the severity of these problems. Data retrieved from this Phase will be analysed to identify type and nature of medicines related problems. Phase 2 will be a prospective identification of MRPs and their clinical significance to measure the current situation with comparison of the results from the previous Phase (Phase 1) and identify errors and areas with high need of improvement. The last Phase (Phase 3) will produce a list of recommendations and ways of intervention to improve practice. A panel of experts will be asked for their opinion of the recommendations and how to implement them into practice. Patients aged 0-18 years old who will be admitted to the Paediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at Evelina London Children's Hospital at the time of the study will be included. Patients who are in isolated rooms or there are no access to their medical notes will be excluded. Also patients admitted to the PICU but are on only nutritional products and no medications, will be excluded. Sample size that has to be investigated for Phase 1 and Phase 2 is 121 medical notes of patients from neonatal intensive care unit and 268 medical notes of patients from paediatrics intensive care unit.

**Phase 1:**

Retrospective study to identify prevalence of Medicines Related Problems and their clinical significance  
This is a retrospective study which will be about information that happened in the previous period during 2014. It will be conducted at the hospital for the purpose of identification of medicines related problems in terms of prevalence and their clinical significance. It will use a case-note review. Patients' information will be retrieved from drug charts and medical notes by using a data collection form to identify medicines related problems associated with unlicensed and off-label medicines' use in paediatric in-patients. Differences in the use of medicines will also be evaluated against the standard hospital guideline and the British National Formulary for Children (BNF for Children).

**Phase 2:**

Prospective study to detect MRPs & categorize their clinical significance  
This is a prospective study which will be for the current time in the ward. It will be conducted in the Paediatrics Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at Evelina London Children's Hospital to identify medicines related problems associated with the use of unlicensed and off-label medicines and their clinical significance. It will also include an investigation of patients' pathways to detect the area with higher rate of errors. A panel of experts, (of the research team), will be asked to assess the clinical significance rating. The finding from this study will be evaluated to produce a list of recommendations to improve paediatric practice.

**Phase 3:**

Proposed Recommendations & Ways of Intervention to reduce MRPs:  
This is a prospective study to use the findings from Phase 2 to develop a list of recommendation in order to prevent medicines related problems associated with the use of off-label and/or unlicensed medicines in paediatrics inpatients. A number of focus group sessions will be used in order to engage the healthcare professionals in the setting to discuss the produced recommendations and how they can work collaboratively to implement these recommendations into practice. The focus groups will be organised, led and recorded by the moderator (researcher). The data collected from these focus groups will be analysed to be taken into consideration for improving the practice.

**A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?**

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

Give details of involvement, or if none please justify the absence of involvement.

This project designed as a case-note review where only medical records and drug charts will be reviewed for information. There is no intended contact with patients or their guardians at any point of the study. Members of the public who are out of the research team will not be involved in this project.

#### 4. RISKS AND ETHICAL ISSUES

##### RESEARCH PARTICIPANTS

#### A16. What is the sample group or cohort to be studied in this research?

Select all that apply:

- Blood
- Cancer
- Cardiovascular
- Congenital Disorders
- Dementias and Neurodegenerative Diseases
- Diabetes
- Ear
- Eye
- Generic Health Relevance
- Infection
- Inflammatory and Immune System
- Injuries and Accidents
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Oral and Gastrointestinal
- Paediatrics
- Renal and Urogenital
- Reproductive Health and Childbirth
- Respiratory
- Skin
- Stroke

Gender: Male and female participants

Lower age limit: 0 Days

Upper age limit: 18 Years

#### A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Patients who are under 18 years old and who were admitted to the Paediatric Intensive Care Unit and/or Neonatal Intensive Care Unit within the study duration and on medications will be included.

#### A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Patients who are in isolated rooms or there are no access to their medical notes will be excluded. Also patients who admitted to the Paediatric/Neonatal Intensive Care Units but they are on only nutritional products but not medications

will be excluded.

#### RESEARCH PROCEDURES, RISKS AND BENEFITS

**A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.**

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Daily review of patients' case-notes for Phase 2	2	2	1	The researcher will review the medical notes in the paediatric intensive care units.
Focus groups for healthcare professionals for Phase 3	1	0	1	The researcher will design and invite healthcare professionals to focus group to ask about their opinion of the list of recommendations
Obtaining Consents for focus groups for Phase 3	1	0	48	The researcher will send an email with the consent form attached for the healthcare professionals who will be invited for the focus groups, and will allow them 48 hours to respond. Then the researcher will contact them physically to sign the form. All the signed forms will kept with the research documents in a locked drawer.

**A21. How long do you expect each participant to be in the study in total?**

For the whole period of the study programme (2years from January 2015- December 2016) divided as following:

Phase 1 will take up to 8months

Phase 2 will take up to 8months

Phase 3 will take up to 8months

**A22. What are the potential risks and burdens for research participants and how will you minimise them?**

*For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.*

There is no expected risks for participants, researcher and healthcare providers in the setting at the time of the study. There is no burden on nurses. The researcher will only view the medical notes and drug charts of patients. The researcher will ask the hospital supervisor (Stephen Tomlin) in case of unclear information on the patients' notes.

**A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?**

Yes  No

**A24. What is the potential for benefit to research participants?**

Findings of the study will improve the healthcare quality provided for the study participants by providing a list of recommendations to reduce medicines related problems associated with the use of off-label and unlicensed medicines.



**A26. What are the potential risks for the researchers themselves? (if any)**

There is no expected risks for participants, researcher and healthcare providers in the setting at the time of the study.

**RECRUITMENT AND INFORMED CONSENT**

*In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.*

**A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).**

**Phase 1:**

A list of patients who admitted to PICU and NICU in the last six months will be retrieved from the medical records department by the hospital supervisor (ST). Then the researcher will apply a computer randomisation to retrieve the required sample size. Patients' records, medical notes and drug charts will be reviewed by the researcher under arrangement with the hospital supervisor. The hospital supervisor will be contacted in case of ambiguity or unclear information which needed for the researcher to complete the data collection form.

**Phase 2:**

All patients are admitted to paediatric/neonatal intensive care units at the time of the study will be included and their medical records and drug charts will be reviewed by the researcher. Information collected by the researcher will be further evaluated by panel of experts from the research team.

**Phase 3:**

Healthcare professionals will be invited to participate in focus groups. This will be organised by the researcher and the supervisory team. Selecting these participants will be according to the job description of the professionals as nurses, prescribers, or pharmacists.

**A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?**

Yes  No

Please give details below:

**A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?**

Yes  No

**A29. How and by whom will potential participants first be approached?**

**Phase 1:**

The researcher will be introduced by the hospital supervisor to the staff of the paediatric and neonatal intensive care units. A list of patients who admitted to PICU and NICU in the last six months will be retrieved from the medical records department by the hospital supervisor (ST). Then the researcher will apply a computer randomisation to retrieve the required sample size. Patients' records, medical notes and drug charts will be reviewed by the researcher under arrangement with the hospital supervisor. The hospital supervisor will be contacted in case of ambiguity or unclear information which needed for the researcher to complete the data collection form.

**Phase 2:**

The hospital supervisor (the clinical pharmacist) will introduce the researcher to the staff who are working at the pharmacy department, PICU and NICU to facilitate the process of the data collection. The researcher will have an honorary contract and will be counted as a member of the staff.

Healthcare professionals will be invited, by the researcher under arrangement with the hospital supervisor, to participate into focus groups. Selecting these participants will be according to the job description of the professionals as nurses, prescribers, or pharmacists.

**A30-1. Will you obtain informed consent from or on behalf of research participants?**

Yes  No

*If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.*

*If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.*

*If you are not obtaining consent, please explain why not.*

For Phase 1:

Explicit patients' consents are not required as this project is a non-interventional project and will not affect the clinical care of these patients, or cause any changes in the practice by any measure. Furthermore, this study is based on case note review and review of medical records whether prospectively or retrospectively does not require any contact with patients and/or their carers.

Phase 2:

Explicit patients' consents are not required and data will be collected from medical notes and drug charts.

Phase 3:

Healthcare professionals who will be invited for focus groups, will be asked to sign consent forms before they join the group discussion. This consent form will be sent via emails.

Please enclose a copy of the information sheet(s) and consent form(s).

**A30-2. Will you record informed consent (or advice from consultees) in writing?**

Yes  No

**A31. How long will you allow potential participants to decide whether or not to take part?**

48 hours will be given for all healthcare professionals who will be invited to take part for focus groups, in order to respond and sign the consent form.

**A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters)**

All the healthcare professionals are expected to have a good level of communication skills.

**CONFIDENTIALITY**

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

**Storage and use of personal data during the study**

**A38. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)**

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations

- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
  - Manual files including X-rays
  - NHS computers
  - Home or other personal computers
  - University computers
  - Private company computers
  - Laptop computers

Further details:

**A37. Please describe the physical security arrangements for storage of personal data during the study?**

University of Hertfordshire's computers will be used for data storage. All computers used in the study will be password-protected. During data collection at the study site (Evelina Hospital), data collection forms will always be in the possession of the researcher or in a lockable cupboard with keys on the researchers. Research team members will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The research team will only collect the minimum required information for the purposes of the study. Data will be held securely, in a locked room, or locked cupboard or filing cabinet. Access to the information will be limited to the chief investigator and the research team. Access will be restricted by user identifiers and passwords. Data will be stored on encrypted sticks.

**A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.**

All patients' relevant information will be protected through different numbers of measures: Confidentiality agreement will be signed by the researcher, Patients' information will not be discussed in public, and electronic devices, where the data will be stored, will be password protected. Data collected will not include any identifiers or patients' identifiable information and all the collected parameters will be presented anonymously. All the collected data will be destroyed after three years after the completion of the project.

**A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.**

The chief investigator and the local collaborator.

**Storage and use of data after the end of the study**

**A41. Where will the data generated by the study be analysed and by whom?**

It will be analysed by the researcher using University of Hertfordshire computers, department of pharmacy.

**A42. Who will have control of and act as the custodian for the data generated by the study?**

Title Forename/Initials Surname  
Mrs WUDAN ELHJAZI

Post	PhD student
Qualifications	MSc in Clinical Pharmacy, International Practice & Policy,
Work Address	School of Life & Medical Sciences, Department of Pharmacy University of Hertfordshire Hatfield
Post Code	AL10 9AB
Work Email	w.eh(jzi)@herts.ac.uk
Work Telephone	00441707281051
Fax	00441707284506

A43. How long will personal data be stored or accessed after the study has ended?

- Less than 3 months  
 3 – 6 months  
 6 – 12 months  
 12 months – 3 years  
 Over 3 years

*If longer than 12 months, please justify:*

The data will be used for production of list of recommendations. Focus groups will be designed in order to discuss these recommendations. Further updates and improvements might require reviewing the data again.

A44. For how long will you store research data generated by the study?

Years: 3  
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

The collected data will be stored in the university computer and can be accessed only by the research team. The data will be destroyed immediately after the PhD programme completion.

#### INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

- Yes  No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- Yes  No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- Yes  No

## NOTIFICATION OF OTHER PROFESSIONALS

**A48-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?**

Yes  No

*If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.*

## PUBLICATION AND DISSEMINATION

**A60. Will the research be registered on a public database?**

Yes  No

*Please give details, or justify if not registering the research.*

The research might be registered through the Evelina London Children's Hospital where this project will be conducted (NHS organisation), and through the university website (University of Hertfordshire).

*Registration of research studies is encouraged wherever possible.*

*You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A6-1.*

**A61. How do you intend to report and disseminate the results of the study? Tick as appropriate:**

- Peer reviewed scientific journals  
 Internal report  
 Conference presentation  
 Publication on website  
 Other publication  
 Submission to regulatory authorities  
 Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators  
 No plans to report or disseminate the results  
 Other (please specify)

**A62. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?**

The results will be published in an anonymous way and will not include any individual participant or any identifiers. All identifiable information will be presented anonymously and will not be able to identify patients through these information.

**A63. Will you inform participants of the results?**

Yes  No

*Please give details of how you will inform participants or justify if not doing so.*

The findings will be evaluate the medicines related problems in general and will not identify an exact patient's problem. However healthcare professionals of the setting will be informed of the results, and involved in the proposed focus groups and their opinions will be evaluated for further improvement of the recommendation.

**A64. How has the scientific quality of the research been assessed? Tick as appropriate:**

- Independent external review
- Review within a company
- Review within a multi-centre research group
- Review within the Chief Investigator's Institution or host organisation
- Review within the research team
- Review by educational supervisor
- Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

The research team have done the initial review for the project protocol. A second review has been done by an independent body who is the Research associate dean of the department of Pharmacy in University of Hertfordshire. By the end of the reviewing process, the university has agreed to sponsor the research project.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

**A68. How have the statistical aspects of the research been reviewed? Tick as appropriate:**

- Review by independent statistician commissioned by funder or sponsor
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator's Institution
- Review by a statistician within the research team or multi-centre group
- Review by educational supervisor
- Other review by individual with relevant statistical expertise
- No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Mrs	SUSAN	BAKER
Department	Statistical Services and Consultancy Unit		
Institution	University of Hertfordshire		
Work Address	DeHavilland Campus		
	University of Hertfordshire		
	Hatfield		
Post Code	AL10 9AB		
Telephone	01707285529		
Fax			
Mobile			
E-mail	s.m.f.baker@herts.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.



**A67. What is the primary outcome measure for the study?**

Prevalence, type and nature of medicines related problems associated with the use of unlicensed and off-label medicines in paediatrics in-patients, and the level of severity of these problems.

**A68. What are the secondary outcome measures? (if any)**

The research secondary outcome aims:

- To identify prescribing errors.
- To identify preparation and administration errors.
- To identify monitoring errors.
- To identify adverse drug reactions.
- To identify where more errors occur during patients' pathways.
- To categorise those medicines related problems according to their clinical significance.
- To recommend ways of intervention to prevent medicines related problems associated with unlicensed and off-label medicines' use in paediatrics.

**A69. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.**

Total UK sample size: 194

Total International sample size (Including UK):

Total in European Economic Area:

Further details:

Phase 1 & 2:

Sample size that has to be investigated for Phase 1 is 194 case-notes for patients who were admitted to intensive care unit at Evelina Children Hospital.

**A80. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.**

The sample size for this Phase has been calculated following sample size by proportion calculation equation (<http://www.select-statistics.co.uk/sample-size-calculator-proportion>), taking into account a 95% confidence level, and 5% margin of error. The percentages were taken from the literature depending on the setting.

Neonatal Intensive Care Unit:

A study conducted by Sharon Conroy stated that 90% of patients were administered an unlicensed or off-label medicines in a neonatal population (Conroy S, 1999). Taking into account that the same percent might be found in the NICU at Evelina Hospital, the proper sample size that has to be investigated is 121 neonates as there was 952 neonates were admitted to the setting during the previous year. Thus Phase 1 sample size will be 60 patients' case-notes because Phase 1 will investigate six months admission.

Paediatric Intensive Care Unit:

The number of patients that were admitted to PICU at Evelina Hospital in 2013 was 1249 patients, so the sample size required to complete the first Phase of the project is 134 patients' case-notes (268 patients' case-notes for 12 months). That was counted according to the information retrieved from the literature that 67% of patients in paediatric intensive care unit received either off-label and/or unlicensed medicines (Conroy S, 2000).

**A81. Will participants be allocated to groups at random?**

Yes  No

**A82. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.**

Advanced computer programmes such as Statistical Package for the Social Sciences (SPSS) and Excel will be applied

In order to obtain a proper data management and statistical analysis, and to relate different variables with each other in regard to the findings from the studies.

#### 8. MANAGEMENT OF THE RESEARCH

**A83. Other key investigators/collaborators.** Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

	<b>Title</b>	Forename/Initials	Surname
	MR	STEPHEN	TOMLIN
<b>Post</b>	Consultant Pharmacist – Children's Services, Pharmacy Department, Guy's & St Thomas' NHS Foundation Trust		
<b>Qualifications</b>	BPharm (Hons) - 1990 FRPharmS – 2011 FFRPS - 2013		
<b>Employer</b>	EVELINA LONDON CHILDREN'S HOSPITAL		
<b>Work Address</b>	PHARMACY DEPARTMENT, EVELINA LONDON CHILDREN'S HOSPITAL ST THOMAS'S HOSPITAL, WESTMINSTER BRIDGE RD LONDON, ENGLAND		
<b>Post Code</b>	SE1 7EH		
<b>Telephone</b>	0044207 1889202		
<b>Fax</b>	0044207 1889155		
<b>Mobile</b>	07766603154		
<b>Work Email</b>	Stephen.Tomlin@gstf.nhs.uk		

#### A84. Details of research sponsor(s)

##### A84-1. Sponsor

###### Lead Sponsor

**Status:**  NHS or HSC care organisation **Commercial status:**  
 Academic  
 Pharmaceutical industry  
 Medical device industry  
 Local Authority  
 Other social care provider (including voluntary sector or private organisation)  
 Other

*If Other, please specify:*

###### Contact person

**Name of organisation** University of Hertfordshire  
**Given name** Professor John  
**Family name** Senior  
**Address** University of Hertfordshire, Department of Pharmacy  
**Town/city** Hatfield  
**Post code** AL10 9AB



Country UNITED KINGDOM  
 Telephone +441707 284000  
 Fax +441707 284115  
 E-mail research-sponsorship@herts.ac.uk

Is the sponsor based outside the UK?

Yes  No

*Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.*

A86. Has external funding for the research been secured?

- Funding secured from one or more funders  
 External funding application to one or more funders in progress  
 No application for external funding will be made

What type of research project is this?

- Standalone project  
 Project that is part of a programme grant  
 Project that is part of a Centre grant  
 Project that is part of a fellowship/ personal award/ research training award  
 Other

Other – please state:  
 self-funded PhD

A88. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A84-1)? Please give details of subcontractors if applicable.

Yes  No

A87. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

Yes  No

*Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.*

A88-1. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname  
 Ms Elizabeth Smith  
 Organisation NIHR GSTFT/KCL Biomedical Research Centre  
 Address 16th floor, Tower Wing, Guy's Hospital  
 Great Maze Pond,  
 London

Post Code SE1 9RT  
 Work Email liz.smith@gstt.nhs.uk  
 Telephone +44 (0)20 7188 7188 Ext: 54426  
 Fax 0044207 188 8330  
 Mobile

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

**A69-1. How long do you expect the study to last in the UK?**

Planned start date: 01/01/2015  
 Planned end date: 31/12/2016  
 Total duration:  
 Years: 1 Months: 11 Days: 31

**A71-1. Is this study?**

- Single centre  
 Multicentre

**A71-2. Where will the research take place? (Tick as appropriate)**

- England  
 Scotland  
 Wales  
 Northern Ireland  
 Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

- Yes  No

**A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:**

- NHS organisations in England 1  
 NHS organisations in Wales  
 NHS organisations in Scotland  
 HSC organisations in Northern Ireland  
 GP practices in England  
 GP practices in Wales  
 GP practices in Scotland  
 GP practices in Northern Ireland  
 Social care organisations  
 Phase 1 trial units  
 Prison establishments  
 Probation areas  
 Independent hospitals  
 Educational establishments

<input type="checkbox"/> Independent research units
<input type="checkbox"/> Other (give details)
Total UK sites in study: 1

**A73-1. Will potential participants be identified through any organisations other than the research sites listed above?**

Yes  No

**A74. What arrangements are in place for monitoring and auditing the conduct of the research?**

Regular meetings every two weeks will be carried out with the chief investigator and the supervisory team to ensure a good level of monitoring.

**A78. Insurance/ Indemnity to meet potential legal liabilities**

*Note: In this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

**A78-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.**

*Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (NHS sponsors only)  
 Other insurance or indemnity arrangements will apply (give details below)

University of Hertfordshire

Please enclose a copy of relevant documents.

**A78-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.**

*Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.*

- NHS indemnity scheme will apply (protocol authors with NHS contracts only)  
 Other insurance or indemnity arrangements will apply (give details below)

University of Hertfordshire

Please enclose a copy of relevant documents.

**A78-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?**

*Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.*

- NHS Indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)  
 Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

University of Hertfordshire

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

Yes  No  Not sure

#### PART B: Section 7 - Children

1. Please specify the potential age range of children under 18 who will be included and give reasons for carrying out the research in this age group.

Medical notes and drug charts for children between 0-18 years will be reviewed. Paediatric patients who received unlicensed and off-label medicines might be at risk of developing medicines related problems as these medicines have no safety studies into this population.

2. Indicate whether any children under 18 will be recruited as controls and give further details.

No, this is a case-note review.

3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.

Not applicable.

4. If you intend to provide children under 18 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.

Not applicable

Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.

## PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

Research site		Investigator/ Collaborator/ Contact	
Institution name	EVELINA LONDON CHILDREN'S HOSPITAL	Title	MR
Department name	DEPARTMENT OF PHARMACY	First name/ Initials	STEPHEN
Street address	Westminster Bridge Rd	Surname	TOMLIN
Town/city	LONDON		
Post Code	SE1 7EH		

**PART D: Declarations****D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
  - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
  - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
  - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
  - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
  - May be sent by email to REC members.
10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

**Contact point for publication(Not applicable for R&D Forms)**

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator  
 Sponsor

- Study co-ordinator
- Student
- Other – please give details
- None

**Access to application for training purposes** (Not applicable for R&D Forms)

Optional – please tick as appropriate:

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Mrs WIJDAN ELHIJAZI on 20/04/2015 11:11.

Job Title/Post:        PhD student  
Organisation:        University of Hertfordshire  
Email:                w.eh|zi|herts.ac.uk

**D2. Declaration by the sponsor's representative**

*if there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.*

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publicly accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Professor John Senior on 20/04/2015 12:23.

Job Title/Post: Pro Vice-Chancellor (Research & International)  
Organisation: University of Hertfordshire  
Email: j.m.senior@herts.ac.uk



**D8. Declaration for student projects by academic supervisor(s)**

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.
2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.
3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.
4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

**Academic supervisor 1**

This section was signed electronically by Dr Andrzej Kostrzewski on 20/04/2015 14:20.

Job Title/Post: Academic Lead Clinical Development  
Organisation: University of Hertfordshire  
Email: a.kostrzewski@herts.ac.uk

## Appendix 7: University of Hertfordshire sponsorship



Mrs Wijdan Elhijazi (Dr Andrzej Kostrzewski)  
Department of Pharmacy  
School of Life and Medical Sciences

University of Hertfordshire  
Hatfield  
AL10 9AB  
UK

tel +44 (0)1707 284000  
fax +44 (0)1707 284115  
herts.ac.uk

1 October 2014

Dear Wijdan,

**Re: UNIVERSITY OF HERTFORDSHIRE SPONSORSHIP IN PRINCIPLE for the following:**  
**RESEARCH STUDY TITLE:** Medicines Related Problems Associated with the Use of Unlicensed and Off-Label Medicines in Paediatric In-patients.  
**NAME OF CHIEF INVESTIGATOR:** Mrs Wijdan Elhijazi  
**IF STUDENT, NAME OF SUPERVISOR:** Dr Andrzej Kostrzewski  
**UNIVERSITY OF HERTFORDSHIRE ETHICS PROTOCOL NUMBER:** LMS/PG/NHS/00290

This letter is to confirm your research study detailed above has been reviewed and accepted, and I agree to give University of Hertfordshire sponsorship in principle.

Before you commence your research you must be in full compliance with all NHS Governance requirements. You must also secure full University of Hertfordshire sponsorship, for which you will need to have supplied the following documentation:

- Final version of the submitted IRAS form (pdf)
- Approval from the relevant NRES (NHS) Research Ethics Committee (REC) as well as confirmation of favourable opinion of any possible amendments
- Evidence of relevant NHS Permissions (eg Research Passport) and NHS Trust Management Permissions (previously known as R&D Approval) as they are received
- The final version of the protocol
- The final versions of the patient information leaflet and informed consent form
- One page summary CV for the Chief Investigator (CI) and, if research student project, for the Supervisor
- Any other regulatory permissions required for your research, eg from the National Information Governance Board (NIGB), under the Human Tissue Act or the Ionising Radiation (Medical Exposure) Regulations
- If applicable, copies of any contracts/agreements with external organisations (eg funders, collaborators, co-sponsors) involved in your research study

As a condition of receiving full sponsorship, it is the responsibility of the Chief Investigator to inform the Sponsor of any changes to the duration or funding of the project, changes of investigators, changes to the protocol and any future amendments, or deviations from the protocol, which may require re-evaluation of the sponsorship arrangements. It is also the responsibility of the Chief Investigator to inform the funder, the NRES (NHS) Research Ethics Committee (REC) and the relevant University of Hertfordshire Ethics Committee with Delegated Authority (ECDA) and any other relevant authority of any of these changes.

I look forward to receiving the above documents before you commence your research. Please email these to [research-sponsorship@herts.ac.uk](mailto:research-sponsorship@herts.ac.uk) so the University can confirm sponsorship. In the meantime, we wish you well in pursuing this interesting research study.

Yours sincerely,

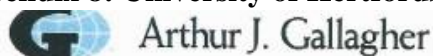
Professor JM Senior  
Pro Vice-Chancellor (Research and International)

Encl: Insurance certificate



A Charity Exempt from Registration under the  
Second Schedule of the Charities Act 1993

## Appendix 8: University of Hertfordshire indemnity letter



Station Square  
One Gloucester Street  
SWINDON  
SN1 1GW

Telephone 01793 468319  
Fax 01793 468838  
Email [ukpublicsector@ajg.com](mailto:ukpublicsector@ajg.com)  
[www.ajginternational.com/gh](http://www.ajginternational.com/gh)

30th July 2014

Our Ref: 5068828

### TO WHOM IT MAY CONCERN

#### University of Hertfordshire and Subsidiary Companies

**Subsidiaries:** As agreed with Insurers

We act as Insurance Brokers and Consultants to University of Hertfordshire and hereby certify that the following described insurance is in force at this date.

<b>Type of Insurance:</b>	PROFESSIONAL INDEMNITY
<b>Limit of Indemnity:</b>	£5,000,000 any one claim / in the aggregate any one period of insurance
<b>Insurers:</b>	Royal & Sun Alliance Insurance Group
<b>Policy Number:</b>	RKK423027/37
<b>Period of Insurance</b>	1 <sup>st</sup> August 2014 to 31 <sup>st</sup> July 2015

The policy includes the following endorsement:

"It is understood and agreed that this Endorsement applies only in respect of the Client(s) referred to below.

The Insurers understand that any named Client(s) could make a Claim against the Insured which could entitle the Insured to indemnity under this Policy. If a Claim occurs the Insurers will, if requested by the Insured, pay directly to the Client the amount of indemnity which Insurers agree the Insured is entitled to for the Claim under this Policy. When Insurers make such a payment to a Client then their receipt shall be a valid discharge of all liability which Insurers have to the Insured to make any payment under this Policy for the Claim. This Endorsement does not restrict Insurers rights:

- a) to defend a Claim on the Insured's behalf or
- b) to pay the Insured the Limit of Indemnity.

It is a legal requirement world-wide that anyone seeking a new policy of insurance/reinsurance or cover for additional risks or renewal under an existing policy, must disclose any information that might influence the insurers/reinsurers in fixing the premium or determining whether to accept the risk. Under English law, failure to do so may entitle insurers/reinsurers to avoid cover from inception and to seek repayment of paid claims. **If you are in any doubt as to whether information is material you should disclose it.**

Arthur J. Gallagher (UK) is a trading name of Heath Lambert Limited, which is authorised and regulated by the Financial Conduct Authority, Registered Office: The Walbrook Building, 25 Walbrook, London EC4N 8AW. Registered No 1199129 England and Wales



It is understood that the Clients to which this Endorsement applies are not parties to this insurance and have no contractual or other rights or obligations under it. Subject otherwise to the Terms and Conditions of the Policy. For the purposes of this Endorsement the Client is NHS London (London Strategic Health Authority).\*

This Letter is provided for you as a matter of information only. The issuing of this document does not make the person or organisation to which it has been issued an additional Insured, nor does it modify in any manner the Contracts of Insurance between the Insured and Insurers. Any amendment, change or extension of such contracts can only be effected by specific endorsements attached thereto.

Should the above-mentioned Contract of Insurance be cancelled, assigned or changed during the above policy period in such a manner as to affect this document, no obligation to inform the holder of the Document is required by Arthur J. Gallagher (UK).

If you have any further queries regarding our client's insurance cover, please do not hesitate to contact the undersigned.

Yours sincerely

A handwritten signature in black ink that reads 'Street'.

Stephen Street  
Client Service Advisor

**Appendix 9: Data collection Form for PICU retrospective study**

**ID:**

Age	GENDER	WEIGHT	HIEGHT	Length of Stay	Allergy	Diagnosis

**MEDICATIONS:**

NAME	Strength	DATE	DOSE	ROUTE	FREQU- ENCY	MRP	MRP Category	Licensing status	Comments

**Comments:**

### Appendix 10: Retrospective study's medicines and their associated MRPs

Medicine	Licencing status	Number of times medicine prescribed	Number of patient	Number of times medicine associate with MRPs	Number of patients developed MRPs
MORPHINE	UL	193	151	79	77
CLONIDINE	UL	146	135	0	0
PARACETAMOL	L	120	119	1	1
FUROSEMIDE	L	110	102	43	43
SPIRONOLACTONE	UL	97	93	0	0
CEFUROXIME	L	87	85	0	0
ROCURONIUM	OL	76	71	0	0
POTASSIUM CHLORIDE	L	74	71	1	1
LACTULOSE	L	72	72	0	0
MILRINONE	UL	72	72	0	0
FENTANYL	OL	68	59	1	1
KETAMINE	L	51	49	0	0
CO-AMOXICLAV	L	49	44	2	2
PARACETAMOL	OL	43	32	13	13
PROPOFOL	L	42	40	0	0
GENTAMICIN	L	41	40	7	7
IBRUPOFEN	L	31	30	0	0
ADENOSINE	L	29	7	0	0
DOPAMINE	L	22	22	0	0
BENZYL PENICILLIN	L	21	21	0	0
CAPTOPRIL	UL	19	18	0	0
CHLORPHENIRAMINE	OL	18	18	0	0
LORAZEPAM	OL	18	17	0	0
OMEPRAZOLE	UL	17	17	0	0
ACICLOVIR	L	16	16	0	0
VITAMIN K	L	15	15	0	0
CEFTRIAZONE	L	15	15	0	0
MIDAZOLAM	OL	14	14	0	0
FLUCLOXACILLIN	L	14	14	3	3
ASPRIN	L	14	14	1	1
PREDNISOLONE	L	13	13	0	0
GLYCERIN	L	12	12	0	0

<b>CEFOTAXIME</b>	L	12	12	0	0
<b>PANTOPRAZOLE</b>	L	12	12	0	0
<b>HEPARIN</b>	OL	11	11	0	0
<b>AMIODARONE</b>	OL	11	9	0	0
<b>MORPHINE</b>	L	11	11	4	4
<b>DALTEPARIN</b>	OL	9	8	0	0
<b>PHENYTOIN</b>	L	9	7	1	1
<b>PROPRANOLOL</b>	L	8	8	0	0
<b>TEICOPLANIN</b>	L	8	8	0	0
<b>DOMPERIDONE</b>	OL	8	8	0	0
<b>ONDANSETRON</b>	L	8	8	0	0
<b>CLINDAMYCIN</b>	L	8	7	0	0
<b>SALBUTAMOL</b>	L	8	7	1	1
<b>DEXAMETHASONE</b>	L	7	7	0	0
<b>SILDENAFIL</b>	OL	7	7	0	0
<b>ADRENALINE</b>	L	7	7	0	0
<b>KAY-CEE-L</b>	L	7	7	0	0
<b>DIGOXIN</b>	OL	7	6	0	0
<b>SYTRON</b>	L	7	7	1	1
<b>MOVICOL</b>	L	5	5	0	0
<b>MEROPENEM</b>	OL	5	5	0	0
<b>RANITIDINE</b>	L	5	5	0	0
<b>VANCOMYCIN</b>	L	5	5	1	1
<b>CLARITHROMYCI N</b>	OL	5	5	0	0
<b>ABIDEC</b>	L	5	5	0	0
<b>AMOXICILLIN</b>	L	5	5	0	0
<b>NORADRENALINE</b>	OL	5	5	0	0
<b>METRONIDAZOLE</b>	L	5	4	0	0
<b>TAZOCIN</b>	L	4	4	0	0
<b>FLECAINIDE</b>	UL	4	4	0	0
<b>MUPIROCIN</b>	L	4	4	0	0
<b>PHENOBARBITON E</b>	L	4	2	0	0
<b>ORAMORPH</b>	OL	4	4	0	0
<b>DNASE</b>	L	4	4	0	0
<b>NALOXONE</b>	L	4	4	0	0
<b>MONTELUKAST</b>	L	4	4	0	0
<b>NYSTATIN</b>	OL	4	4	0	0
<b>DINOPROSITONE</b>	UL	4	4	0	0
<b>BUDESONIDE</b>	OL	4	4	0	0
<b>DALIVIT</b>	L	4	4	0	0

<b>PERIPHERAL DOPAMINE</b>	L	3	3	0	0
<b>DICLOFENAC</b>	L	3	3	1	1
<b>CYCLIZINE</b>	OL	3	3	0	0
<b>FOLIC ACID</b>	L	3	3	0	0
<b>CARNITINE</b>	UL	3	3	0	0
<b>PROSTIN</b>	L	3	3	0	0
<b>DIHYDROCODIEN E</b>	L	3	3	2	2
<b>CARVEDILOL</b>	OL	3	3	0	0
<b>AZITHROMYCIN</b>	L	3	3	1	1
<b>TRIMETHOPRIM</b>	OL	3	3	0	0
<b>MAGNESIUM SULPHATE</b>	UL	2	2	0	0
<b>SERETIDE 125</b>	L	2	2	0	0
<b>GLYCOPYRROLAT E</b>	OL	2	2	0	0
<b>LISINOPRIL</b>	OL	2	2	0	0
<b>AMLODIPINE</b>	OL	2	2	0	0
<b>CEFRUROXIME</b>	L	2	2	0	0
<b>ALFACALCIDOL</b>	L	2	2	0	0
<b>SENNA</b>	OL	2	2	0	0
<b>CLOBAZAM</b>	L	2	2	0	0
<b>LEVOTHYROXINE</b>	L	2	2	0	0
<b>MAGNESIUM GLYCOPHOSPHAT E</b>	UL	2	2	0	0
<b>FLUCONAZOLE</b>	L	2	1	0	0
<b>ACETAZOLAMIDE</b>	L	2	2	0	0
<b>TRANEXAMIC ACID</b>	OL	2	2	1	1
<b>SODIUM VALPORATE</b>	L	1	1	0	0
<b>UROKINASE</b>	L	1	1	0	0
<b>BECLOMETHASON E</b>	L	1	1	0	0
<b>ATROPINE</b>	L	1	1	0	0
<b>ACTRAPID INSULIN</b>	L	1	1	0	0
<b>FENTANYL</b>	L	1	1	0	0
<b>NOVORAPID</b>	L	1	1	0	0
<b>DALTEPARIN</b>	L	1	1	0	0
<b>PENICILLIN V</b>	L	1	1	0	0
<b>GAVICON</b>	OL	1	1	0	0



<b>SODIUM CHLORIDE</b>	L	1	1	0	0
<b>LOPERAMIDE</b>	OL	1	1	0	0
<b>OXYCODIENE</b>	L	1	1	1	1
<b>VORICONAZOLE</b>	L	1	1	0	0
<b>CALCIUM</b>	L	1	1	0	0
<b>VIGABATRIN</b>	OL	1	1	0	0
<b>CIPROFLOXACIN</b>	L	1	1	0	0
<b>PANCURONIUM</b>	L	1	1	0	0
<b>SANDO-K</b>	L	1	1	0	0
<b>ENOXAPARIN</b>	L	1	1	0	0
<b>SODIUM PHOSPHATE</b>	OL	1	1	0	0
<b>SODIUM CHLORIDE</b>	UL	1	1	0	0
<b>AMINOPHYLLINE</b>	OL	1	1	0	0
<b>RIFAMPICIN</b>	L	1	1	0	0
<b>HEPARIN</b>	L	1	1	0	0
<b>POTASSIUM CANRENOATE</b>	L	1	1	0	0
<b>CAFFEINE CITRATE</b>	OL	1	1	0	0
<b>COLECALCIFEROL</b>	OL	1	1	0	0
<b>LEVETIRACETAM</b>	OL	1	1	0	0
<b>AMIKACIN</b>	L	1	1	0	0
<b>STIRIPENTOL</b>	L	1	1	0	0
<b>ENOXIMONE</b>	OL	1	1	0	0
<b>OMEPRAZOLE</b>	OL	1	1	0	0
<b>NITROPRUSSIDE</b>	L	1	1	0	0
<b>NEOSTIGMINE</b>	UL	1	1	0	0
<b>METHYLEPREDNISOLONE</b>	L	1	1	0	0
<b>SODIUM FEREDETATE</b>	OL	1	1	0	0
<b>ATENOLOL</b>	OL	1	1	0	0
<b>VITAMIN D</b>	L	1	1	0	0
<b>CETRIZINE</b>	L	1	1	0	0
<b>POTASSIUM CITRATE</b>	L	1	1	0	0
<b>SLOW K</b>	L	1	1	0	0
<b>DOCUSATE</b>	OL	1	1	0	0
<b>SODIUM LANTUS</b>	L	1	1	0	0

<b>LANSOPRAZOLE</b>	OL	1	1	0	0
<b>BACLOFEN</b>	L	1	1	0	0
<b>SUXAMETHONIUM</b>	L	1	1	0	0
<b>IPRATROPIUM</b>	L	1	1	0	0
<b>PEPTAC</b>	L	1	1	0	0
<b>FLECANIDE</b>	OL	1	1	0	0
<b>PENTASA</b>	L	1	1	0	0
<b>ESMOLOL</b>	OL	1	1	0	0
<b>CHLORAL HYDRATE</b>	OL	1	1	0	0
<b>TEMAZEPAM</b>	OL	1	1	0	0
<b>DOPUTAMINE</b>	L	1	1	0	0

**Appendix 11: Retrospective study panel’s Severity Scoring summary:**

<b>Case number</b>	<b>Member 1 Pharmacist</b>	<b>Member 2 Consultant</b>	<b>Member 3 Nurse</b>
<b>Case 1</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 2</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 3</b>	<b>Moderate</b>	<b>Moderate</b>	<b>Moderate</b>
<b>Case 4</b>	<b>Moderate</b>	<b>Moderate</b>	<b>Moderate</b>
<b>Case 5</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 6</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 7</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 8</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 9</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 10</b>	<b>No harm</b>	<b>No harm</b>	<b>Low</b>
<b>Case 11</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 12</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 13</b>	<b>Moderate</b>	<b>Moderate</b>	<b>Moderate</b>
<b>Case 14</b>	<b>Low</b>	<b>Low</b>	<b>No harm</b>
<b>Case 15</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 16</b>	<b>Low</b>	<b>Low</b>	<b>Low</b>
<b>Case 17</b>	<b>Moderate</b>	<b>Moderate</b>	<b>Moderate</b>

Case= MRP

Panel= 3 assessors (Consultant, Pharmacist, Nurse)

Scoring system= 5levels (No harm, Low, moderate, Severe, Death)




**Day 2:**

<b>Medicine</b>	<b>Initial dose</b>	<b>New dose</b>	<b>Why stopped</b>	<b>cha</b>	<b>Comments</b>

### Appendix 13: PICU prospective study medicines and associated problems

Medicine	Licensing status	Number of times medicine prescribed	Number of patients	Number of times medicine associated with MRPs	Number of patients developed MRPs
MORPHINE	UL	164	127	80	77
CLONIDINE	UL	121	114	4	4
PARACETAMOL	L	105	104	3	3
FUROSEMIDE	L	92	86	48	48
SPIRONOLACTONE	UL	80	78	0	0
CEFUROXIME	L	73	71	0	0
MILRINONE	UL	64	64	0	0
ROCURONIUM	OL	60	57	0	0
POTASSIUM CHLORIDE	L	54	51	1	1
LACTULOSE	L	53	53	0	0
FENTANYL	OL	47	43	1	1
KETAMINE	L	39	37	0	0
CO-AMOXICLAV	L	38	35	1	1
PROPOFOL	L	33	31	0	0
PARACETAMOL	OL	31	22	10	10
IBRUPROFEN	L	30	29	0	0
GENTAMICIN	L	18	18	5	5
LORAZEPAM	OL	18	17	0	0
DOPAMINE	L	17	17	0	0
CHLORPHENIRAMINE	OL	14	14	0	0
MIDAZOLAM	OL	14	14	0	0
ADENOSINE	L	13	5	0	0
CAPTOPRIL	UL	13	12	0	0
OMEPRAZOLE	UL	13	13	0	0
ACICLOVIR	L	13	13	0	0
PREDNISOLONE	L	12	12	0	0
CEFTRIAZONE	L	12	12	0	0
ASPRIN	L	12	12	1	1
PANTOPRAZOLE	L	10	10	0	0
SALBUTAMOL	L	9	8	2	2
AMIODARONE	OL	9	7	0	0
ONDANSETRON	L	8	8	0	0
FLUCLOXACILLIN	L	8	8	1	1
BENZYL PENICILLIN	L	8	8	0	0
MORPHINE	L	8	8	2	2
DALTEPARIN	OL	8	6	1	1
GLYCERIN	L	8	8	0	0

<b>PHENYTOIN</b>	L	8	6	1	1
<b>KAY-CEE-L</b>	L	7	7	0	0
<b>DOMPERIDONE</b>	OL	7	7	0	0
<b>SYTRON</b>	L	7	7	1	1
<b>TEICoplanin</b>	L	7	7	0	0
<b>HEPARIN</b>	OL	7	7	0	0
<b>PROPRANOLOL</b>	L	6	6	0	0
<b>DIGOXIN</b>	OL	6	4	1	1
<b>CEFOTAXIME</b>	L	6	6	0	0
<b>CLINDAMYCIN</b>	L	6	5	0	0
<b>CLARITHROMYCIN</b>	OL	5	5	0	0
<b>SILDENAFIL</b>	OL	5	5	0	0
<b>DEXAMETHASONE</b>	L	5	5	0	0
<b>ABIDEC</b>	L	5	5	0	0
<b>ADRENALINE</b>	L	5	5	0	0
<b>RANITIDINE</b>	L	4	4	0	0
<b>VITAMIN K</b>	L	4	4	0	0
<b>PHENOBARBITONE</b>	L	4	2	0	0
<b>TAZOCIN</b>	L	4	4	0	0
<b>DALIVIT</b>	L	4	4	0	0
<b>DNASE</b>	L	4	4	0	0
<b>VANCOMYCIN</b>	L	4	3	2	2
<b>MEROPENEM</b>	OL	4	4	0	0
<b>MONTELUKAST</b>	L	4	4	0	0
<b>AZITHROMYCIN</b>	L	3	3	1	1
<b>ORAMORPH</b>	OL	3	3	0	0
<b>NYSTATIN</b>	OL	3	3	0	0
<b>MOVICOL</b>	L	3	3	0	0
<b>NORADRENALINE</b>	OL	3	3	0	0
<b>CYCLIZINE</b>	OL	3	3	0	0
<b>METRONIDAZOLE</b>	L	3	2	0	0
<b>VANCOMYCIN</b>	UL	3	2	3	2
<b>MAGNESIUM SULPHATE</b>	UL	2	2	0	0
<b>FOLIC ACID</b>	L	2	2	0	0
<b>AMLODIPINE</b>	OL	2	2	0	0
<b>CLOBAZAM</b>	L	2	2	0	0
<b>NALOXONE</b>	L	2	2	0	0
<b>MAGNESIUM GLYCOPHOSPHATE</b>	UL	2	2	0	0
<b>SERETIDE</b>	L	2	2	0	0
<b>TRIMETHOPRIM</b>	OL	2	2	0	0
<b>BUDESONIDE</b>	OL	2	2	0	0
<b>AMOXICILLIN</b>	L	2	2	0	0
<b>FLUCONAZOLE</b>	L	2	1	0	0
<b>DIHYDROCODIENE</b>	L	2	2	1	1
<b>ALFACALCIDOL</b>	L	2	2	0	0

<b>PROSTIN</b>	L	2	2	0	0
<b>GLYCOPYRROLATE</b>	OL	2	2	0	0
<b>GENTAMICIN</b>	UL	2	2	2	2
<b>DINOPROSITONE</b>	UL	2	2	0	0
<b>LISINOPRIL</b>	OL	2	2	0	0
<b>ACETAZOLAMIDE</b>	L	2	2	0	0
<b>TRANEXAMIC ACID</b>	OL	2	2	1	1
<b>CO-AMOXICLAV</b>	UL	2	2	2	2
<b>MUPIROCIN</b>	L	2	2	0	0
<b>LEVOTHYROXINE</b>	L	2	2	0	0
<b>ACTRAPID INSULIN</b>	L	1	1	0	0
<b>OMEPRAZOLE</b>	OL	1	1	0	0
<b>IPRATROPIUM</b>	L	1	1	0	0
<b>FLECAINIDE</b>	OL	1	1	1	1
<b>CARVEDILOL</b>	OL	1	1	0	0
<b>LANTUS</b>	L	1	1	0	0
<b>AMINOPHYLLINE</b>	OL	1	1	0	0
<b>BECLOMETHASONE</b>	L	1	1	0	0
<b>BACLOFEN</b>	L	1	1	0	0
<b>ESMOLOL</b>	OL	1	1	0	0
<b>PENTASA</b>	L	1	1	0	0
<b>LOPERAMIDE</b>	OL	1	1	0	0
<b>DEXTROS</b>	L	1	1	1	1
<b>FENTANYL</b>	L	1	1	0	0
<b>LANSOPRAZOLE</b>	OL	1	1	0	0
<b>VORICONAZOLE</b>	L	1	1	0	0
<b>FLECANIDE</b>	OL	1	1	0	0
<b>SLOW K</b>	L	1	1	0	0
<b>DALTEPARIN</b>	L	1	1	1	1
<b>CALCIUM</b>	L	1	1	0	0
<b>NOVORAPID</b>	L	1	1	0	0
<b>CETRIZINE</b>	L	1	1	0	0
<b>DOCUSATE SODIUM</b>	OL	1	1	0	0
<b>POTASSIUM CITRATE</b>	L	1	1	0	0
<b>NEOSTIGMINE</b>	UL	1	1	0	0
<b>ATENOLOL</b>	OL	1	1	0	0
<b>CARNITINE</b>	UL	1	1	0	0
<b>SODIUM VALPORATE</b>	L	1	1	0	0
<b>SODIUM FEREDETATE</b>	OL	1	1	0	0
<b>ENOXIMONE</b>	OL	1	1	0	0
<b>VITAMIN D</b>	L	1	1	0	0
<b>PEPTAC</b>	L	1	1	0	0
<b>PERIPHERAL DOPAMINE</b>	L	1	1	0	0
<b>FLECAINIDE</b>	UL	1	1	0	0



<b>METHYLEPREDNISOLONE</b>	L	1	1	0	0
<b>CIPROFLOXACIN</b>	L	1	1	0	0
<b>SODIUM CHLORIDE</b>	L	1	1	0	0
<b>NITROPRUSSIDE</b>	L	1	1	0	0
<b>SENNA</b>	OL	1	1	0	0
<b>LEVETIRACETAM</b>	OL	1	1	0	0
<b>PENICILLIN V</b>	L	1	1	0	0
<b>STIRIPENTOL</b>	L	1	1	0	0
<b>SODIUM PHOSPHATE</b>	OL	1	1	0	0
<b>POTASSIUM CANRENOATE</b>	L	1	1	0	0
<b>PANCURONIUM</b>	L	1	1	0	0
<b>RIFAMPICIN</b>	L	1	1	0	0
<b>GAVISCON</b>	OL	1	1	0	0
<b>VIGABATRIN</b>	OL	1	1	0	0
<b>SANDO-K</b>	L	1	1	0	0
<b>AMIKACIN</b>	L	1	1	0	0
<b>UROKINASE</b>	L	1	1	0	0

**Appendix 14: NICU prospective study medicines and associated problems**

<b>Medicine</b>	<b>Number of times medicine prescribed</b>	<b>Number of patients</b>	<b>Number of MRPs associated with</b>	<b>Number of patients developed MRPs</b>
<b>FENTANYL</b>	108	87	1	1
<b>BENZYL PENICILLIN</b>	92	87	45	45
<b>MORPHINE</b>	92	74	36	35
<b>DEXAMETHASONE</b>	91	87	0	0
<b>CEFOTAXIME</b>	89	87	0	0
<b>SODIUM CHLORIDE</b>	88	87	0	0
<b>CUROSURF</b>	87	87	0	0
<b>ATROPINE SULPHATE</b>	87	87	0	0
<b>GLYCERYL TRINITRATE</b>	87	87	0	0
<b>FOLIC ACID</b>	87	87	0	0
<b>CAFFEINE CITRATE</b>	87	87	0	0
<b>SUXAMETHONIUM CHLORIDE</b>	87	87	0	0
<b>PHYTOMENADIONE</b>	87	87	0	0
<b>PARACETAMOL</b>	82	74	9	9
<b>CLONIDINE</b>	71	66	4	4
<b>FUROSEMIDE</b>	52	51	27	27
<b>SPIRONOLACTONE</b>	49	47	0	0
<b>CEFUROXIME</b>	47	45	13	13
<b>POTASSIUM CHLORIDE</b>	40	38	0	0
<b>MILRINONE</b>	39	39	0	0
<b>ROCURONIUM</b>	32	30	0	0
<b>LACTULOSE</b>	25	25	0	0
<b>KETAMINE</b>	20	18	0	0
<b>PROPOFOL</b>	20	19	0	0
<b>CO-AMOXICLAV</b>	18	17	16	15
<b>IBRUPOFEN</b>	17	16	0	0
<b>GENTAMICIN</b>	11	11	4	4
<b>LORAZEPAM</b>	10	9	0	0
<b>CHLORPHENIRAMINE</b>	10	10	0	0
<b>DOPAMINE</b>	9	9	0	0
<b>ADENOSINE</b>	9	2	9	2
<b>ASPRIN</b>	9	9	1	1
<b>OMEPRAZOLE</b>	9	9	0	0
<b>PANTOPRAZOLE</b>	8	8	0	0
<b>MIDAZOLAM</b>	8	8	0	0
<b>CEFTRIAZONE</b>	7	7	0	0
<b>CAPTOPRIL</b>	7	7	0	0
<b>FLUCLOXACILLIN</b>	7	7	1	1

<b>PREDNISOLONE</b>	7	7	0	0
<b>SYTRON</b>	7	7	1	1
<b>ACICLOVIR</b>	6	6	0	0
<b>SALBUTAMOL</b>	6	5	0	0
<b>AMIODARONE</b>	6	4	0	0
<b>ONDANSETRON</b>	6	6	0	0
<b>GLYCERIN</b>	5	5	0	0
<b>PHENYTOIN</b>	5	4	1	1
<b>HEPARIN</b>	5	5	0	0
<b>CLINDAMYCIN</b>	4	4	0	0
<b>DOMPERIDONE</b>	4	4	0	0
<b>DALTEPARIN</b>	4	3	0	0
<b>SILDENAFIL</b>	4	4	0	0
<b>ADRENALINE</b>	4	4	4	4
<b>KAY-CEE-L</b>	4	4	0	0
<b>VITAMIN K</b>	4	4	0	0
<b>ABIDEC</b>	3	3	0	0
<b>METRONIDAZOLE</b>	3	2	0	0
<b>TEICOPLANIN</b>	3	3	0	0
<b>NORADRENALINE</b>	3	3	0	0
<b>DIGOXIN</b>	3	2	1	1
<b>MORPHINE</b>	3	3	1	1
<b>CYCLIZINE</b>	3	3	0	0
<b>MOVICOL</b>	3	3	0	0
<b>ALFACALCIDOL</b>	2	2	2	2
<b>DNASE</b>	2	2	0	0
<b>AMOXICILLIN</b>	2	2	2	2
<b>MAGNESIUM SULPHATE</b>	2	2	0	0
<b>PHENOBARBITONE</b>	2	1	0	0
<b>LISINOPRIL</b>	2	2	0	0
<b>TRANEXAMIC ACID</b>	2	2	1	1
<b>RANITIDINE</b>	2	2	0	0
<b>CLOBAZAM</b>	2	2	0	0
<b>LEVOTHYROXINE</b>	2	2	0	0
<b>PROPRANOLOL</b>	2	2	0	0
<b>FLUCONAZOLE</b>	2	1	0	0
<b>DALIVIT</b>	2	2	0	0
<b>MEROPENEM</b>	2	2	0	0
<b>CO-AMOXICLAV</b>	2	2	2	2
<b>DINOPROSITONE</b>	2	2	0	0
<b>MONTELUKAST</b>	2	2	0	0
<b>ORAMORPH</b>	2	2	0	0
<b>CLARITHROMYCIN</b>	2	2	0	0
<b>TRIMETHOPRIM</b>	2	2	0	0
<b>DOCUSATE SODIUM</b>	1	1	0	0

PENICILLIN V	1	1	0	0
ACETAZOLAMIDE	1	1	0	0
IPRATROPIUM	1	1	0	0
SANDO-K	1	1	0	0
VANCOMYCIN	1	1	1	1
TAZOCIN	1	1	0	0
BUDESONIDE	1	1	0	0
VANCOMYCIN	1	1	0	0
MUPIROCIN	1	1	0	0
LANSOPRAZOLE	1	1	0	0
LANTUS	1	1	0	0
NYSTATIN	1	1	0	0
SODIUM VALPORATE	1	1	0	0
POTASSIUM CITRATE	1	1	0	0
ACTRAPID INSULIN	1	1	0	0
AMIKACIN	1	1	1	1
NOVORAPID	1	1	0	0
SERETIDE	1	1	0	0
RIFAMPICIN	1	1	0	0
CIPROFLOXACIN	1	1	1	1
PERIPHERAL DOPAMINE	1	1	0	0
GLYCOPYRROLATE	1	1	0	0
AZITHROMYCIN	1	1	0	0
ENOXIMONE	1	1	0	0
BACLOFEN	1	1	0	0
GAVISCON	1	1	0	0
CALCIUM	1	1	0	0
NALOXONE	1	1	0	0
CARNITINE	1	1	0	0
STIRIPENTOL	1	1	0	0
ESMOLOL	1	1	0	0
FENTANYL	1	1	0	0
CARVEDILOL	1	1	0	0
SODIUM PHOSPHATE	1	1	0	0
MAGNESIUM GLYCOPHOSPHATE	1	1	0	0
DALTEPARIN	1	1	1	1
METHYLEPREDNISOL ONE	1	1	0	0
LOPERAMIDE	1	1	0	0
FLECAINIDE	1	1	0	0
BECLOMETHASONE	1	1	0	0
PEPTAC	1	1	0	0
NEOSTIGMINE	1	1	0	0
PROSTIN	1	1	0	0

<b>DIHYDROCODIENE</b>	1	1	1	1
<b>POTASSIUM CANRENOATE</b>	1	1	0	0
<b>LEVETIRACETAM</b>	1	1	0	0
<b>OMEPRAZOLE</b>	1	1	0	0

### Appendix 15: Summary of the three studies' findings

Setting	Design	Total patients	Patients with MRPs	Total medicines	Medicines with MRPs	Total MRPs	Total L	L with MRPs	Total OL & UL	OL & UL with MRPs	MRPs categories	MRPs severity	preventability
PICU	Retrospective study	194	53% (102)	2000	8% (165)	165	1085	7% (71)	915	10.3% (94)	84% ADRs & 16% TEs	5% no harm 71% low harm 24% moderate harm	30.3%
PICU	Prospective study	147	79% (116)	1578	11% (178)	178	831	9% (72)	747	14.2% (106)	83% ADRs & 17% TEs	6% no harm 72% low harm 22% moderate harm	34%
NICU	Prospective study	87	90% (78)	1978	9% (186)	186	1139	9% (103)	839	10% (83)	100% ADRs	6% no harm 92% low harm 2% moderate harm	None