Can Electronic Prescribing Prevent Harmful Paediatric Prescribing Errors?

By

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Declaration

Whilst registered as a candidate for the above degree, I have not been registered for any other research award. The results and conclusions embodied in this thesis are the work of the named candidate and have not been submitted for any other academic award

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Abstract

Introduction

Electronic prescribing (EP) has been shown to be effective in reducing prescribing errors in a range of settings including paediatrics. However, the lack of a consistent definition of error and a variety of error detection methods makes it difficult to draw conclusions about the impact on patients. An ability to clearly understand and consistently measure how EP systems can prevent harmful prescribing errors in children is, therefore, required. In addition, an evaluation of a range of EP systems in current use can help to gain an understanding of how to improve EP in the future. The aims of this work were to: firstly develop a range of paediatric prescribing indicators that are likely to cause harm if prescribed. Secondly, test a range of EP and clinical decision support (CDS) systems currently in use for their ability to prevent the errors described by the paediatric prescribing indicators.

Method

An eDelphi consensus study was carried out with 21 expert panellists from the UK. Panellists were asked to score each prescribing error for its likelihood of occurrence and severity of outcome should the error occur. Indicators were included in the final list if a consensus of 80% or higher was achieved and were in the high risk categories. The indicators were then sent to a group of hospitals using EP in their paediatric departments. The paediatric pharmacists simulated the indicators in their EP systems and provided feedback on whether the error could be prescribed and what level of CDS was presented to the prescriber during the prescribing process.

Results

In the consensus process two rounds of scoring took place. These identified 41 paediatric prescribing indicators with a high risk rating and greater than 80% consensus. The most common error type within the indicators was dose (n = 19) and the most common drug classes were antimicrobial (n = 10) and cardiovascular (n = 7). The indicators were converted into a set of prescribing errors which were then tested using eight different EP systems across 15 different sites. In 90% of tests the error was permitted by the EP system i.e. it was possible to prescribe the error. Levels of CDS varied, both between different systems and the same system at different sites. Allergy, drug name and therapeutic duplication errors were most likely to be prevented by the CDS. Drug-drug interactions, clinical contraindications and duration errors were least likely to be prevented.

Conclusions

A set of 41 paediatric prescribing indicators describing potential harm for the hospital setting were successfully identified. Simulation of the errors in EP systems in use in the UK showed that the majority of them would not be prevented. Post-prescribing checks were in place to prevent the errors reaching the patients. The future development and implementation of EP and CDS for the paediatric population needs to take into account the different requirements for paediatric patients. Careful development of intelligent CDS in order to ensure paediatric patients are protected from prescribing errors likely to cause harm is also required.

Contents

List of Tables

List of figures

Abbreviations

Abbreviation	Definition
ABW	Actual Body Weight
ACE	Angiotensin Converting Enzyme
ADE	Adverse Drug Event
ADH	Anti-Diuretic Hormone
ADR	Adverse Drug Reaction
ARB	Angiotensin Receptor Blocker
AZT	Zidovudine
BNF	British National Formulary
BNFC	British National Formulary for Children
BSA	Body Surface Area
CDS	Clinical Decision Support
CF	Cystic Fibrosis
CI	Confidence Interval
CMO	Chief Medical Officer
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclo Oxygenase-2
CPOE	Computerised Physician Order Entry
DE	Dispensing Error
DKA	Diabetic Ketoacidosis
DoH	Department of Health
EC	Enteric Coated
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Authority
eMAR	Electronic Medication Administration Record
EP	Electronic Prescribing
EPMA	Electronic Prescribing and Medicines Administration
HRA	Health Research Authority
IBW	Ideal Body Weight
INR	International Normalised Ratio
iu	International Units
IV	Intravenous
LFT	Liver Function Tests
MAE	Medication Administration Error
ME	Medication Error
MHRA	Medicines and Healthcare Regulatory Authority
MPE	Medication Prescription Errors
NHS	National Health Service
NHSE	National Health Service England

Abbreviation	Definition
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Healthcare Research
NPPG	Neonatal and Paediatric Pharmacists Group
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning Service
NSAID	Non-Steroidal Anti-inflammatory Drug
NYHA	New York Heart Association
OE	Opportunity for Error
PE	Prescribing Error
PICU	Paediatric Intensive Care Unit
PIL	Patient Information Leaflet
PN	Parenteral Nutrition
PO	Per Orum (oral administration)
PSI	Patient Safety Incident
RCPCH	Royal College of Paediatrics and Child Health
RR	Risk Ratio
RV	Rule Violations
SC	Subcutaneous
SEM	Standard Error of the Mean
SSRI	Selective Serotonin Reuptake Inhibitor
u	Units
UHS	University Hospital Southampton
UK	United Kingdom
US	United States (of America)
VTE	Venous Thrombo-embolism
WHO	World Health Organization

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Chapter 1 Introduction

This thesis reports a programme of research into paediatric prescribing errors, the development of a set of paediatric prescribing indicators and the use of these indicators to test the ability of a range of electronic prescribing systems to prevent them. Chapter 1 will summarise the current knowledge and thinking around medication errors generally, focussing on prescribing errors in children. Methods used to determine their causes and impact will also be discussed. The chapter concludes with a statement of the aims and objectives of the author's research. Chapter 2 will describe the process of developing a set of paediatric prescribing indicators from a wide range of sources. Chapter 3 will describe the process of gaining consensus on the indicators in order to create a list of prescribing errors likely to cause harm. Chapter 4 will describe the use of these indicators to test a range of electronic prescribing (EP) systems in use in the UK. Finally Chapter 5 will provide a discussion of the whole programme of research along with limitations, future work and make conclusions.

1.1 Background

The increase in understanding of the extent and consequences of adverse events in healthcare over the preceding 15 years has resulted in a number of large scale policy changes in both the UK and the US. The landmark Harvard Medical Practice Study found that an adverse event occurred in 3.7% of hospital admissions in the US.[1, 2] Estimates in the UK suggest that adverse events occur in 10% of hospital admissions equivalent to around 850,000 events per year, costing approximately £2bn a year in additional hospital stays.[3]

As a result of this increased awareness, the Chief Medical Officer published a report in 2000, "An Organisation With A Memory"[3] which described the necessity to promote patient safety by reducing errors. It acknowledged that the UK like many other countries' had little systematic learning from adverse events and service failures. The report highlighted many types of adverse event and attributed a significant cost to them both in terms of additional hospital stays and litigation. A similar report had been published in the US.[4] These two reports acknowledged that both system failures and human factors contributed to errors. They also acknowledged the potential contribution of new technology to improve patient safety.

The Department of Health's response to this report was to publish a series of documents outlining its plans for implementing the recommendations from "An Organisation With A Memory". Firstly "Building a safer NHS for Patients"[5] outlined the development of a national system for learning from error and adverse events and the creation of a new independent body, the National Patient Safety Agency (NPSA), with the core aim of improving patient safety by reducing the risk of harm through error.

Secondly in January 2004 a comprehensive report was published specifically relating to the issue of medication errors within the NHS outlining numerous actions and recommendations for all areas of the NHS to improve patient safety and reduce medication errors.[6] The NPSA went on to develop the National Reporting and Learning System (NRLS) which has since become a vast repository of patient safety incidents reported within healthcare in the UK. Medication errors form a significant proportion of the reported incidents and as such, the NPSA produced numerous alerts and reports in an attempt to reduce harm from specific medication errors.[7-9]

1.2 Definitions

To enable a proper exploration and understanding of the area of adverse events in healthcare a good understanding of some of the key terminology is essential. Definitions of key terms relevant to this thesis and in their relation to healthcare are summarised in Table 1.1.

Table 1.1 Definitions of common terms used in this thesis

Term	Definition
Adverse event	Any event or circumstance leading to unintentional harm or suffering[10]
Patient safety incident (PSI)	Any unintended or unexpected incident which could have or did lead to harm for one or more patients receiving healthcare[10]
Adverse drug event (ADE)	Injury resulting from medical intervention related to a drug[11]
Adverse drug reaction (ADR)	A response to a medicinal product that is noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse, off-label use and abuse of the medicinal product.[12]

Medication Error (ME)	A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care 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[13]
Prescribing Error (PE)	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice[14]
Dispensing Error (DE)	An unintended deviation from an interpretable written prescription or medication order, or any unintended deviation from professional or regulatory references, or guidelines affecting dispensing procedures, was also considered a dispensing error[15]
Medication Administration Error (MAE)	A deviation from the prescriber's medication order as written on the patient's chart, manufacturers' preparation/administration instructions, or relevant institutional policies[16]

1.2.1 Adverse Events

Studies relating to adverse events experienced by patients and their impact use a variety of definitions to describe the various different types of event.

The Harvard Medical Practice study published in 1991[1, 2] was a landmark study conducted in the US; the authors defined an adverse event as “an unintended injury that was caused by medical management and that resulted in measurable disability”. By this definition, therefore, events which do not cause harm are excluded. However, as the understanding of the nature and causes of these incidents has increased, an awareness of the need to include “near misses” has necessitated an evolution of the definition to remove the need for harm to have occurred. In the UK the NPSA has defined both adverse events and patient safety incidents (Table 1.1). Patient safety incidents are a subset of adverse events.

Medication errors, therefore, are a subgroup of patient safety incidents. The US National Co-ordinating Council for Medication Error Reporting and Prevention has the most comprehensive definition of a medication error[13]:-

> *"A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care 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."*

This definition is also used by the NPSA in the UK and the World Health Organization.

Medication errors therefore, are preventable and many do not cause harm.[7] For example a dispensing label describing the formulation as tablets rather than capsules, or a prescription for omeprazole twice a day when the intention was for the patient to receive it once a day.

Some medication errors can cause an adverse drug reaction; for example if the wrong dose of a drug is prescribed and administered, there is an increased likelihood of a toxic effect if the dose is too high. These reactions, caused by a medication error are preventable. However, a proportion of adverse drug reactions are idiosyncratic and therefore, not predictable or preventable. Many studies do not distinguish between errors and adverse drug reactions which can be important when evaluating the results.

Many published studies use the term adverse drug event (ADE) which includes both medication errors and adverse drug reactions (ADR). The term ADE was used by the early researchers as a definition in order to include harm resulting from drugs being used inappropriately. It therefore includes most of the preventable drug-related harm that occurs to patients due to errors.[17] More recently both the European Medicines Authority (EMA) and the Medicines Healthcare Regulatory Authority (MHRA) have amended their definition of an ADR. The MHRA definition is:

> *"An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility".*[12]

It therefore, includes both reactions caused by the normal use of a medicinal product as well as reactions caused by a medication error.

1.3 Medication Errors

The use of medication to treat disease, alleviate symptoms and prevent illness is the most common intervention used in healthcare. The vast majority of medication does not cause harm. Analysis of medication errors reported to the National Reporting and Learning System (NRLS) suggests that 80% of medication errors cause no harm.[7] However, all medicines carry some level of risk. Patients can experience adverse reactions from the medicines they take and the pharmaceutical industry and government bodies such as the MHRA collects information on these as part of a post marketing surveillance strategy.

The precise incidence of medication errors in the NHS is not known. There is no clear definitive research detailing the incidence of medication errors as a whole in the UK. In the US, early work by Bates *et al*[11] reported a rate of actual ADEs as 6.1% and potential ADEs as 5.5% of admissions. In the UK, preventable ADEs are thought to cost an estimated £750 million.[7] The audit commission report "A spoonful of sugar" quoted an increase in deaths from medication errors from 20 to 200 per year from 1990 to 2000.[18] It is often more useful to group medication errors by the part of the drug use process in which they occurred e.g. prescribing, dispensing and administration.

Reports of prescribing error rates vary between 9 and 15% of medication orders in the UK,[19, 20] and can often cause considerable harm to patients.[21] The EQUIP study by Dornan *et al*[20] used pharmacist intervention methodology to identify prescribing errors made by hospital doctors in a range of hospitals in the UK. The mean prescribing error rate was 8.9 per 100 medication orders. It was noted that errors were most often made at the time of the patient's admission.

Dispensing errors are specifically confined to the pharmacy department. Beso *et al*[22] studied dispensing error rates in a busy hospital pharmacy and reported the rate as 2.1% for errors identified within the pharmacy (internal errors) and 0.02% for errors identified outside of the pharmacy (external errors).

Medication administration errors (MAE) are less commonly studied and reported incidences vary between 5.6 and 19% of error opportunities.[23, 24] One problem with the MAE literature is a lack of clear definition of an

administration error. A review of MAE studies looking at methodological variance[25] identified 16 reports with three different error definitions. The overall MAE rate was calculated as 5.6% for non-IV error opportunities. The use of opportunity for error (OE) as a denominator in MAE studies has become common practice and allows studies to be compared with more rigour. This review included studies undertaken on both adult and paediatric wards. A second review looking specifically at the prevalence of MAE in health care settings, identified a mean of 19.6% error rate when wrong time errors were included and a rate of 8% when wrong time errors were excluded.[16]

By categorising medication errors into these functional groups it is possible to address the solutions to the specific errors in a more targeted way.

1.4 Medication Errors in Children

Studies of medication error rates in children have not been reported as extensively as in adults. Those paediatric studies that have been published tend to concentrate on prescribing errors.[26, 27] Kaushal *et al*[28] reviewed medication orders for ME, potential ADEs and ADEs in paediatric hospital units. The results were then compared with previously published adult work. While the ME rates were similar between adults and children the potential ADE (medication errors with the potential to cause an adverse event) rate was three times higher. Holdsworth *et al*[29] prospectively reviewed medical records for ADEs and potential ADEs for paediatric inpatients. They reported a rate of 6 per 100 admissions for ADEs and 8 per 100 admissions for potential ADEs. These results suggested that the errors were common in hospitalised children; in particular those with more complicated medical conditions. Specific error types have also been investigated within the paediatric setting. Ghaleb *et al*[30] studied both the prescribing and administration error rate in children admitted to five London hospitals. The prescribing error rate was 13.1% of medication orders and the administration error rate was 19.2% of OE. A study involving a specialist paediatric hospital in north west England reported an error rate of 7% of medication orders.[31]

It is clear from these reports that there is a significant ME rate within the hospital paediatric population which in some cases considerably exceeds reported rates for adults.

Medication ordering is one of the most complex aspects of medical care, requiring physicians to simultaneously integrate a thorough understanding of available medicines, disease processes and patient specific information in the context of a particular clinical circumstance.[32] This increased error rate could be due to the added level of complexity of prescribing for children with the need to take into account weight, clinical indication, altered physiology and pharmacokinetics.

Since medication related harm is associated with a substantial proportion of potentially avoidable mortality and morbidity in both adults and children there is a considerable focus of attention on improving prescribing safety.[3, 6]

1.5 Causes of Medication Error

To help understand how medication errors occur it is important to have an understanding of their classification which can be contextual, modal or psychological. Contextual classification relates to the time and place at which an error occurred. Categories such as prescribing, dispensing and administration errors are commonly used contextual classifications. The literature on medication errors usually uses this type of classification and reports will often include a single type of error such as prescribing errors. The advantage of using this classification is that it helps to focus solutions in a particular area. Further sub-classification of medication errors is also common (Table 1.2). These categories are used by the NRLS and aid the thematic analysis of medication errors. In addition, within a single institution such as University Hospital Southampton (UHS) this classification is used in a similar way. It allows one to interrogate the ME database and to target specific areas that may require improvement, such as prescriptions for the wrong dose of a specific drug or dispensing errors involving drugs with similar sounding names.

Table 1.2 Common error types and their description

Error Type	Description	Example
Contraindication	Contraindication to use of the medicine in relation to drugs or conditions	Warfarin prescribed to a patient with active bleeding
Mismatching between patient and medicine (wrong patient)	Patient given someone else's medicine	Patient administered enoxaparin intended for another patient
Omitted Medicine/ingredient	Omission or delay in a patient receiving a dose of a drug at the correct time	Lack of stock of medicines on a ward leads to a missed dose
Patient allergic to treatment	Patient administered a medicine to which they have a documented allergy	Amoxicillin prescribed to a patient with a documented allergy to penicillin
Wrong/omitted/passed expiry date	Use of a drug beyond its expiry date.	Administration of a dose of co-amoxiclav suspension that has past its expiry.
Wrong/omitted patient information leaflet (PIL)	Usually dispensing of a medicine with the wrong leaflet	Dispensing a pack of aspirin without the PIL
Wrong/omitted verbal patient directions	Providing the wrong (or no) instructions during a verbal counselling episode	Failing to counsel a patient about their newly started warfarin therapy
Wrong/transposed/ omitted medicine label	Any mistake in the labelling of a medicine, usually at dispensing	Patient dispensed two medicines with the labels on the wrong packaging.
Wrong/unclear dose or strength	Wrong doses	Child prescribed 10mg/kg of ranitidine instead of 1mg/kg
Wrong drug	Wrong drug	Amiloride dispensed instead of amlodipine
Wrong formulation	Wrong formulation	Solid dose form prescribed instead of liquid
Wrong frequency	Correct drug and correct dose but used at the wrong frequency	Paracetamol 1g administered more frequently than every 4 hours.
Wrong method of preparation/supply	Incorrect preparation of a medicine	Erythromycin injection reconstituted with sodium chloride 0.9% instead of water for injection
Wrong quantity	Wrong quantity of a medicine provided to a patient	1 week course of flucloxacillin provided instead of the necessary 2 week course.
Wrong route	Medicine prescribed or administered by the wrong route	Depot Intramuscular injection administered intravenously
Wrong storage	Medicine stored inappropriately	Infliximab injection stored at room temperature rather than in the refrigerator

Modal classification describes the way in which an error occurs e.g. omission, substitution. These types of error can occur in any of the contexts mentioned above. Errors of omission occur commonly when prescribing for patients on admission to hospital. Without a clear drug history prescribers can fail to prescribe all the medicines required for their patients, resulting in omitted or

delayed doses. The process of medicine reconciliation is designed to reduce this type of error and is now seen as an integral part the hospital admission process as well as at other points at which care is transferred.[33, 34]

The use of a psychological classification helps to better explain events than pure description and is based on work by James Reason.[35, 36] The advantage of this classification is that it uses a generic error-modelling system that can be applied to all types of human error. This allows comparison with other industries in which errors have significant consequences such as the aviation industry. The disadvantage is that it tends to focus on the individual making the error rather than the system they are working in.

This is not the only approach to looking at human error. Jens Rasmussun also made a case that human error cannot be studied independently of individual working within an institution, but rather within the context of their work. His work related to human error in the context of the Dutch Nuclear Industry.[37] He suggested that the human worker is in a continuous state adaptation and learning. His work is similar in nature to that of James Reason but presents an extremely complex view of the nature of human error and psychology, making it, in the opinion of the author, less useful as a way to help healthcare workers gain an understanding of human error and the reasons why errors occur.

The underlying theories proposed by Reason have been applied to a medication safety and specifically a prescribing context by Aronson *et al*.[38] The key error types are outlined below together with appropriate examples.

Knowledge-based Error

An error caused by lack of knowledge of the patient or drug (or both). Examples include prescribing gentamicin without taking into account the patient's reduced renal function, or prescribing a penicillin containing antibiotic without knowing the patient's allergy status. These types of errors ought to be avoidable with adequate knowledge and access to reliable up to date information. Interception of such errors can occur by using computerised decision support and cross checking by pharmacists and nurses. Clearly education and training has a major role to play in helping to avoid knowledge based errors.

Rule-based Error

The use of an inappropriate/bad rule or applying a good rule in the wrong way. An example could be prescribing a solid formulation for a patient with a naso-gastric tube when there is a suitable liquid alternative.

Action-based Error

Action based errors are often referred to as slips. The intended action is correct, but a slip in attention results in an error. For example, having the intention to prescribe cefotaxime but selecting cefuroxime on the electronic system; writing clonazepam instead of the intended clobazam; or picking up a bottle of sodium chloride oral solution instead of sodium bicarbonate. One way of helping to prevent these errors is to create conditions in which they are unlikely. In the last example above having different packaging and labelling for the two similar preparations, or stocking only the most commonly used preparation. Technical errors such as adding the wrong diluent to an injection or writing illegibly are also classed as action-based errors. They may be reduced by the use of checklists and reminders. Electronic prescribing (EP) systems have the potential to influence this type of error.

Memory-based Errors

Often regarded as lapses, an example might be forgetting to specify a maximum frequency for a prescription for "when required" paracetamol; or knowing a patient is allergic to penicillin but forgetting. These types of errors are hard to avoid or prevent; some electronic prescribing systems have the functionality to reduce these types of error.

Latent Factors

The psychological classifications detailed above are referred to as active failures. Humans work within systems and there are several properties of systems that can make them more error prone. In the case of medication errors these latent factors may increase the likelihood of an error occurring.

1.5.1 Causes of Medication Errors in Children

The most commonly reported medication error in children is wrong dose.[7] This is to be expected when the vast majority of doses need to be individualised using either the patient's age, weight or in some instances body surface area (BSA). This increases the opportunity for error. In particular the need to calculate a dose heightens the risk of error with mathematical operations, decimal points, trailing zeros and various units of measure.

Added to this is the lack of availability of appropriate commercially available formulations which enable children's doses to be easily administered. A lack of knowledge of these formulations and concentrations can lead to significant dosing errors.

The lack of an appropriate formulation can necessitate the use of an unlicensed medicine or "special". These formulations may be used by a specific hospital and may not be readily available in the community. This can increase the risk of missed doses when a preparation is only available from a single supplier that might not be recognised by the community pharmacy.

Unfamiliarity with the paediatric population has also been cited as contributing to medication errors in children.[39]

1.6 Reducing Medication Errors

In this section strategies and solutions for reducing medication errors are discussed, particularly in relation to paediatric medication errors. The role of electronic prescribing specifically is reviewed in Section 1.8

1.6.1 Individual Perspective

General Principles of Good Prescribing

The ten principles of good prescribing (see Table 1.3) are included in a paper by Aronson.[38] They follow the natural process of prescribing and take into account the patient, the drug and the prescriber. They are completely generalisable to all prescribing.

Table 1.3 Principles of good prescribing[38]

Area	Description
Indication	Be clear about the reasons for prescribing and the risks and benefits.
History	Take into account the patient medication history (including over the counter medicines and allergies)
Diseases	Take into account other factors/co-morbidities that might alter the benefits and harms of treatment (e.g. renal function)
Patient	Take into account the patients/carers expectations and concerns
Effectiveness	Select effective, safe and cost effective medicine. Consider benefit versus harm, best formulation, dose regimen and individualisation
Information	Utilise national and local guidelines
Order	Write clearly with an awareness of common mistakes that lead to error.
Monitor	Monitor the treatment
Communicate	Ensure your prescribing decisions are clearly documented, take particular care in relation to healthcare interfaces
Knowledge	Prescribe within the limitations of your knowledge

1.6.2 Prescribing for Children - Additional Measures

Bearing in mind the general principles in Table 1.3 and the causes of medication errors in children there are some specific points that must be considered when prescribing for children.[40]

- Age and Weight - Check that information is accurate and up to date.
- Dose rounding. Doses need to be rounded to an amount that can be easily administered yet are still suitable for the individual patient. A knowledge of the available formulations is essential.
- Calculations – Complex calculations should be double checked by a second party; for critical or high risk medicines; calculations should be documented.

Drug Administration

Nursing staff should utilise the 6 'rights' of medicine administration[41] ensuring the right:-

- Patient
- Drug
- Route
- Dose
- Frequency
- Documentation

This list while easy to recall could be argued does not contain all the elements that require a check at the point of administration. Specifically formulation is not included. There are specific groups of patients for whom the correct formulation is vital such as infants, children and patients with enteral feeding tubes. In addition, an acknowledgement that there is a patient at the end of the administration process could also be considered. This may seem obvious but responding to any patient queries in relation to the administration is paramount. Their concerns should be listened to and checks made with the prescriber.

1.6.3 Organisational Perspective

In addition to ensuring safe working environments, there are several organisational initiatives that can help to reduce medication errors. Standardising equipment and prescription charts have been cited as possible ways to improve medication safety.[20] A well developed reporting system and fair blame culture is also vital to reduce barriers to reporting errors and aid learning.[42] The work of the NRLS has been vital in this regard and safety

warnings based on the reported medication errors are regularly published.[43] There is no direct evidence to show the importance of communication in preventing drug errors; however conclusions may be drawn from analysis of identified errors. This is supported by Fortescue *et al*[44] who noted that 47.4% of inpatient drug errors could have been prevented by improved communication between doctors and patients.

Clinical Pharmacy Service

A systematic review of the interventions of hospital pharmacists in improving drug therapy in children[45] concluded that pharmacist review of medication charts was very important in identifying medication errors and is likely to be the most effective method of improving drug therapy in children. The conclusion was based on a review of 14 studies, reporting on the interventions made by hospital pharmacists on paediatric patients. There was one UK based study by Guy *et al*[46] which reviewed interventions by both pharmacists and nursing staff to prevent prescribing and administration errors in a specialist children's hospital. Over 4 weeks the pharmacists detected 190 interventions, 0.5% of which were regarded as life threatening. A more recent study, not included in the review, reported on prescribing errors intercepted by pharmacists in the paediatric and obstetric setting of a tertiary hospital in Spain.[47] While one of the aims of this study was to observe any difference between the interventions in the two clinical settings, the paediatric intervention rate was 2.4%. All the interventions were scored for severity; of the 1357 paediatric interventions 224 (16.5%) were deemed at least serious in nature.

Education and Training

The Department of Health highlighted the importance of both training and competency assessment for junior doctors in paediatrics.[6] Davey *et al*[48] showed that prescribing errors by junior doctors could be reduced by 46% following the introduction of a prescribing tutorial. The introduction of a bedside prescribing guideline, however, did not have an effect on error rate. In a controlled study, Gordon *et al*[49] showed a significant difference (63% versus. 79% $p<0.0001$) in the scores on a prescribing assessment between two groups of junior doctors, one of which had completed an e-learning intervention. The positive impact of the intervention remained even after three months, with the e-learning group showing significantly higher scores.

1.7 Electronic Prescribing

1.7.1 Description and Definitions

Electronic prescribing was defined in the UK by Connecting for Health in 2009:

> *The utilisation of electronic systems to facilitate and enhance the communication of a prescription or medicine order, aiding the choice, administration and supply of a medicine through knowledge and decision support and providing a robust audit trail for the entire medicines use process.*[50]

This definition clearly covers all the aspects of, not just the prescribing process but the entire medicines use process. A common misconception is that electronic prescribing is just the electronic transmission of prescriptions between care settings. Another term that is also used to describe electronic prescribing particularly in the US, is Computerised Physician Order Entry (CPOE). This can cover other types of order made by medical staff in addition to medicines.

1.7.2 Effect on Medication Errors

The effect of electronic prescribing or CPOE on medication errors has been the subject of several review articles in the last 15 years.[51-56] The earliest review by Kaushal *et al*[55] published in 2003, was a systematic review of CPOE and clinical decision support (CDS) systems on medication safety. A total of 12 studies were identified some of which assessed isolated CDS devoted to a specific drug group such as antibiotics or specific drugs such as theophylline. The authors concluded that the use of CPOE and isolated CDS can substantially reduce medication error rates. The most recent systematic review by Radley *et al*[52] identified 16 studies and undertook a meta analysis to derive a summary estimate of the effect of CPOE on medication errors. They concluded that:

> *CPOE can substantially reduce the frequency of medication errors in inpatient acute settings; however, it is unclear whether this translates into reduced harm for patients.*[52]

1.8 Impact of Electronic Prescribing in the Paediatric Population

The following section is devoted to the literature review. In addition to the search strategy this section contains two sub-sections dealing with the detection of medication errors and clinical decision support (CDS). It is

important to have an understanding of both of these areas when appraising the literature.

1.8.1 Search Strategy

An extensive search of the published literature was carried out using the following search terms: prescribing, error, paediatrics, children, infants, electronic prescribing, e-prescribing, medication error, administration error and dispensing error. The following databases were interrogated, Embase, Medline, and CINAHL using the search strategy listed in Appendix 1.

1.8.2 Medication Error Detection

Reporting a medication error (as with all errors) in the NHS is voluntary and reactive and as a result, not all errors are reported in this way.[57] When reviewing any evidence relating to the rate of medication errors or one of the specific processes such as prescribing, it is vital to take into account not only the definition of an error used in the study, but also the method of identification. There is no gold standard method of identifying prescribing errors[58] and this can be assumed for all types of medication error. Table 1.4 lists the common types of detection method their advantages and disadvantages.

Table 1.4 Medication error detection methods

Method	Description	Advantages	Disadvantages	Example(s)
Pharmacist Intervention	Pharmacist documentation of errors identified during prescription monitoring process	Easy to undertake as part of normal working patterns	Tends to focus on prescribing errors rather than other processes	Equip Study[20] Ghaleb *et al*[30] Dean *et al*[59]
Incident Report Analysis	Review of spontaneous routine incident reports	Easy to interrogate and collect	Relies on spontaneous reporting so significantly under -reports	Ross *et al*[60] Sari *et al*[57]
Trigger Tool	Screening for specific triggers such as abnormal laboratory results or prescriptions for antidotes such as flumazenil	Targets specific incident types which cause high levels of harm	Time consuming, may miss low level errors.	Rozich *et al*[61]
Record Review	Retrospective review of healthcare records	Comprehensive	Time consuming, relies on small number of individuals to	Woloshynowych *et al*[62] Neale *et al*[63]

			identify incidents. Relies on comprehensive and accurate records	
Observation	Direct observation of a part of the medication use process	Accurate, likely to spot error that may have not been considered	Observation bias – staff may be less likely to undertake their normal routines or workarounds in the knowledge that they are being observed	Ghaleb *et al*[30]

The sensitivity of a routine system for reporting patient safety incidents was studied by Sari *et al.*[57] They retrospectively reviewed the case notes of 1,006 hospital admissions for patient safety incidents. This information was then compared with the reports submitted to their incident reporting system. They identified 325 incidents, of which only 10% had been reported using the incident reporting system. This would suggest that a large proportion of patient safety incidents are not reported. Errors that do not reach the patient or have been considered as causing no harm are rarely reported. Other barriers to reporting may include fear of discipline and lack of error awareness.[42]

In addition it is difficult to compare results when different denominators are used to calculate rates; this is where the development of prescribing indicators can help to level the playing field in relation to comparing results.

1.8.3 Clinical Decision Support

When reviewing the literature in relation to electronic prescribing, one important element of a system to consider is the level of clinical decision support (CDS). Table 1.5 lists the most common elements of CDS with an associated description and a classification for the purpose of the literature review. This list was derived from the descriptions used in the papers that were reviewed and the taxonomy used by Stultz *et al.*[64] In addition the author has further categorised each functionality into basic or advanced to enable systems described in the literature to be easily distinguished.

Table 1.5 Clinical decision support details and category

Description	Detail	Basic/Advanced
Allergy Checking	System checks the patient's allergies with the drug being prescribed and warns prescriber.	Basic
Drug-Drug Interaction	System checks for known drug interaction and provides warning to prescriber often with details of cause of interaction and possible consequence.	Basic
Therapeutic Duplication	Prescriber is warned when a drug is selected in a similar therapeutic class to one already prescribed.	Basic
Order sets - Basic	Pre-defined orders of specific combinations of treatment which can be selected to enable ease of use e.g. acute post-op pain order set.	Basic
Hard Stop	System allows entry of stop date for a prescription at which time the prescription stops without review	Basic
Soft Stop	System allows entry of a date for review of the prescription. Prescription is not necessarily stopped but alert provided to users requesting a review.	Basic
Dose Range Checking	Checking the dose entered against a pre-existing dose range for the patients weight. Prescriber is provided with a warning if the dose is outside pre-set limits.	Advanced
Clinical Rules	Prescription is automatically checked against the patients clinical parameters such as diagnosis, renal function and liver function and an order amended or warning provided	Advanced
Dose Rounding	Automatic rounding of a dose to a suitable value based on formulation and variation	Advanced

1.8.4 Literature Review

A search for studies investigating the impact of electronic prescribing on prescribing errors in paediatric patients retrieved 15 studies. The studies are summarised in Tables 1.6 and 1.7. Table 1.6 provides a summary of the pertinent study characteristics and details of the intervention and its level of CDS. Table 1.7 summarises the results.

None of the 15 studies reported any randomised methodology, 10 studies used a retrospective review to look at both pre and post EP implementation data; two were retrospective for pre-implementation and four studies were entirely prospective. Only two of the studies were conducting in the UK, with 10 from the US and one each from Israel, Iran and Canada. In terms of error identification methodology, nine reports used a retrospective review of case notes or electronic records, two use incident reporting and five used pharmacist interventions. The majority of specific paediatric populations

involved in the trials were general paediatric patients, four reports specifically related to critical care areas and two involved neonatal units.

Han *et al*[65] assessed the change in mortality of patients transferred to their hospital for specialist tertiary care. This was the earliest report to use mortality data as an outcome and one of the first reports of the use of EP in a paediatric setting. The EP system that was used had a basic level of clinical decision support (CDS), with the possible additional benefit of dose checking, but this was not clear. The retrospective review of admission data showed a statistically significant increase in mortality from 2.8% in the 13 months prior to EP, to 6.57% ($p<0.001$) in the 5 months following implementation. There were no significant demographic or clinical differences between the two groups. Several limitations in the study were identified in the report. These included the specific population that was studied, who were patients admitted through inter-facility transport and as such, may not have been generalisable to a whole hospital population. A specific problem in relation to time critical medicines such as IV antibiotics was highlighted. Following the implementation of EP there were increased delays in doses as drugs had to be ordered on the system prior to preparation within the pharmacy. The study period following the implementation was short at only 5 months, which may not have allowed for full acclimatisation for users of the system. It is possible that, as users became accustomed to the system the results may have improved; however, other studies have shown an immediate effect on MEs.[66] Another confounder highlighted by the authors was that the EP system was part of a new clinical application system that was implemented hospital wide. As a result, other computerised systems were implemented concurrently. This may have affected the education and training of staff required to use multiple new systems.

Del Beccaro *et al*[67] studied the effect of computerised physician order entry (CPOE) on risk adjusted mortality in a paediatric intensive care unit (PICU). Using similar methodology to Han *et al*[65] they retrospectively reviewed admission data for 13 months before and after implementation. Interestingly the system used in this report was the same as the one implemented in the previous report[65] but is described in slightly more detail. It included an advanced level of CDS with dose checking which, it is suggested was part of the Han *et al* system but with the addition of 230 order sets. The results showed a slight reduction in mortality but this was not statistically significant

(4.22% versus 3.46% p=0.32). There was no difference in demographics between the two study populations.

Following the results reported by Han *et al*[65] where an increase in mortality rate was observed following the introduction of an EP system, Keen *et al*[68] conducted a similar study on NICU and PICU in the US. They showed a small decrease in mortality after the implementation of a basic EP system. The paper does not describe the EP system in detail and the description of the CDS is limited to basic order sets. The system was implemented on high care areas at least 3 years after being used in the other areas within the hospital, implying that users were already very familiar with it. This report highlights the importance of the way in which EP is implemented in a centre. The preparatory phase took approximately 2 years compared with 3 months described by Han *et al*;[65] other differences included a design specifically for the paediatric population and extensive support and training. These were all identified as possible causes of the increase in mortality reported by Han *et al*.[65]

A study published in 2010 by Longhurst *et al*[69] reported a significant decrease in hospital wide mortality following the introduction of an EP system of 20% (p = 0.03). It did include CDS, but this was not clearly defined within the report. As with many other studies of this type, the authors used historical retrospective data as a control. Data were collected over a nine year period with no acclimatisation period. The report detailed the similarities between the two populations and interestingly, a small but statistically significant difference (p <0.01) in the case mix index, suggesting a slightly increased risk of mortality in the intervention group. With a data collection period spanning many years it is possible that another intervention took place that contributed to the mortality. The authors identify specific patient safety initiatives such as catheter related sepsis and surgical site infection interventions having been implemented, however, no significant decreases in these infections had been seen.

In 2003, King *et al*[70] published a study that was conducted in a large tertiary teaching hospital in Ontario. A basic EP system was implemented on 2 medical wards and compared to 3 control wards (1 medical and 2 surgical). This methodology differs from many studies in having a control group studied at the same time as the intervention group. The ME rate was calculated using patient bed days and reported as errors per 1000 patient days. There was a

nine month acclimatisation period. Over the six year study period the team observed a 40% reduction in the ME rate compared to control. However, only 14 out of a total of 804 errors were identified as prescribing errors, the majority being administration errors. This is likely to be because the ME were identified using the hospital's internal incident reporting system. The reliability of this system to collate incidents is variable. Certainly in the UK there is evidence to suggest that only 10% of incidents are reported on a system such as this.[57] Furthermore in the UK, the majority of medication error reports uploaded to the National Reporting and Learning Service (NRLS) are administration errors.[7] Despite the limitations of the error identification method and the paucity of prescribing errors included in the data, this study clearly shows the positive impact of a basic system on ME rates.

Cordero *et al*[71] studied the impact of a CPOE system incorporating EP in a Neonatal Intensive Care Unit (NICU) in Ohio US. The system had an advanced level of CDS which included drug dose calculations and dose range checking. In order to evaluate the impact a single drug, gentamicin, was studied. Records of 117 patients prescribed gentamicin prior to the implementation of EP were retrospectively examined for dose errors and compared with a similar group of patients after implementation. The results showed an impressive reduction in gentamicin dosage errors to zero. The decision support tool used in this study was specifically designed for the use of gentamicin in this population and this study clearly illustrates the value of this targeted approach. Not all EP systems provide this level of support. This also illustrates how important it is to understand the level of CDS used in each study to add clarity to the interpretation of the results and associated conclusions.

The additional impact of a system with advanced CDS in the US was shown by Potts *et al.*[72] This study involved prospectively collecting all errors relating to the medication ordering process for two periods of 2 months before and after the implementation of EP in their PICU. There was a significant reduction in MEs from 39.1% to 1.6% ($p < 0.001$). The authors classified their medication errors into potential ADEs, where the prescriber provided incorrect or inappropriate information; medication prescribing errors (MPEs) where inadequate information was provided requiring interpretation and rule violations (RV) where hospital policy had not been adhered to. MPEs and RVs were almost eliminated and potential ADEs were reduced significantly by

40.9% ($p<0.001$). Most types of potential ADE such as therapeutic duplication, wrong drug, wrong units and allergy were eliminated by the system. However, errors involving dose and frequency were not. The authors suggested that this was because of the lack of CDS that would have assisted the prescriber in choosing the correct indication-specific dose or a specific frequency for the patient. In this study the post implementation data collection was started one month after implementation. This allowed for all staff to be trained on the system. The results clearly show the impact of a system with relatively advanced CDS. Although it did not eliminate all errors; and the authors blame the lack of a paediatric specific CDS; the CDS described in this study is advanced compared to some of the other systems investigated in other studies.[65, 66, 73]

Upperman *et al*[66] conducted a study of the implementation of EP in a Pittsburgh children's hospital. A broad medication error definition was used, encompassing prescribing dispensing and administration. The level of CDS in the system was not well described but consisted of standard warnings. The results were expressed as the number of errors per 1000 doses ± the Standard Error of the Mean (SEM). Errors following the introduction of EP increased insignificantly from 0.3 ± 0.04 per 1000 doses to 0.37 ± 0.05 per 1000 doses ($p=0.3$), however, harmful errors decreased significantly from 0.05 ±0.017 to 0.03 ±0.003 per 1000 doses ($p<0.05$). Errors were identified using the hospital error reporting system as opposed to active observation of errors and the data was collected retrospectively. Prior to implementation there had been a hospital wide drive to increase reporting and this intensified after implementation of EP. In addition, the whole hospital changed at once rather than taking a stepwise approach. The significance of this is unclear but it did mean that there was no control group where the EP system was not being used. The paper therefore, reports a trend of decreasing severity of errors but this has to be tempered by the limitations of the data collection method.

Holdsworth *et al*[74] studied the impact of CPOE on the incidence of ADE in a large cohort of paediatric patients on both PICU and general paediatric wards in the US. The study compared data collected 15 months after the implementation of an advanced CPOE system with similar data collected approximately 4 years previously. ADEs were defined as an injury from a medicine or lack of medicine. Potential ADEs were defined as the potential to result in a significant injury. Both of these parameters showed a significant

decrease after the implementation of CPOE. The post implementation relative risk was 0.64 (95% CI 0.43-0.95) for ADEs and 0.56 (95% CI: 0.34-0.91) for preventable ADEs, compared to pre-implementation data. The authors reported a reduction in dispensing errors, wrong dose errors and drug choice errors. This highlights two important factors to consider when analysing studies conducted in the US and comparing them to UK practice. Firstly, the medicine management systems are often very different. In the study sites there was a unit dose dispensing system electronically linked to the CPOE. This would contribute significantly to the reduction in dispensing errors and is a system that is not in general use in the UK. Secondly, the level of CDS within the system was advanced with both dose range checking and dose recommendation information available for common and alternative indications. In addition, the system included a sophisticated automatic dose rounding tool. The authors noted the significant time difference between the two data collection periods. There were small changes in the medicine management processes between these two periods including formulary revision and highlighting look-alike, sound-alike issues. However, these were regarded as ongoing evolutionary changes, likely to have taken place in any organisation and completely different to the revolutionary change that occurred with the introduction of CPOE. Another important aspect of this study is the acclimatisation period. In this case, post-implementation data were collected after 15 months. This allowed time for the system to be embedded within day to day practice and to identify and resolve any early issues with the system

Walsh *et al*[75] conducted a time series analysis of the change in error rate 7 months before and for 9 months after the implementation of an EP system, which included dose checking, in the US. Medication errors were identified retrospectively using a range of methods including case note review and incident reporting. Identified errors were then reviewed and categorised by a panel. A 7% decrease in non-intercepted errors was found, but no change in the rate of injuries or incomplete/wrong orders. Most importantly the rate of wrong dose errors, the most common type of error, did not change despite the automated weight-based dose checking. The authors compared their results with a study of similar methodology conducted in adults[76] which showed a significant reduction in non-intercepted errors of 55%. The explanations put forward by the authors for this difference are important considerations when comparing paediatric studies as well as medication error studies in general.

Firstly the difference between off-the-shelf systems and home-grown systems; there are numerous advantages and disadvantage between these two system types. Home-grown systems tend to reflect the way in which a hospital works and might be better matched to other systems already in place. Support for the system however, may be difficult to obtain. Off-the-shelf systems usually come with a significant level of support from the vendor yet may require significant changes in working patterns in order for them to be implemented. This important distinction is highlighted by this study with respect to dose errors. The system had CDS which included weight based dosing, but it was primarily designed to identify overdoses based on maximum adult doses and as an off-the-shelf system this was difficult to change. Secondly, the authors left a six month gap after the introduction of EP before collecting data for the same months each year thus allowing for seasonal changes to be taken into account. The time series based nature of this study provided some interesting results. There was a downward trend of incidents for the 6 months prior to implementation of EP. Immediately after implementation the error rate was similar to the initial rate and showed a similar downward trend over the study period. Additionally a peak of errors was noted to occur in September and October in both periods at the beginning of the academic year as opposed to later in March and April. This study's methodology allows for seasonal variations which is an important consideration within paediatrics. In the UK admissions tend to increase in the winter months due to RSV with a resulting increase in pressure on services.[77]

A fascinating study by Kadmon *et al*[78] showed how the evolution of an EP system could affect the prescribing error rate. This was a retrospective review of prescribing errors during the same month each year over 4 years during which an EP system was introduced on the PICU of a tertiary children's hospital in Israel. The authors clearly defined the categories of prescribing errors that were identified. All errors were categorised by an experienced PICU physician with 10% of the errors also categorised by the PICU pharmacist. The overall inter-rater reliability score showed substantial agreement with kappa, $\kappa = 0.788$ (95% CI: 0.638 – 0.938). The study identified three types of prescription error: potential ADE (previously defined) as well as medication prescription errors (MPE) defined as an incomplete or illegible prescriptions and rule violations (RV) which were defined as prescriptions not adhering to the institute's prescription writing policy, a similar

categorisation was used by Cordero *et al.*[71] Other studies may include incomplete and illegible prescriptions as potential ADEs arguing that these also have the potential to cause harm.

Initial post implementation results showed only a small reduction in total prescription errors (8.2% to 7.8%) and potential ADEs (2.5% to 2.4%). The centre then introduced an advanced CDS which included: default drug doses, routes and frequencies as well as a dose range checking system designed only to prevent overdosing. No other CDS was included in the system. Following this the prescribing error rates dropped significantly to 4.4% (p=0.0004) as did the potential ADE rate to 0.8% (p=0.0014). It is important to note that these data were collected immediately after the introduction of the CDS as opposed to the previous data collection period which occurred 1 year after the initial introduction of the EP system. This occurred because of the need to keep data collection to the same month each year (September) thus reducing potential bias due to seasonal case load differences. The lack of improvement in prescribing error rate after 1 year of EP followed by the relatively sudden drop immediately after CDS implementation is very powerful and highlights the importance of the CDS in preventing errors. In addition the CDS targeted the most common type of error found in paediatrics and more importantly in a PICU, that of wrong doses. For systems that are to be used in children this report shows the importance and value of dose range checking in EP systems.

Jani *et al*[73] studied dosing errors specifically as part of wider prescribing error work which was undertaken before and after the implementation of EPMA in a large tertiary UK paediatric hospital. Errors from outpatients and discharge prescriptions were collected in addition to inpatient errors for the renal and urology patients. In this case errors were identified prospectively by pharmacists during their normal working pattern. This observational technique has become the gold standard for identification of prescribing errors and was used in the EQUIP study.[20] A total of 8,723 prescriptions were analysed across the two collection periods. The EP system that was implemented had very basic CDS including weight range checking. There was a reduction in dosing error rates from 2.2% to 1.2% and absolute reduction of 1% (p<0.001). Most of the reduction in dose errors was observed in the outpatient and discharge prescribing rather than the inpatient setting where there was a small but negligible increase. The authors postulated that this was due to the

relatively small number of errors observed with inpatients and these errors tended to be ones would have been prevented only by more advanced CDS. It is not clear from the paper whether there was an acclimatisation period; however, subsequent communication with the authors revealed that there was a 5 month acclimatisation period for the inpatient setting only.[79] Many other studies have shown a greater reduction but most of these have studied systems with more advanced CDS. In addition to number of errors, the severity of the errors was also evaluated using a validated severity scoring system involving 5 judges who gave a score to each error of between 0 and 10.[80] There was a reduction in the severity of the errors with the potential to result in minor and moderate outcomes (p=0.009 and 0.019 respectively). There was also a reduction in severity of dose errors with the potential for severe outcomes but this was not statistically significant (p=0.11). This study shows that both the number and severity of dosing errors can be reduced using very basic EPMA systems in a specific group of patients, but with most impact on less severe errors.

Kazemi *et al*[81] prospectively studied the introduction of an EP system with CDS in a neonatal unit in Iran. They focused attention specifically on antibiotics and anticonvulsants and recorded only dose and frequency errors. Following the introduction of the EP system without CDS, the error rate reduced from 52% to 50%. However following the introduction of an advanced CDS which calculated the dose of the antibiotic or anticonvulsant based on indication, age, weight, gestational age and GFR, there was a reduction in the prescribing error rate to 33% (p<0.001). In a similar way to Kadmon *et al*[78], this study highlights the importance of CDS in particular, in relation to dosing errors. However, the study reported an extremely high error rate initially. Several reasons were given for this including the lack of any ward based clinical pharmacy service and the need to transcribe all doses onto paper based charts even in the presence of an electronic system. All the data collection periods were the same length but they did not occur at the same time of year; however, there is less likely to be seasonal case load bias within a neonatal unit unless there is a seasonal variation in births. It is inferred that data collection took place immediately following the implementation of the various EP and CDS systems. If so this would not have given prescribers the opportunity to become acquainted with the system and may have resulted in a less pronounced reduction than data collected a little

later after acclimatisation. While showing some excellent results, the initial high error rate and the different nature of services in Iran need to be taken into account.

Sullins *et al*[82] studied the introduction of EP at one site and electronic medication administration record (eMAR) in a second, both in the US. The objective was to understand whether the order of implementation would make a difference to medication errors. The EP site was a children's hospital, the eMAR site was an adult hospital. Errors from medication charts were collected retrospectively for a periods of 30 days before and after implementation of each system. The national definition for medication errors was used.[13] The medication error rate in the EP centre was reduced by 13.3%. The errors were classified into prescribing administration and dispensing errors. Interestingly the prescribing error rate increased slightly after implementation, this being balanced out by a larger reduction in administration errors. The number of actual errors was relatively small, with an increase from 20 to 23 errors. This increase was attributed to wrong timing errors. The authors cite the limited training opportunities for staff on the system and its complexity. The definition used in this study meant that both documentation errors and errors of omission were included. In addition, there is no detail in the report of the EP system and its level of CDS. This again illustrates the importance of the timing on the data collection period in relation to the implementation

O'Meara and Shaheen[83] presented the results of an audit of prescribing errors after the introduction of EP in neonates and children at the Neonatal and Paediatric Pharmacists Group (NPPG) annual conference in 2013, they were published in abstract form only. Prescribing errors were identified using observational techniques on six paediatric wards and one neonatal ward. The prescribing error rate increased from 8.5% to 15.7% following EP implementation. The authors also scored the severity of the prescribing errors and this showed that there was an increase in the number of minor errors and a decrease in the number of severe and moderate errors after the implementation of EP. Unfortunately the abstract does not detail the EP product that was used so the level of CDS is unknown. Also it is not clear how soon after the implementation of EP the post EP data were collected. The basic results allude to a reduction in the severity and therefore, impact of

prescribing errors; the elimination of some errors but the identification of new errors has been reported elsewhere.[73]

1.8.5 Summary

Fifteen studies investigating the impact of an EP system on paediatric prescribing errors were identified during the literature review. Eleven showed a decrease in either medication errors or mortality associated with the implementation of an EP system and 4 showed an increase. The significance of the changes varied considerably. Six studies reported a statistically significant reduction in error rate or mortality.[69, 70, 72, 73, 78, 81] One study reported a statistically significant increase in mortality.[65] As discussed above the authors of this study and subsequent similar work[67, 68] have been able to show why such a significant increase was seen.

In general it can be concluded that EP systems reduce the incidence of medication errors in the broadest sense, when using the widest possible definition and including all error types such as legibility and legality.

What cannot be concluded, however, is what the impact of EP is on the patient. Studies assessing mortality show some improvement, with the exception of Han *et al*[65] as discussed. Studies that have used error rates as their outcome often show a reduction in errors, however, differences in timing of the intervention, in error detection methods and the presence or absence of CDS make it difficult to draw wider conclusions.

In relation to error detection, two studies used spontaneous incident reporting,[66, 70] five used pharmacist interventions[72-74, 81, 83] and four used retrospective record review.[71, 75, 78, 82] Differences between error detection methods are summarised in Table 1.4. There was no correlation between error detection method and a positive or negative impact on error rate following the intervention. In addition, statistically significant reductions in error rates were observed with all methods of error detection.

In relation to the level of CDS, six studies described systems with advanced CDS[71, 72, 74, 75, 78, 81] three had basic CDS[66, 70, 73] and in two studies the CDS was not adequately described.[82, 83] Of the five studies that reported a statistically significant reduction in ME, three had advanced CDS[72, 78, 81] and two had basic CDS.[70, 73] The lack of heterogeneity between the reports does not allow a full meta-analysis. A possible trend towards a reduction in ME,

seen in the reports, with advanced CDS would require a much larger clearly defined study to prove.

Another aspect to consider when reviewing the literature is the impact of the ME on the patient. Only the four mortality studies and four of the studies looking at ME rate included an assessment of the severity of the errors. Within these eight studies there is variation as to the overall decrease in either mortality or ME and the presence of a decrease in the severity of the errors. Four of the studies using error rate as an outcome included an analysis of the severity of the errors.[66, 73, 74, 83] Two of these studies showed a decrease in harmful ADEs,[66, 74] but neither was statistically significant.

It is clear from this body of work that there are advantages in implementing EP in the paediatric secondary care setting. Reductions in ME have been shown and these vary depending on the level of CDS and the error detection method. However, what is not clear is what the impact EP has on the patient and their outcome. It can be inferred that reducing medication errors will result in a reduction in harm but, as the vast majority of MEs result in no harm[7] it is not possible with current evidence to be confident in this conclusion. The development of a tool specifically dedicated to detecting harmful ME would therefore, be an ideal way of addressing this problem. Prescribing indicators are a solution to this problem.

Table 1.6 Characteristics of studies describing the impact of electronic prescribing on paediatric prescribing errors

Study Author	Setting	Design	Error detection method	System	CDS	Outcome(s)	Denom	AP
Han *et al* 2005[65]	US / General Paediatric	Pre & Post Retrospective	Record Review	OTS	Basic	Mortality	Patients	No
Del Beccaro *et al* 2006[67]	US / PICU	Pre & Post Retrospective	Record Review	OTS	Advanced	Mortality	Patients	No
Keene *et al* 2007[68]	US / NICU & PICU	Pre & Post Retrospective	Record Review	OTS	Not well described Basic	Mortality	N/A	No
Longhurst *et al* 2010[69]	US / General Paediatric	Pre & Post Retrospective	Record Review	OTS	Yes but not described	Mortality per 100 discharges	N/A	No
King *et al* 2003[70]	Canada / General Paediatric	Pre & Post Retrospective	Incident Reports	OTS	Basic but linked to lab results	Any event in prescribing, dispensing, administration or monitoring	Per 1000 bed days	9 Months
Cordero *et al* 2004[71]	US / NICU (VLBW)	Pre & Post Retrospective	Record Review	OTS	Advanced	Gentamicin dose error (+/-10%)	Patients prescribed gentamicin	No
Potts *et al* 2004[72]	US / PICU	Prospective cohort	Pharmacist Intervention	HG	Advanced	All ME Incomplete, incorrect or inappropriate	Medication Orders	1 month
Upperman *et al* 2005[66]	US / General Paediatric	Pre Retrospective and Post Prospective	Incident Reports	OTS	Basic	All Medication errors	Medication orders	Not Stated
Holdsworth *et al* 2007[74]	US / General Paediatric	Pre Retrospective and Post Prospective	Pharmacist Intervention	OTS	Advanced	Actual and potential and preventable Injury from medicine or lack of medicine	Patients	15 months
Walsh *et al* 2008[75]	US / General Paediatric	Pre & Post Retrospective	Record Review	OTS	Advanced	ADEs and MEs Actual and preventable injury	Per 1000 patient days	

Table 1.6 Characteristics of studies describing the impact of electronic prescribing on paediatric prescribing errors continued

Study Author	Setting	Design	Error detection method	System	CDS	Outcome(s)	Denom	AP
Kadmon *et al* 2009[78]	Israel / PICU	Pre & Post Retrospective	Record Review	OTS	Advanced	Potential ADEs - An incorrect prescription that could cause harm.	Prescribed Items	12 Months
Jani *et al* 2010[73]	UK / General Paediatric	Pre & Post Prospective	Pharmacist Intervention	OTS	Basic	Dosing Errors at prescribing stage	Prescribed Items	Not Specified
Kazemi *et al* 2011[81]	Iran / NICU	Pre & Post Prospective	Pharmacist Intervention	OTS	Advanced	Antibiotics and Anticonvulsant Erroneous dose or frequency.	Medication days (a day in which a prescribed medication was administered)	No
Sullins *et al* 2012[82]	US / General Paediatric	Pre & Post Retrospective	Record Review	OTS	Not Detailed	All ME	Medication orders	2 months
O'Meara, Shaheen 2014[83]	UK / General Paediatric	Pre & Post Prospective	Pharmacist Intervention	OTS	Basic	Prescribing errors	Medication orders	Not Stated

Key:- VLBW = Very Low Birth Weight (Birth weight ≤1.5kg), OTS = Off-the –shelf, HG = Home-grown, Denom = Denominator. AP = Acclimatisation Period, ME = Medication Error, PICU = Paediatric Intensive Care Unit, NICU = Neonatal Intensive Care Unit, ADE = Adverse Drug Event

Table 1.7 Summary of results from reports of the impact of electronic prescribing on paediatric prescribing errors

Study	Level of CDS	AP (months)	Pre-Int data	Post - Int result	Main outcome significance (p)	Error Severity Result	Notes/Conclusions
Han *et al* 2005[65]	Basic	No	2.8%	6.57%	p<0.001	N/A	Significant increase in mortality
Del Beccaro *et al* 2006[67]	Advanced	No	4.22%	3.46%	Not reported	N/A	Assessed mortality pre and post intervention. No significant difference
Keene *et al* 2007[68]	Not well described - Basic	No	3.16%	2.41%	p=0.466	N/A	Mortality did not increase
Longhurst *et al* 2010[69]	Yes but not described	No	1.008	0.716	p=0.03	N/A	Significant reduction in mortality expressed as deaths per 100 discharges
King *et al* 2003[70]	Basic but linked to lab results	9	4.49	3.13	p < 0.001	Not Included	40% reduction compared to control wards expressed as ME rate per 1000 bed days
Cordero *et al* 2004[71]	Advanced	No	12%	0%	Not reported	Not Included	Reduction in gentamicin dose errors
Potts *et al* 2004[72]	Advanced	1	39.1%	1.6%	p < 0.001	Not Included	Potential ADEs reduced from 2.2 to 1.3% (p<0.001)
Upperman *et al* 2005[66]	Basic	N/S	3%	3.7%	p=0.3	Decrease (not significant)	Insignificant increase in errors
Holdsworth *et al* 2007[74]	Advanced	15	6.3	3.1	Not reported	Decrease (not significant)	RR reported as 0.64 (95%CI:0.43-0.95)
Walsh *et al* 2008[75]	Advanced		44.7	50.9		Not Included	As per 1000 patient days. No statistically significant difference
Kadmon *et al* 2009[78]	Advanced	12	2.5%	2.4 0.8%* 0.7%	p=0.66 p<0.005	Not included	*Significant decrease associated with addition of basic dose range checking.
Jani *et al* 2010[73]	Basic	N/S	2.2%	1.2%	p<0.001	No Change	Additional decrease in severity of errors
Kazemi et al[81]	Advanced	No	51%	34%	p<0.001	Not Included	Addition of CDS showed largest decrease
Sullins *et al* 2012[82]	Not Detailed	2	Not Given	Not Given		Not Included	Reduction of 13.3% (p=0.24)
O'Meera, Shaheen[83]	Basic	N/S	8.5%	15.7%	Not reported	No Change	Increase in prescribing error rate but no change in severity.

Key: AP=Acclimatisation Period, Int.=Intervention, RR = Risk Ratio, N/S = Not Stated, ME = Medication Error, ADE = Adverse Drug Event, CDS = Clinical Decision Support

1.8.6 Prescribing Indicators

Indicators are:

> *…explicitly defined and measurable items relating to the structures, processes or outcomes of care.*[84]

Indicators are often used in healthcare to measure a specific activity, such as the immunisation rate or screening rates for prostate cancer. Quality indicators are used to determine the level of quality of care for a specific activity and performance indicators may be used to monitor performance in a specific area such as health promotion.

A prescribing indicator, therefore, is a specific measurable item referring to the process of prescribing aimed at identifying specific prescribing practices that are likely to cause harm or are easily resolved using an intervention. They have the advantage of focussing on a distinct set of criteria and being a valid method of measuring or monitoring an area of prescribing where a change is expected over time. Prescribing indicators have been used in many different ways in the UK to assess different aspects of prescribing activity.[85] The main focus has been on their use to analyse the cost of prescribing in primary care,[86] however more recently indicators have been developed to analyse the quality and safety of prescribing.[87, 88] In primary care, a set of indicators has been included in the PINCER tool and shown to be an effective method for reducing a range of medication errors.[89] In all cases the indicators relate to adult care rather than children and infants. Table 1.6 summarises some examples of previously published prescribing indicators.

Table 1.8 Examples of prescribing indicators

Population/indicator type	Example Indicator	Reference
Adult Primary Care - Performance	Generic prescribing rate	Campbell *at al*[86]
Adult Primary Care - Performance	Ratio of co-trimoxazole items to trimethoprim items	Campbell *at al*[86]
Adult Primary Care – Quality	NSAID in a patient with heart failure	Avery *et al*[88]
Adult Secondary Care – Quality	Gentamicin prescribed to a patient with renal impairment without dose adjustment	Thomas *et al*[90]
Paediatric High Acuity indications-quality	% of patients receiving IV fluids within 60 mins of Emergency Department (ED) arrival with DKA	Stang *et al*[91]

NSAID = Non-steroidal anti-inflammatory drug, IV = Intravenous, DKA = Diabetic Ketoacidosis

Indicators for use in secondary care have been slower to materialise. Thomas *et al*[90] developed an extensive range of indicators designed to assess the

impact of EPMA on prescribing errors in the hospital setting. They used an eDelphi approach to gain consensus on 80 indicators.

To date, no such indicators have been developed for paediatric prescribing. Stang *et al*[91] published work on quality indicators for high acuity paediatric conditions in 2013. Using a Rand modified Delphi approached they identified indicators related to specific conditions such as diabetic ketoacidosis (DKA), anaphylaxis and status epilepticus.

As has already been described, prescribing for children is significantly different to prescribing for adults. There are differences in the doses used as well as the range of drugs. Therefore, a set of specific paediatric prescribing indicators that can be used to assess aspects of electronic prescribing in the paediatric population is required.

1.9 Aim and Objectives

The aim of this research was to ascertain the effectiveness of current EP systems to prevent a specific group of paediatric prescribing errors (identified using pre-defined indicators).The objectives were:

- To develop a set of high risk paediatric prescribing indicators for use as an evaluation tool for EP systems
- To establish the performance of a range of EP implementations in preventing specific prescribing errors identified using pre-defined indicators.
- To understand the attributes, level of clinical decision support (CDS) and general settings of an EP implementation that can reduce the risk of the indicator paediatric prescribing errors.

Chapter 2 eDelphi Exploratory Round

2.1 Introduction

This chapter describes an overview of the methodology for the indicator development. In addition, it describes in detail:-

- The development of the initial list of potential prescribing indicators.
- Recruitment of an expert panel.
- Creation of a final list of indicators for consensus scoring in Rounds 1 and 2.

2.2 The eDelphi Process

The Delphi technique is method of gaining consensus from an expert panel on a question or issue for which little or no high quality evidence exists. A set of 41 paediatric prescribing errors was developed using an eDelphi methodology to gain consensus from an expert panel.

There are three common methodologies for determining consensus within healthcare: nominal group processes, consensus development panels and the Delphi technique. The nominal group process involves four phases, three of which involve face to face presentation and discussion about a set of solutions to the proposed problem. The solutions to the problem under discussion are generated anonymously by the panel members for subsequent discussion. It has been used particularly for the appropriateness of interventions in health care.[92] Consensus development panels are organised conferences or events specifically planned to discuss a topic. They are commonly used to formulate policy and strategic plans. It is a multidisciplinary approach involving a great deal of face to face discussion. Specific methodology is not agreed and the logistics and cost involved make it unfeasible for most researchers.[93]

The eDelphi method allowed an electronic transfer of a large amount of information to each of the expert panel members. It was chosen as an efficient way of conducting multiple rounds of scoring in order to gain consensus. In addition this allowed the opinions of a broad range of both medical and paediatric pharmacy experts to be taken into account. It allowed multiple rounds of indicator scoring to be conducted until convergence or stability of opinion is gained. It was also a more efficient and cost effective method as it does not require face to face discussion as with the other

methods.[94] In addition it was used in the development of the adult prescribing indicators[90] on which this work was based.

In this work the process was conducted electronically via email, hence the eDelphi designation.

Figure 2.1 is a diagrammatic representation of the eDelphi process used in this research, together with explanations of specific methodology and output.

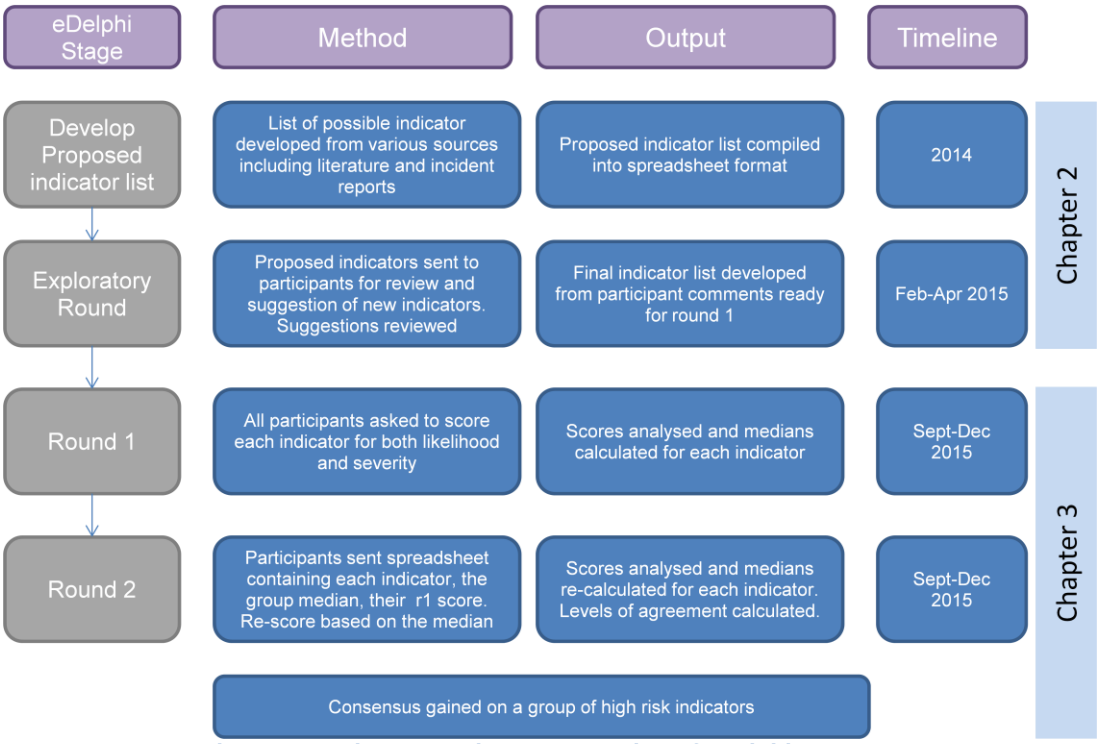


Figure 2.1 - Diagrammatic representation of eDelphi process

2.3 Expert Panel Selection

A list of potential panellists was generated by the investigator through the paediatrician network via the Royal College of Paediatrics and Child Health (RCPCH, http://www.rcpch.ac.uk) and the paediatric pharmacist network via the Neonatal and Paediatric Pharmacists Group (NPPG, http://www.nppg.org.uk). Additional contacts were made through research links with the National Institute of Healthcare Research (NIHR) programme grant research team who had developed the adult indicators.[90] Each potential panellist was sent an email invitation together with a summary of the proposed research (Appendix 2). Potential panellists were general paediatricians, paediatric pharmacists and paediatric pharmacologists from across the UK. Following initial contact, each participant was asked to complete a participant

details form (Appendix 3) detailing years of relevant experience as well as experience of electronic prescribing systems. Thirty nine potential participants were identified using this process of which 15 either did not respond or declined to take part following the initial request. This left 24 participants who returned completed participant detail forms. These individuals were subsequently sent the initial indicators for the exploratory round. This achieved the target number of at least 20 panel members, a similar number used in other Delphi work.[90]

2.4 Identification of Initial Indicators

The initial set of indicators was developed using five key sources:

- Adult indicators previously published[90]
- Literature search
- National reporting and learning system data[95]
- Local intervention and incident reports
- National Alerts.

Figure 2.2 depicts the process followed to generate the initial list of indicators for the exploratory round.

All potential indicators had to adhere to the following inclusion and exclusion criteria:

Inclusion

- The indicator described a prescribing error relating to a specific drug.
- The indicator was specific to the hospital paediatric setting.

Exclusion

- The indicator described a prescribing practice not routinely undertaken in paediatric hospital settings.
- The indicator described an error that would not be amenable to decision support or electronic prescribing.
- Extraction of data for the indicator from hospital records was not likely to be feasible.
- The indicator described a failure to monitor.
- The indicator described an error relating to the administration or dispensing of a drug

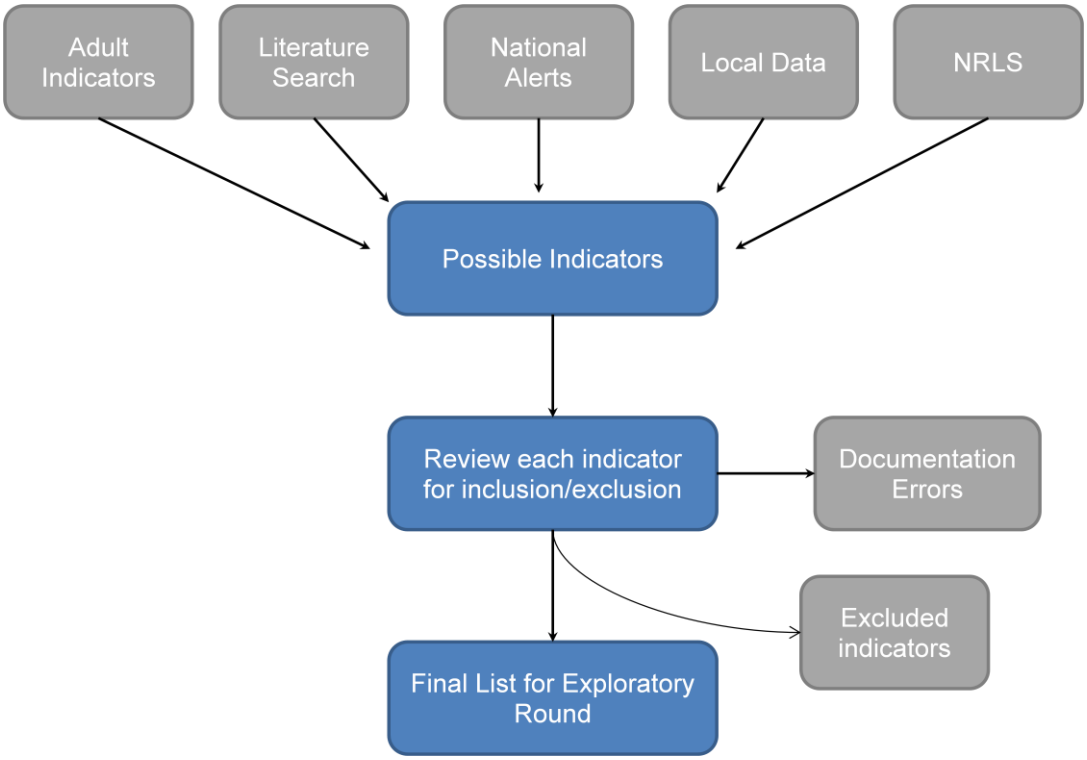


Figure 2.2 A diagrammatic representation of the potential prescribing indicator identification and development.

2.4.1 Adult Indicators

Thomas *et al*[90] published a set of 80 adult prescribing indicators designed to assess the impact of electronic prescribing in secondary care. They used similar methodology to that used in the present work to generate them. Personal communication with the lead author allowed access to their original starting list prior to any eDelphi process. This list contained 110 indicators each of which were assessed against the inclusion and exclusion criteria above. Fifty eight of the adult indicators were excluded. The most common reason for exclusion was that the indicator drug was rarely used in the paediatric setting (n=44); examples of specific drugs in this category included orlistat, aliskerin, glibenclamide and bisphosphonates. Other reasons for exclusion were: that the indication was rare in paediatrics e.g. type II diabetes mellitus, or the indicator related to a co-morbidity that was rare in paediatrics e.g. heart failure or Parkinson's disease. The remaining 52 indicators were included in the final list. Of these, eight required modification to the wording to make them applicable to the paediatric setting, e.g. specific reference to the paediatric dose of domperidone rather than the adult dose. The full table of adult indicators and associated outcome is shown in Appendix 4.

2.4.2 Literature Search

An extensive literature search was carried out for paediatric prescribing errors using the search strategy listed in Appendix 5. Papers detailing individual case reports of medication errors as well as paediatric medication error reviews were identified.[28, 29, 96-111] Underlying themes were very similar to those already discussed, such as wrong dose. Where specific drugs were identified these were included as a potential indicator for assessment. In total 26 indicators were identified using this method (Appendix 6). Of these, eight were included in the exploratory round. The two main reasons for excluding an indicator from this source was that the reports related to administration rather than prescribing errors or the drug was rarely used in paediatric setting in the UK.

2.4.3 National Reporting and Learning System Data

The National Reporting and Learning System (NRLS) was set up by the Department of Health in 2004. It contains all patient safety incidents reported by all NHS healthcare trusts and organisations in England and Wales. Personal communication with the Senior Pharmacist at NHS England allowed the sharing of an internal report detailing medication errors in children between 1st October 2009 and 30th September 2012.[95] During this period a total of 45,242 medication errors were reported to the NRLS involving children or neonates. The majority of these (87%) caused no harm. There were nine incidents of severe harm and three reports of death. The detail relating to the high harm errors was included in the report and used to develop indicators for inclusion. Of the three deaths, two were associated with administration errors and the third was related to the prescribing of a penicillin containing antibiotic to a patient who was allergic to penicillin. This specific cause of harm had been identified with the adult work and was, therefore, already included as an indicator. The moderate harm incidents primarily related to administration errors, however, one described a patient prescribed a dose of meropenem too low for the indication. This was included as a potential indicator and was also identified when reviewing local interventions. The themes identified in the reports included wrong doses and delayed or omitted medicines. As the specific drugs involved in wrong dose errors were not cited, a general documentation error to capture these was developed. Delayed or omitted medicines have been excluded from this work as their prevention is not

amenable to decision support. In total five indicators were identified from the NRLS data all of which were included in the exploratory round (Appendix 7).

2.4.4 Local Intervention and Incident Monitoring

The clinical pharmacy service at University Hospital Southampton NHS Foundation Trust (UHS) monitors its intervention activity on an annual basis. Pharmacy interventions are defined as any activity in which a member of the pharmacy team has had an impact on a patient's care. Pharmacist intervention monitoring is one of the error detection methods described in Chapter 1. In addition to identifying medication errors, pharmacists also provide patient counselling, medicines administration advice and ensure safe and secure storage of medicines.

A review of the paediatric pharmacy interventions in UHS from 2012 and 2013 was carried out to identify common medication errors. They were assessed against the inclusion and exclusion criteria and then, if suitable, added to the initial indicator list.

In UHS an incident reporting system is in operation similar to the one described by Dean *et al*.[112] This database was interrogated for all medication errors reported by the paediatric and neonatal departments between 2010 and 2013. In total 197 errors were identified. These were reviewed by the author for possible inclusion as an initial indicator. A total of 27 possible indicators were identified (Appendix 8). One was excluded as it related to a dispensing error, leaving 26 for inclusion in the exploratory round.

2.4.5 National Alerts

Both the MHRA and the NPSA/NHS England publish medication safety alerts as a result of their national surveillance projects. Alerts pertaining to medicines used in children published since 2002 were scrutinised for potential inclusion. Many of these had already been identified by other sources, particularly the adult indicators. Specific paediatric examples included the use of hypotonic sodium chloride solutions for IV maintenance therapy[113] and the use of codeine in children under the age of 12.[114] In total 11 possible indicators were identified using this source. One was excluded as it related to an administration error and one was excluded as it involved a drug rarely used in children. This left nine potential indicators included in the exploratory round (Appendix 9).

2.5 Documentation Errors

During review of the indicators with the adult indicator team a group of indicators that were clearly going to be difficult to measure using the proposed audit tool were identified. Therefore, a group of non-drug specific errors termed “documentation errors” was developed. The term documentation error was used as these errors were not drug specific and could be attributed to any drug and the process of writing a prescription by hand. The documentation errors were circulated with each round of scoring so that the expert panel were aware of them. An example of these included “a 10 times overdose”. In this case the indicator was not drug specific and so it would be very difficult to assess the likelihood and severity. However, these types of error do occur in paediatric practice and are well documented in the literature. In order to fully assess the impact of an electronic prescribing system, identification of this type of error is essential. These documentation errors would not be subject to the eDelphi process as they did not describe an error associated with a specific drug; rather they describe an aspect of poor prescribing practice. An initial list of 20 documentation errors was identified (Appendix 10).

2.6 Initial List of Prescribing Indicators

Appendices 4 and 6 - 9 contain lists of all the indicators identified using each of the above methods together with the decision as to whether they were included in the exploratory list.

For each possible indicator identified from the sources above the following elements were recorded.

- Code Number
- Description
- BNF Code
- Supporting information
- Reference
- Error type

2.7 Exploratory Round

Appendix 11 shows the final list of 100 prescribing indicators errors that were used in the exploratory round together with their sources. The expert panel members were asked to review each of the indicators and recommend modifications they deemed necessary. Panel members were also asked to

suggest additional indicators at this stage and were provided with a form to use for this purpose (Appendix 12). The responses were assessed by the research team against the inclusion and exclusion criteria and available evidence of their clinical merit. The research team consisted of the author and a co-researcher who had worked on the adult indicators.[90]

The expert panel members were also provided with the list of documentation errors (Appendix 10) and asked to amend them as required and suggest additions.

2.8 Results

2.8.1 Expert Panel

From the group of 24 participants identified during panel selection, 21(87.5%) complete responses for the exploratory round were received. This expert panel consisted of 8 pharmacists with a total of 181 years of experience and 60 years exposure to electronic prescribing. There were 13 physicians with a total of 243 years of paediatric experience and 31 years of exposure to electronic prescribing. The panellist attributes are summarised in Table 2.1.

Table 2.1 Expert panel members, years of experience and their hospital setting

Position	Yrs Exp	Yrs Exp	Type of Hospital
Senior Paediatric Pharmacist	35	2	General Teaching
Clinical Pharmacy Manager	25	3	Specialist Children's
Neonatal Pharmacist	32	0	General
Consultant Pharmacist	26	21	General Teaching
Medication Safety Pharmacist	20	11	General Teaching
Clinical Pharmacist	12	5	Specialist Children's
Lead Informatics Pharmacist	22	15	General Teaching
Paediatric Pharmacist	9	3	Specialist Children's
Ass Professor of Child Health	18	1	Specialist Children's
Consultant Paediatrician	19	1	Specialist Children's
Consultant Paediatrician	24	1	Specialist Children's
Consultant Neonatologist	19	0	Specialist Children's
Specialist Registrar	10	0	Specialist Children's
Consultant Paediatrician	30	0	General Teaching
Sr Lec Paediatric Pharmacology	20	0	Specialist Children's
Consultant Paediatrician	20	14	General Teaching
Consultant Neonatologist	20	0	General
Consultant Paediatrician	19	10	General
Consultant Paediatrician	17	4	General
Consultant Paediatrician	19	0	General
Consultant Paediatrician	14	0	General

2.8.2 Exploratory Round

Responses from each panel member were analysed. Nine of the original 100 indicators were rejected by the expert panel either because they would be

captured under the documentation errors or because practice across the UK varied to such an extent that the indicator was not a useful measure. In most cases participants had included comments against indicators that they felt required amendment, either due to typography or minor wording changes. Indicators without comment were deemed suitable. Participants also had the opportunity to suggest further indicators. Of the 21 responses, 15 participants provided at least one further indicator with one respondent offering another 10 indicators. A total of 74 new unique indicators were suggested from within the responses. Each new indicator was reviewed by the research team and either rejected or included for round 1 as either a new prescribing indicator or as a new documentation error using the inclusion/exclusion criteria. Of these 74 new indicators 34 were approved for inclusion in the round 1, 33 were rejected and 7 were approved as documentation errors (Table 2.2)

Table 2.2 Results of exploratory round

Outcome	Number (n=74)
Included	34 (46%)
Rejected	33 (45%)
Documentation Error	7 (9%)

Following these amendments the final list of indicators was completed. It contained 125 indicators, 91 from the original list circulated to the expert panel and 34 new indicators suggested by the panel (Table 2.5). In addition seven further indicators were included in the list of documentation errors Appendix 10.

Table 2.3 summarises the error types that were described by the indicators. The error types of the expert panel suggestions are also summarised. This shows a wide variety of error types and also indicates the expert panel's engagement with the process.

Table 2.3 Error types included in the indicators and those suggested by the expert panel

Error Type	Original Indicators	Suggested	Total
Adverse Effect	9		9
Contraindication	12	1	13
Wrong Dose	17	11	28
Dose Frequency	10	5	15
Dose/rate	2	1	3
Drug Choice	5		5
Drug-Disease	0	2	2

Drug-Disease Interaction	1		1
Drug-Drug Interaction	15	3	18
Drug-Food Interaction	1		1
Monitoring	4	4	8
Omitted Drug	3		3
Other	2	5	7
Route of Administration	1	0	1
Therapeutic Duplication	8	1	9
Treatment Duration	2		2
Grand Total	91	34	125

2.8.3 Reasons for Exclusion

Table 2.4 details the excluded indicators suggested by participants and the reasons for exclusion. The most common reason was that the indicator was not specific and would be captured by the documentation errors. Other reasons for exclusion included: description of a system attribute rather than an indicator, wide UK variation and an indicator that was not easily auditable.

Errors of omission were excluded because they were unlikely to be amenable to decision support. The current maturity of EP systems within UK hospitals was such that there are limited links between primary and secondary care. Only validated and secure links such as these or assessment of co-morbidities would make it possible to assess errors of omission on admission. The need to focus on drug specific indicators to make the scoring by the expert panel as easy as possible and to identify those high risk errors most likely to be prevented by EP was felt to outweigh the addition of a large number of errors of omission.

Table 2.4 Exploratory round - number of indicators excluded and reasons

Reason for Exclusion	No Excluded	Description	Example(s)
Documentation	11	Indicator will be covered by the documentation error monitoring	A “when required” medication prescribed without an indication. A dose prescribed that is impossible to measure without further manipulation
System attribute	9	Proposed indicator was a desired attribute of an e-prescribing system rather than an error	Presentation of both adult and paediatric prescribing orders without filtering based on age of patient.

Table 2.4 Exploratory round - number of indicators excluded and reasons continued

Reason for Exclusion	No Excluded	Description	Example(s)
Not Easily auditable	6	Indicator no easily assessed easily within normal ward activity	Delay in administration of vaccinations. Vancomycin prescribed intravenously for *C. difficile*
UK Variation	6	Wide variation of policy or practice around UK secondary care	Prescribing anti-convulsant by brand name.
Not specific enough	4	Indicator does not relate to a specific drug	Prescribing based on actual weight rather than dosing weight
Cause rather than error	2	Indicator describes the cause of an error rather than an error	Prescribing a dose from an out-of-date reference source
Omission	2	Indicator describes an error of omission not included in study	Inhalers not prescribed on admission
Trigger	2	Indicator describes a trigger event which may or may not mean an error has occurred	Strong opioids prescribed without naloxone
Monitoring	2	Indicator describes an error in monitoring rather than prescribing	Incorrect timing of digoxin levels
Administration	1	Indicator describes an error in drug administration rather than prescribing	Timing of IV antibiotics changed to awake times rather than optimal timings
Rare use	1	Drug rarely used in the UK	Prescription of triamcinolone without reference to the salt
Poor evidence	1	Poor evidence that indicator is a medication error	Phenytoin liquid prescribed to be administered concurrently with enteral feeds
Discharge error	1	Indicator relates to error occurring only at the point of discharge from hospital rather than the inpatient stay.	Changing phosphate supplement on discharge e.g. from sodium glycerophosphate to Phosphate Sandoz®

2.8.4 Documentation Errors

As described above, during the development process for the indicators it became clear that non-drug specific error types were important to recognise. A group of these was identified during the indicator identification process and these are listed in Appendix 10. The expert panel members were privy to these documentation errors during the exploratory round so as to make it clear to them that while they were not prescribing indicators, the intention was to

collect information on general errors during the evaluation. Following comments from the expert panel, three of the original 20 documentation errors were removed either because they were too complex to capture easily, duplicated with another documentation error or because it was deemed suitable as a specific prescribing indicator. The expert panel suggested eight further documentation errors, seven of which were included in the information for the subsequent eDelphi rounds and one was excluded as duplication. The results of this process are also shown in Appendix 10

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel.

No	Indicator	BNFC	Supporting Information	Error Type
1	Domperidone prescribed at > 1.2mg/kg/day max 20mg *(prolongation of QT interval, sudden cardiac death)*	1.3.0	Increased risk of arrhythmias and sudden cardiac death	Dose
2	Digoxin loading dose or frequency (oral or IV) prescribed incorrectly according to BNFC	2.1.1	Risk of supratherapeutic doses increasing risk of adverse effects	Dose
3	Digoxin maintenance dose started too soon or too late after completion of loading doses.	2.1.1	Risk of supratherapeutic doses increasing risk of adverse effects	Dose
4	Digoxin dose not reviewed in light of reduced renal function	2.1.1	Risk of supratherapeutic doses increasing risk of adverse effects	Monitoring
5	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*	2.2.3	Increased risk of severe hyperkalaemia	Drug-Drug Interaction
6	Amiodarone prescribed to a patient with abnormal thyroid function tests *(increased risk of thyroid disorders)*	2.3.2	Amiodarone can cause thyroid abnormalities	Adverse Effect
7	Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*	2.4.0	Beta-adrenoceptor blocking drugs are known to cause broncho-constriction in asthmatics, and can cause acute deterioration	Adverse Effect
8	ACE inhibitor or angiotensin-II receptor antagonist prescribed to a patient with a potassium level >5.0 mmol/litre *(can cause or exacerbate hyperkalaemia)*	2.5.5	ACE inhibitors and angiotensin-II receptor antagonists can cause hyperkalaemia and are contraindicated in patients with a potassium concentration about the desired reference range	Adverse Effect
9	Low molecular weight heparin prescribed to be administered concomitantly with unfractionated heparin*(increased risk of bleeding)*	2.8.1	Increased risk of bleeding	Therapeutic Duplication

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
10	Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment *(increased risk of bleeding)*	2.8.1	Increased risk of bleeding with the dose of low molecular weight heparin is not adjusted for renal function	Dose
11	Low molecular weight heparin prescribed at the wrong frequency according to the BNFC or product literature	2.8.1	Risk of supra or subtherapeutic levels of low molecular weight heparin	Dose Frequency
12	Warfarin prescribed to a patient with a concurrent bleeding problem *(risk of bleeding)*	2.8.2	High risk of bleeding when warfarin prescribed to patients with a past medical history of bleeding disorders	Contraindication
13	Warfarin prescribed concomitantly with a NSAID *(increased risk of bleeding)*	2.8.2	Increased risk of bleeding when co-prescribed with NSAID	Drug-Drug Interaction
14	NSAID (excluding low dose aspirin) prescribed to a patient with chronic renal failure *(increased risk of deteriorating renal function)*	2.8.2	Sodium and water retention may occur risk of decreasing renal function	Adverse Effect
15	NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without anti-secretory drugs or mucosal protectants *(increased risk of peptic ulceration and bleeding)*	2.8.2	Risk of GI ulcer / Reflux	Adverse Effect
16	Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	2.9.0	High risk of bleeding when antiplatelets prescribed to patients with a past medical history of bleeding disorders	Contraindication
17	Aspirin prescribed to pt <16 without appropriate indication *(risk of Reye's syndrome)*	2.9.0	Risk of Reye's Syndrome	Contraindication
18	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*	2.9.0	Risk of supratherapeutic or subtherapeutic dose of heparin	Dose/rate

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
19	Long-acting beta-2-agonist inhaler prescribed to a patient who is not also on an inhaled corticosteroid *(evidence base - not in line with British Thoracic Society guidelines)*	3.1.1	Not in line with British Thoracic Society guidelines)	Omitted Drug
20	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	3.1.1	Risk of supratherapeutic or subtherapeutic dose of salbutamol	Dose/Rate
21	Ivacaftor co-prescribed with an interacting drug with no dose adjustment of interacting drug *(risk of subtherapeutic levels of interacting drug)*	3.7.0	Risk of supratherapeutic or subtherapeutic levels of ivacaftor due to enzyme induction or inhibition	Drug-Drug Interaction
22	More than one paracetamol-containing product prescribed to be administered concomitantly *(maximum dose exceeded)*	4.7.1	Concomitant prescribing of more than one paracetamol containing product can result in doses over the daily limit for the age group	Therapeutic Duplication
23	Codeine phosphate prescribed to a patient under the age of 12 *(contraindicated)*	4.7.1	MHRA guidance restrict use of codeine in children due to risk of fatal toxicity	Adverse Effect
24	Tramadol prescribed concomitantly with antiepileptics *(increased risk of seizures in patients with uncontrolled epilepsy)*	4.7.1	Increased risk of seizures	Drug-Disease Interaction
25	Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates risk of toxicity)*	4.7.1	Increased risk of opioid toxicity	Therapeutic Duplication
26	Regular opiates prescribed without concurrent use of laxatives *(risk of severe constipation)*	4.7.2	Risk of severe constipation	Adverse Effect
27	Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)*	4.7.2	Oral and intramuscular doses are not equivalent, risk of therapeutic failure or toxicity	Therapeutic Duplication
28	Phenytoin dose not reviewed in light of low albumin *(potential for toxicity)*	4.8.1	Increased risk of phenytoin toxicity	Monitoring

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
29	Failure to increase dose of anticonvulsant in line with weight for epilepsy *(increased risk of seizure)*	4.8.1	Increased risk of seizures	Dose
30	Prescribing an incorrect starting dose of lamotrigine when used in combination with sodium valproate *(increased risk of ADR)*	4.8.1	Increased risk of adverse reaction in particular rashes	Adverse Effect
31	Clonazepam prescribed when clobazam required or vice versa	4.8.1	Risk of incorrect dose of the wrong drug and subsequent toxicity or therapeutic failure	Drug Choice
32	Prophylactic antimicrobials and treatment antimicrobials prescribed to be administered concomitantly *(increased risk of resistance)*	5.0.0	Risk of antimicrobial resistance	Therapeutic Duplication
33	Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) *(risk of hypersensitivity reactions)*	5.1.1	Contraindicated in pts with history of penicillin allergy. Risk of hypersensitivity reaction	Contraindication
34	Dose change for metronidazole not made when switching from an IV dose >400mg to oral *(risk of overdose)*	5.1.11	Increased risk of supratherapeutic dose of metronidazole	Dose
35	Quinolone antibiotic prescribed to a patient who is also receiving theophylline *(possible increased theophylline level)*	5.1.12	Possible increased theophylline level	Drug-Drug Interaction
36	Quinolone antibiotic prescribed to a patient with epilepsy *(increased risk of seizure threshold being reduced)*	5.1.12	Quinolone antibacterials lower the seizure threshold	Contraindication

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
37	Oral quinolone antibacterial prescribed at the same time as iron *(reduced absorption of quinolones)*	5.1.12	Iron reduces the absorption of quinolone antibacterials. At last 4 hours should separate the administration of a quinolone and iron	Drug-Drug Interaction
38	Oral Quinolones and enteral feeds prescribed concomitantly *(risk of treatment failure with quinolone)*	5.1.12	Reduced absorption of quinolone	Drug-Food Interaction
39	Intravenous ciprofloxacin prescribed twice daily instead of three times a day in children over 1 month old *(risk of therapeutic failure)*	5.1.12	Risk of subtherapeutic levels of ciprofloxacin	Dose Frequency
40	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	5.1.13	Risk of peripheral neuropathy and reduced therapeutic effect	Contraindication
41	Ceftriaxone prescribed at a total daily dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis in a patient > 1 month of age *(risk of under dosage)*	5.1.2	Potential subtherapeutic dose for severe infection/sepsis	Dose
42	Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or respiratory exacerbation of CF *(potential under treatment)*	5.1.2	Potential subtherapeutic dose for severe infection/sepsis	Dose
43	Co-prescribing of meropenem with sodium valproate *(increased risk of seizure)*	5.1.2	Reduction in valproate levels leading to increased risk of seizure	Drug-Drug Interaction
44	Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment *(increased risk of toxicity)*	5.1.4	Increased risk of toxicity	Dose
45	Gentamicin prescribed at a dose exceeding maximum stated in local protocol e.g. 7mg/kg/day to a child > 1month (risk of toxicity)	5.1.4	Increased risk of toxicity	Dose

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
46	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	5.1.4	Risk of excessive dosing and toxicity	Dose
47	Gentamicin prescribed at a dose exceeding 5mg/kg/dose to a neonate *(risk of toxicity)*	5.1.4	Increased risk of toxicity	Dose
48	Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*	5.1.5	Macrolide antibacterials can reduce the metabolism of warfarin, causing an increase in the INR and an increased risk of bleeding	Drug-Drug Interaction
49	Co-prescribing of macrolides with interacting drug *(QT prolongation)*	5.1.5	Risk of prolongation of QT interval and ventricular arrhythmia	Drug-Drug Interaction
50	Co-prescribing of a macrolide with domperidone *(QT prolongation)*	5.1.5	Risk of prolongation of QT interval and ventricular arrhythmia	Drug-Drug Interaction
51	Co-prescribing of a macrolide with an anticonvulsant *(risk of toxicity or subtherapeutic levels)*	5.1.5	Risk of supratherapeutic or subtherapeutic levels of anticonvulsant	Drug-Drug Interaction
52	Co-prescribing of a macrolide with ciclosporin or tacrolimus *(increases plasma levels of anti-rejection agent)*	5.1.5	Increased plasma concentration of ciclosporin	Drug-Drug Interaction
53	Co-prescribing of a macrolide with midazolam *(risk of sedation)*	5.1.5	Increased risk of sedation	Drug-Drug Interaction
54	Vancomycin prescribed intravenously to a patient with at least mild renal impairment without dose adjustment *(increased risk of toxicity)*	5.1.7	Increased risk of toxicity	Dose
55	Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	5.1.7	Increased risk of infusion reactions	Adverse Effect

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
56	Rifampicin co-prescribed with an interacting drug with no dose adjustment of interacting drug *(risk of subtherapeutic levels of interacting drug)*	5.1.9	Risk of subtherapeutic levels of interacting drug due to enzyme induction	Drug-Drug Interaction
57	Fluconazole prescribed more frequently than every 72 hours for a neonate < 14 days old *(risk of toxicity)*	5.2.1	Increased risk of toxic effects, Neonates have a 72 or 48 hour frequency based on age.	Dose Frequency
58	Fluconazole prescribed as standard dose from day 2 of treatment in a patient with an estimated GFR of < 50 ml/min/1.73m^2 *(risk of toxicity, normally halve dose after first day)*	5.2.1	Increased risk of toxic effects. Patients with renal failure <50ml/min/1.73m2 have standard dose for one dose then halved.	Dose Frequency
59	Fluconazole prescribed more frequently than every 48 hours for a neonate between 14 and 28 days old *(risk of toxicity)*	5.2.1	Increased risk of toxic effects. Neonates have a 72 or 48 hour frequency based on age.	Dose Frequency
60	Amphotericin B prescribed without additionally stating both brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid)*	5.2.3	Specification of brand name to reduce risk of wrong formulation being administered and resulting toxicity	Other
61	Failure to adjust dose or frequency of ganciclovir in the presence of altered renal function *(risk of toxicity or treatment failure)*	5.3.2	Risk of supratherapeutic or subtherapeutic levels of ganciclovir	Dose Frequency
62	Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	6.1.1	Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia especially if given more than 1 stat dose. Not managing the long-term condition	Dose Frequency
63	Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) *(increased risk of hypoglycaemia)*	6.1.1	Insulin should be prescribed at meal times to avoid the risk of hypoglycaemia	Dose Frequency

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
64	Oral prednisolone and intravenous hydrocortisone prescribed to be administered concomitantly simultaneously *(risk of toxicity)*	6.3.2	Increased risk of adverse effects	Therapeutic Duplication
65	Oral prednisolone and steroid inhalers prescribed to be administered concomitantly *(risk of toxicity)*	6.3.2	Increased risk of adverse effects	Therapeutic Duplication
66	Prednisolone EC prescribed for patient with Inflammatory Bowel Disease (reduced absorption of prednisolone)	6.3.2	Reduced absorption of predinsolone	Contraindication
67	Desmopressin prescribed for nocturnal enuresis at any other time than at bedtime (risk of fluid overload)	6.5.2	Risk of over hydration	Dose Frequency
68	Dose reduction of immunosuppressant not made despite low White Cell Count (risk of neutropenia)	8.0.0	Increased risk of neutropenia and subsequent infection, (list of common immunosuppressants will be included during data collection)	Monitoring
69	Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*	8.1.0	Risk of methotrexate toxicity	Omitted Drug
70	Failure to prescribe mesna for patients receiving alkylating agents *(risk of toxic symptoms)*	8.1.0	Risk of bladder toxicity	Omitted Drug
71	Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count *(risk of bone marrow suppression)*	8.1.3	Risk of bone marrow suppression	Monitoring
72	Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	8.1.3	Oral methotrexate should be dosed ONCE WEEKLY, and the prescription clear as to which day of the week this should be	Dose Frequency
73	Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*	8.1.3	Risk of liver toxicity	Contraindication

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
74	Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*	8.1.3	Trimethoprim suppresses activity of dihydrofolate reductase - potential for additive effect to produce folate deficiency. Increased risk of haematological toxicity when methotrexate given with trimethoprim (including trimethoprim containing compound - co-trimoxazole)	Contraindication
75	Methotrexate prescribed to be administered on the same day as folic acid *(reduced efficacy of methotrexate)*	8.1.3	Concomitant administration of folic acid with methotrexate will reduce efficacy of methotrexate	Contraindication
76	Allopurinol prescribed concomitantly with azathioprine *(allopurinol enhances effect of azathioprine and increases risk of toxicity)*	8.1.3	Increased risk of toxicity and enhanced effects of azathioprine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Drug-Drug Interaction
77	Allopurinol prescribed concomitantly with mercaptopurine *(allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*	8.1.3	Increased risk of toxicity and enhanced effects of mercaptopurine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Drug-Drug Interaction
78	Tacrolimus prescribed without reference to brand name *(variation in pharmacokinetics and dosing)*	8.2.2	Risk of subtherapeutic levels due to differences in pharmacokinetics	Other
79	Calcium resonium prescribed when the potassium concentration is within the desired reference range (3.5–5.3 mmol/litre) *(risk of hypokalaemia)*	9.2.1	Calcium resonium should be stopped when the potassium concentration is within the desired reference range, as it continues to work for a few days once discontinued	Treatment Duration
80	Potassium chloride supplements continued for longer than is required (based on age appropriate local reference ranges approx 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*	9.2.1.1	Failure to act on potassium chloride monitoring and continuing treatment for longer than required risks hyperkalaemia	Treatment Duration

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
81	Prescribing of sodium chloride 0.18% with glucose 4% solutions as post-operative intravenous fluid *(risk of cerebral oedema)*	9.2.2	Risk of cerebral oedema	Drug Choice
82	Potassium chloride infusions exceeding 40 mmol/litre prescribed to administered via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*	9.2.2	Intravenous administration of potassium chloride solutions exceeding 40mmol/litre should be prescribed via the central route to avoid arrhythmias	Route of Administration
83	Incorrect stock parenteral nutrition bag prescribed based on local protocol	9.3.0	Risk of inappropriate nutrition	Drug Choice
84	More than one NSAID prescribed to a patient at a time *(increased risk of bleeding)*	10.1.1	Increased risk of bleeding when more than one NSAID is prescribed.	Therapeutic Duplication
85	Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m^2)	10.2.2	Increased risk of toxic effects	Dose
86	Live vaccine prescribed to an immunosuppressed patient, including those on corticosteroids *(increased risk of reaction or infection)*	14.0.0	Risk of reaction/infection	Contraindication
87	Prescribing the incorrect vaccines for childhood immunisation based on the current vaccination guidelines *(risk of serious childhood infection)*	14.1.0	Lack of immunity for serious childhood infections	Drug Choice
88	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration	15.1.4	Risk of supratherapeutic or subtherapeutic dose of midazolam	Dose
89	Acetylcysteine prescribed at a dose inconsistent with the product literature for paracetamol poisoning	General	Risk of sub or supratherapeutic doses with treatment failure or toxicity	Dose

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
90	Dose change for ciprofloxacin not made when switching from IV to oral *(risk of overdose)*	5.1.12	Risk of supratherapeutic dose of ciprofloxacin	Dose
91	A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)*	General	Risk of anaphylaxis	Contraindication
92	Dose of paracetamol prescribed inappropriate for route of administration *(potential overdose due to change in route or misreading of BNFC)*	4.7.1	Risk of paracetamol overdose	Dose
93	Amiodarone prescribed to a patient on digoxin without review of the digoxin dose	2.3.2	Risk of digoxin toxicity	Drug-Drug Interaction
94	Caffeine citrate maintenance dose prescribed to start too soon or too late after loading dose *(should be 24 hours)*	3.5.1	Risk of sub or supra therapeutic dose	Dose Frequency
95	Oral quinolone prescribed to be administered at the same time as an oral calcium	5.1.12	Risk of treatment failure	Drug-Drug Interaction
96	Ceftriaxone prescribed at a dose greater than 50mg/kg in a patient < 1month old	5.1.2	Risk of supratherapeutic dose of Ceftriaxone	Dose
97	Aciclovir prescribed to a patient with at least mild renal impairment without dose adjustment	5.3.2	Increased risk of toxicity	Monitoring
98	Desmopressin nasal formulation prescribed for nocturnal enuresis *(increased incidence of side effects)*	6.5.2	Risk of toxicity due to increased bioavailability of nasal formulation	Contraindication
99	Dose of cefotaxime exceeding 200mg/kg/day in patients <4 weeks old	5.1.2	Risk of toxicity	Dose
100	Amiodarone loading dose prescribed incorrectly according to BNFC	2.3.2	Risk of sub or supra therapeutic dose	Dose

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
101	Aciclovir prescribed at a dose of 250mg/m2 instead of 500mg/m2 for herpes simplex encephalitis in patients aged between 3 months and 12 years	5.3.2	Risk of treatment failure	Dose
102	Thiopurines (azathioprine and 6MP) prescription in presence of abnormal liver function tests (LFTs will be defined)	8.1.3	Increased risk of toxicity	Monitoring
103	Intravenous aminophylline prescribed without appropriate monitoring or adjustment of dose in relation to theophylline levels	3.1.3	Risk of sub or supra therapeutic levels	Monitoring
104	Ranitidine dose not altered when switching between oral and IV routes	1.3.1	Risk of sub or supra therapeutic doses	Dose
105	IV cefuroxime prescribed using the oral dose (20mg/kg/dose twice daily)	5.1.2	Subtherapeutic dose leading to potential treatment failure	Dose
106	Gabapentin prescribed without gradually increasing the dose	4.8.1	Increased risk of toxicity	Dose
107	Theophylline prescribed without reference to the brand	3.1.3	Risk of sub or supratherapeutic doses and subsequent treatment failure or toxicity	Other
108	Furosemide prescribed twice daily in neonates < 31 weeks gestational age	2.2.2	Risk of toxicity	Dose Frequency
109	Prescription for beclometasone inhaler without reference to the brand	3.2.0	Difference in bioavailability between Qvar and Clenil brands. Risk of toxicity or treatment failure	Other
110	Prescription for Intramuscular ceftriaxone without co-prescription of lidocaine for reconstitution	5.1.2	Lidocaine used to prepare ceftriaxone and reduce pain at injection site.	Other
111	Concomitant prescription of ibuprofen/indometacin and hydrocortisone in neonatal patient	2.14.0	Risk of spontaneous gastrointestinal perforation	Drug-Drug Interaction

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
112	Co - prescribing of nebulised tobramycin and intravenous tobramycin in CF patients	5.1.4	Risk of toxicity	Therapeutic Duplication
113	Prescription of NSAIDS in suspected toxic shock syndrome *(contraindicated but patients are pyrexial)*	10.1.1	Risk of enhanced cytokine release contributing to shock, organ failure etc	Drug-Disease
114	Regular prescription of anti-pyretic in paediatric oncology patients	4.7.1	Risk of masking neutropenic sepsis	Drug-Disease
115	Maintenance fluids prescribed such that >3litres of fluid would be administered in 24 hours	9.2.2	Exceeds maximum adult maintenance fluid	Dose/Rate
116	Failure to increase of hydrocortisone to “sick day doses” from “maintenance” doses in those adrenally suppressed	6.3.2	Reduces risk of shock	Dose
117	Prescription of mycophenolate with no reference to salt or brand	8.2.2	Risk of sub or supratherapeutic levels	Other
118	Failure to increase dose of prophylactic trimethoprim with increasing weight	5.1.13	Risk of sub therapeutic levels and treatment failure	Dose
119	Failure to increase frequency of IV benzylpenicillin over the first 5 weeks of life	5.1.1	Risk of treatment failure	Dose Frequency
120	Failure to increase frequency of oral or IV flucloxacillin over the first 4 weeks of life	5.1.1	Risk of treatment failure	Dose Frequency
121	Failure to increase the frequency of IV cefotaxime over the first 4 weeks of life	5.1.2	Risk of treatment failure	Dose Frequency
122	Sodium supplements continued for longer than is required (based on age appropriate local reference ranges approx 135 - 145 mmol/litre) *(increased risk of hypernatraemia)*	9.2.1	Risk of hypernatraemia	Monitoring

Table 2.5 Final list of indicators used for subsequent rounds of scoring. Shaded indicators are those suggested by the expert panel. Continued

No	Indicator	BNFC	Supporting Information	Error Type
123	Prescribing caffeine using base rather than salt i.e. caffeine rather than caffeine citrate *(risk of sub-therapeutic dosing)*	3.5.1	Risk of subtherapeutic dosing	Other
124	Dose value of alfacalcidol in nanograms expressed as micrograms	9.6.4	Risk of 1000 time overdose	Dose
125	Prescribing a fluid containing dextrose rather than glucose	9.2.2	Risk of confusion at drug selection/administration stage	Drug Choice

BNFC = British National Formulary for Children, ACE – Angiotensin Converting Enzyme, NSAID = Non-Steroidal Anti-Inflammatory Drug, WHO = World Health Organization, ADR = Adverse Drug Reaction, CF = Cystic Fibrosis, GFR = Glomerular Filtration Rate, EC = Enteric Coated, 6MP = 6-Mercaptopurine

2.9 Discussion

This chapter has described the process of development of a list of prescribing indicators that were subsequently reviewed by an expert panel for both severity and likelihood (as reported in Chapter 3). The process of development involved the generation of an initial list of indicators from a range of sources and the additional comments and suggestions from the expert panel who reviewed this initial list. The resulting list contained 125 indicators.

The inclusion and exclusion criteria for the indicators meant that they had to relate to specific drugs. In the paediatric setting the most common prescribing error is widely reported as being wrong dose. It is impossible to capture all wrong dose prescribing errors using specific prescribing indicators as this would require an indicator for every possible drug; however, it is important to be able to identify these errors as easily as possible when studying the impact of an electronic prescribing system. This problem was resolved by the development of the documentation errors. Providing the expert panel with the assurance that general dosing errors would be captured using these documentation errors enabled them to focus on drug specific indicators that were likely to cause harm. The indicators did include wrong dose errors, but these were attributed to drugs such as gentamicin, enoxaparin, and the antimicrobials which had been identified during the development process.

Table 2.3 shows the distribution of the indicators by error type. The most common error type was wrong dose. This is to be expected as it has been widely reported that the most common prescribing error type in paediatrics is wrong dose.[30, 39, 96] Interestingly, it was also the most common new indicator suggested by panel members, implying experience of this type of error is relatively common. The next most common error types were drug-drug interactions (n=18), dose frequency (n=15) and contraindication (n=13). In the case of interactions and contraindications the majority of these indicators came from the adult work.[90] The relatively high number of dose frequency errors could be accounted for by two reasons. Firstly, it may be difficult to separately categorise wrong dose errors from dose frequency errors and as stated above wrong dose errors are very common in children. Secondly, dose frequencies change more often in paediatrics. This is shown in several of the indicators relating to the neonatal period where the frequency (but not dose) of benzylpenicillin and flucloxacillin increases over the first four weeks of life.

2.10 Limitations

One possible limitation of this exercise is that not all possible prescribing indicators have been identified. The risk of this was minimised by using a combination of sources for potential indicators including both adult and paediatric literature as well as information from the NRLS which included 60,000 medication errors.[39] In order to further extend the scope of the indicators the expert panel members were asked to provide further indicators. It is clear from the results that the panel were entirely engaged by this process with 15 of them suggesting at least one new indicator and altogether 74 new indicators of which 34 were included in the final list.

Another limitation was the exclusion of indicators that were not amenable to decision support. The most common indicator suggested by the expert panel of this type were errors of omission. Reasons for excluding this type of indicator include the fact that they are unlikely to be amenable to decision support. As EP systems evolve it is likely that they will become advanced enough to identify these types of errors. The indicators should be reviewed at regular periods taking into account both the maturity of EP systems and newly identified prescribing errors or drugs.

Chapter 3 eDelphi Scoring and Consensus

3.1 Introduction

This chapter describes the methodology and results obtained from the eDelphi process using the indicator list described in Chapter 2. The aim was to develop a set of high risk paediatric prescribing indicators for use as an evaluation tool for EP systems.

3.2 Method

The development of the initial indicator list, execution of the exploratory round and subsequent results is described in Chapter 2. This resulted in a list of 125 prescribing indicators (Table 2.5). Figure 3.1 shows the eDelphi process in full together with a timeline.

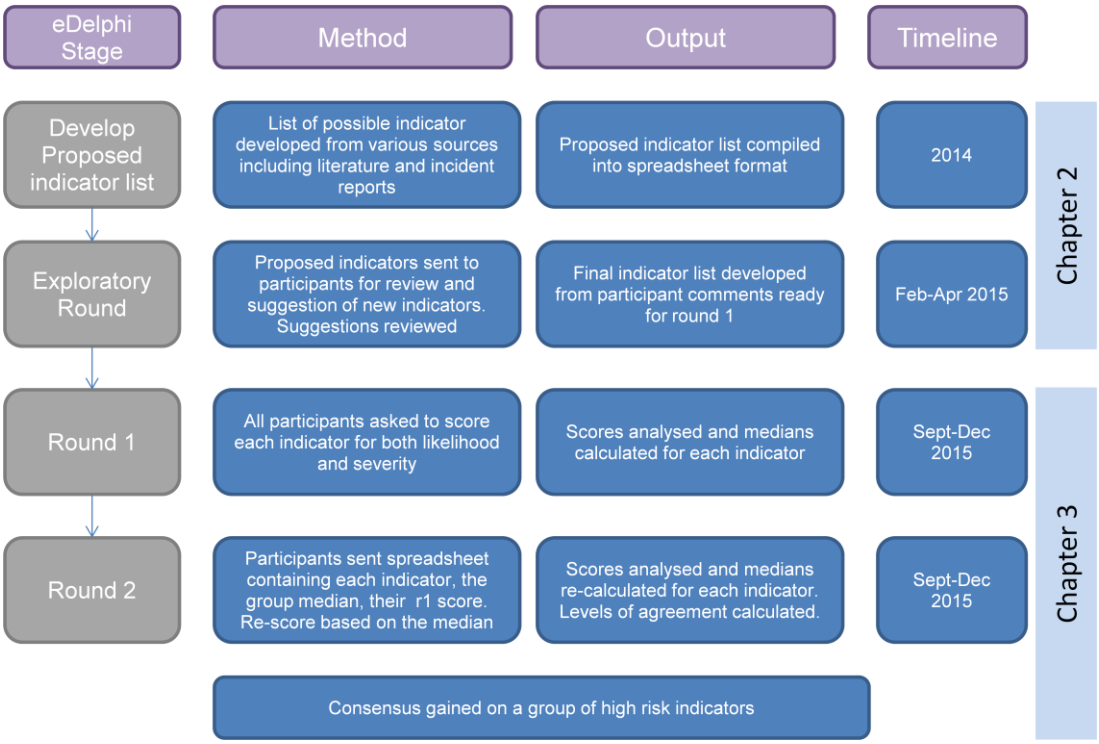


Figure 3.1 - Diagrammatic representation of eDelphi process

3.2.1 Research Approval

The method used in this work was exactly the same as that used by the team who developed the adult indicators. In that case ethical approval was not required as the project was not deemed to be research. Retrospective assessment using the HRA online tool confirmed this. At the time the study took place the HRA were not in existence.

3.2.2 Round 1

An Excel spreadsheet containing a list of all the indicators developed from the exploratory round was circulated via email to each panel member (see Table 2.1 for constituency of panel) together with a set of clear instructions on how to rate each indicator (Appendix 13) .

Panellists were asked to rate each indicator for its likelihood of occurrence and severity of harm should it occur. The scoring system used was based on the National Patient Safety Agency scale in common use in UK hospitals.[115]

The indicators defined in Chapter 2 described specific circumstances where a prescribing error might occur, rather than describing an actual error. The respondents were asked to consider the likelihood of the prescribing error defined by the indicator to occur and the subsequent severity of the resulting harm.

Likelihood scoring – Table 3.1 shows the scoring for degrees of likelihood from rare to almost certain. Panellists were asked to decide how likely it was for a specific prescribing indicator to occur.

Table 3.1 Likelihood scoring and descriptors[115]

Likelihood Score	1	2	3	4	5
Description	**Rare** This will probably never occur	**Unlikely** Do not expect it to occur but it is possible it may do so	**Possible** This might occasionally occur	**Likely** This will probably occur	**Almost Certain** This will undoubtedly occur, possibly frequently

Severity Scoring - Table 3.2 shows the scoring for various degrees of severity from insignificant to catastrophic. Panellists were asked to score each indicator based on the severity of the consequences to the patient, should the prescribing error reach the patient.

Table 3.2 Severity scoring and descriptors[115]

Severity Score	1	2	3	4	5
Description	**Insignificant** No risk of patient injury or harm and no intervention required	**Minor** Minor injury or illness requiring minor intervention	**Moderate** Moderate injury requiring intervention	**Major** Major injury or illness leading to long-term incapacity / disability	**Catastrophic** Leads to death, multiple permanent injuries or irreversible health effects

On receipt of each panellist's scores the results were entered onto a second spreadsheet for analysis. Each indicator had two scores one for likelihood and one for severity. These were then combined to produce a risk score between 1 and 4 using the risk assessment table (Table 3.3). For example a likelihood score of 2 and a severity score of 4 would give a risk score of 3 (high risk). This table was used to simplify all the possible combinations of likelihood and severity into four grades of risk.

Table 3.3 - Risk scoring matrix. Key: 1 = low, 2= medium, 3 = high, 4 = extreme.

	Severity				
Likelihood	1	2	3	4	5
5	2	3	4	4	4
4	2	3	3	4	4
3	1	2	3	3	4
2	1	2	2	3	3
1	1	1	1	2	2

A risk score from each panellist for each indicator was calculated in this way. The median risk scores for each indicator were then calculated, allowing the indicators to be divided into risk groups, based on their median risk scores.

3.2.3 Round 2

For Round 2 an individualised Excel spreadsheet was created for each panellist. It contained the same list of indicators from Round 1, the individual panel member's severity and likelihood scores and the median severity and likelihood scores from Round 1. Panel members were then asked to review their original scores in light of the median scores of the group. Following receipt of the Round 2 scores, the same process was undertaken with the scores to create a risk score and median severity and likelihood scores.

3.2.4 Consensus

Level of consensus was determined by analysing the median risk scores. Indicators with a median risk score of 3 or 4 and at least 80% consensus i.e. 80% of respondents were in agreement, were considered to have achieved an adequate level of consensus. This level of agreement was chosen as it had been previously used in the work published by Thomas *et al*[90] and was also described by Nair *et al*[116] as one of the methods of determining consensus particularly when quantitative data was being collected rather than qualitative.

3.3 Results

3.3.1 Round 1

The first round of scoring was completed by 21 panel members. Seventy four of the indicators achieved high risk scores (3 or 4). There were 11 indicators that had achieved at least 80% consensus of which 8 were in the high risk group.

3.3.2 Round 2

The second round of scoring was completed by all 21 panellists. Eighty six of the indicators achieved high risk scores. There were 57 indicators that achieved at least 80% consensus of which 41 were also considered high risk; these are summarised in Table 3.4. None of the indicators were assessed as extreme risk by the panellists. A full list of all 125 indicators and their consensus scores are shown in Appendix 14.

The 41 indicators included 34 different drugs or classes from the following therapeutic groups: gastrointestinal (n=1), cardiovascular (n=7), respiratory (n=1), central nervous system (n=3), antimicrobials (n=10), endocrine (n=2), immunosuppression (n=6), fluids and electrolytes (n=1), musculoskeletal (n=2) and anaesthesia (n=1).

The most frequent error type identified as high risk was dosing (n= 19) with drug-drug interactions (n=7) and clinical contraindications (n=6) the next two most frequent error types.

Table 3.4 Final list of 41 paediatric prescribing indicators with high risk and greater than 80% consensus

Indicator	Possible Outcome	Therapeutic Class	Error Type	Level of Consensus
Domperidone prescribed at > 1.2mg/kg/day max 20mg *(prolongation of QT interval, sudden cardiac death)*	Increased risk of arrhythmias and sudden cardiac death	Gastrointestinal	Dosing	86%
Prescription of NSAIDS in suspected toxic shock syndrome *(contraindicated but patients are pyrexial)*	Risk of enhanced cytokine release contributing to shock, organ failure etc	Musculoskeletal	Clinical Contraindication	81%
Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m2)	Increased risk of toxic effects	Musculoskeletal	Dosing	90%
Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration	Risk of supratherapeutic or subtherapeutic dose of midazolam	Anaesthesia	Dosing	81%
Digoxin dose not reviewed in light of reduced renal function	Risk of supratherapeutic doses increasing risk of adverse effects	Cardiovascular	Dosing	95%
Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*	Increased risk of severe hyperkalaemia	Cardiovascular	Drug-Drug Interaction	90%
Amiodarone prescribed to a patient on digoxin without review of the digoxin dose	Risk of digoxin toxicity	Cardiovascular	Drug-Drug Interaction	81%
Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*	Beta-adrenoceptor blocking drugs are known to cause bronchoconstriction in asthmatics, and can cause acute deterioration	Cardiovascular	Clinical Contraindication	81%

Table 3.4 Final list of 41 paediatric prescribing indicators with high risk and greater than 80% consensus continued

Indicator	Possible Outcome	Therapeutic Class	Error Type	Level of Consensus
Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment *(increased risk of bleeding)*	Increased risk of bleeding with the dose of low molecular weight heparin is not adjusted for renal function	Cardiovascular	Dosing	86%
Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	High risk of bleeding when antiplatelets prescribed to patients with a past medical history of bleeding disorders	Cardiovascular	Clinical Contraindication	81%
Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*	Risk of supratherapeutic or subtherapeutic dose of heparin	Cardiovascular	Dosing	86%
Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	Risk of supratherapeutic or subtherapeutic dose of salbutamol	Respiratory	Dosing	81%
Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates risk of toxicity)*	Increased risk of opioid toxicity	CNS	Therapeutic Duplication	86%
Dose of paracetamol prescribed inappropriate for route of administration *(potential overdose due to change in route or misreading of BNFC)*	Risk of paracetamol overdose	CNS	Dosing	81%
Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)*	Oral and intramuscular doses are not equivalent, risk of therapeutic failure or toxicity	CNS	Dosing	81%
Phenytoin dose not reviewed in light of low albumin *(potential for toxicity)*	Increased risk of phenytoin toxicity	CNS	Dosing	86%

Table 3.4 Final list of 41 paediatric prescribing indicators with high risk and greater than 80% consensus continued

Indicator	Possible Outcome	Therapeutic Class	Error Type	Level of Consensus
Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) *(risk of hypersensitivity reactions)*	Contraindicated in pts with history of penicillin allergy. Risk of hypersensitivity reaction	Anti-Microbial	Allergy	81%
Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	Risk of peripheral neuropathy and reduced therapeutic effect	Anti-Microbial	Dosing	80%
Ceftriaxone prescribed at a total daily dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis in a patient > 1 month of age *(risk of under dosage)*	Potential subtherapeutic dose for severe infection/sepsis	Anti-Microbial	Dosing	90%
Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or respiratory exacerbation of CF *(potential under treatment)*	Potential subtherapeutic dose for severe infection/sepsis	Anti-Microbial	Dosing	86%
Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment *(increased risk of toxicity)*	Increased risk of toxicity	Anti-Microbial	Dosing	81%
Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	Risk of excessive dosing and toxicity	Anti-Microbial	Dosing	100%

Table 3.4 Final list of 41 paediatric prescribing indicators with high risk and greater than 80% consensus continued

Indicator	Possible Outcome	Therapeutic Class	Error Type	Level of Consensus
Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*	Macrolide antibacterials can reduce the metabolism of warfarin, causing an increase in the INR and an increased risk of bleeding	Anti-Microbial	Drug-Drug Interaction	90%
Co-prescribing of macrolides with interacting drug *(QT prolongation)*	Risk of prolongation of QT interval and ventricular arrhythmia	Anti-Microbial	Drug-Drug Interaction	86%
Co-prescribing of a macrolide with ciclosporin or tacrolimus *(increases plasma levels of anti-rejection agent)*	Increased plasma concentration of ciclosporin	Anti-Microbial	Drug-Drug Interaction	86%
Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	Increased risk of infusion reactions	Anti-Microbial	Administration	81%
Amphotericin B prescribed without additionally stating both brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid*)	Specification of brand name to reduce risk of wrong formulation being administered and resulting toxicity	Anti-Microbial	Drug Name	90%
Failure to adjust dose or frequency of Ganciclovir in the presence of altered renal function *(risk of toxicity or treatment failure)*	Risk of supratherapeutic or subtherapeutic levels of ganciclovir	Anti-Microbial	Dosing	80%
Aciclovir prescribed at a dose of 250mg/m2 instead of 500mg/m2 for herpes simplex encephalitis in patients aged between 3 months and 12 years	Risk of treatment failure	Anti-Microbial	Dosing	90%

Table 3.4 Final list of 41 paediatric prescribing indicators with high risk and greater than 80% consensus continued

Indicator	Possible Outcome	Therapeutic Class	Error Type	Level of Consensus
Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia especially if given more than 1 stat dose. Not managing the long-term condition	Endocrine	Clinical Contraindicatio n	85%
Failure to increase of hydrocortisone to “sick day doses” from “maintenance” doses in those adrenally suppressed	Reduces risk of shock	Endocrine	Dosing	95%
Dose reduction of immunosuppressant not made despite low White Cell Count *(risk of neutropenia)*	Increased risk of neutropenia and subsequent infection, (list of common immunosuppressant will be included during data collection)	Immunosuppressant	Dosing	90%
Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*	Risk of methotrexate toxicity	Immunosuppressant	Drug Omission	80%
Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count *(risk of bone marrow suppression)*	Risk of bone marrow suppression	Immunosuppressant	Clinical Contraindicatio n	90%
Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	Oral methotrexate should be dosed ONCE WEEKLY, and the prescription clear as to which day of the week this should be	Immunosuppressant	Dosing	100%
Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*	Risk of liver toxicity	Immunosuppressant	Clinical Contraindicatio n	85%

Table 3.4 Final list of 41 paediatric prescribing indicators with high risk and greater than 80% consensus continued

Indicator	Possible Outcome	Therapeutic Class	Error Type	Level of Consensus
Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*	Trimethoprim suppresses activity of dihydrofolate reductase - potential for additive effect to produce folate deficiency. Increased risk of haematological toxicity when methotrexate given with trimethoprim (including trimethoprim containing compound - co-trimoxazole)	Immunosuppressant	Drug-Drug Interaction	85%
Allopurinol prescribed concomitantly with mercaptopurine *(Allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of mercaptopurine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Immunosuppressant	Drug-Drug Interaction	80%
Potassium chloride supplements continued for longer than is required (based on age appropriate local reference ranges approx 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*	Failure to act on potassium chloride monitoring and continuing treatment for longer than required risks hyperkalaemia	Nutrition	Dosing	81%
Potassium chloride infusions exceeding 40 mmol/litre prescribed to administered via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*	Intravenous administration of potassium chloride solutions exceeding 40mmol/litre should be prescribed via the central route to avoid arrhythmias	Nutrition	Administration	86%
A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)*	Risk of anaphylaxis	General	Allergy	100%

BNFC = British National Formulary for Children, ACE – Angiotensin Converting Enzyme, NSAID = Non-Steroidal Anti-Inflammatory Drug, WHO = World Health Organization, ADR = Adverse Drug Reaction, CF = Cystic Fibrosis, GFR = Glomerular Filtration Rate, EC = Enteric Coated, 6MP = 6-Mercaptopurine

3.4 Discussion and Conclusion

The eDelphi process identified 41 high risk prescribing indicators for the paediatric hospital setting. They can potentially be used to monitor the impact of electronic prescribing or clinical decision support tools. To the authors' knowledge, this is the first set of prescribing indicators for paediatric patients in the hospital setting.

The consensus process used to derive the indicators involved a panel of experts consisting of 21 paediatricians and paediatric pharmacists all of whom complete two rounds of scoring, limiting any bias introduced by missing responses.

The scoring system used in the eDelphi process was a five point scale. This was chosen as it directly correlated with the well recognised risk assessment scoring system published by the NPSA[117] which is used in all NHS Trusts in England. A 9 point scale could have been chosen to allow participants to respond with a finer degree of detail, however, this was discounted because of the absence of clear descriptors for a nine point scale. The five point scale used included a descriptor for each of the points in relation to both likelihood and severity and therefore was felt to be easier and more intuitive for respondents.

The number of rounds of scoring was limited to 2 because this had produced 41 indicators which covered a range of prescribing error types. In addition it was felt that a further round of scoring would not have derived any greater degrees of consensus and was unlikely to be completed in a timely manner by all participants. The missing data from a third and subsequent rounds would make the degree of consensus less robust In a review of consensus methods Waggoner *et al*[118] concluded that two rounds of scoring was the optimum and that to have more would need to be justified on the basis that adequate consensus had not been achieved and the possible reasons for this

The panel size in this study was similar in size to that used in the work by Thomas *et al*[90] where a panel of 20 participants was used. Waggoner *et al*[118] reviewed consensus methods and concluded that for all methods a panel of 5 to 11 members was beneficial. In conventional Delphi studies the arguments proposed for which consensus is required are proposed by a facilitator. In this work the a larger panel was used because, in addition to obtaining consensus the expertise of the panel was used to review the indicators proposed and

provide suggestions for other indicators that may have been overlooked by the author. This allowed for the development of a more robust list of indicators.

Nearly half (n = 19) of the final 41 indicators related to dosing errors. This is not surprising since dose errors account for the majority of the indicators identified for rounds 1 and 2. This is likely to be influenced by the fact that dosing errors are the most common error type reported in paediatrics.[7, 30, 96] Drugs with known risks such as gentamicin, phenytoin and methotrexate were included in the dosage indicators; however, "lower risk" drugs such as meropenem, ceftriaxone and domperidone are also present. This may reflect, in the case of the antimicrobials, the relatively serious clinical indications in which these drugs are used and the need to prescribe the correct dose to avoid treatment failure as well as heightened awareness as a result of antimicrobial stewardship; or in the case of domperidone the relatively recent publicity relating to adverse reactions.[119]

Previously published work has identified high-alert medicines within paediatrics. Maaskant *et al*[120] published a list containing fourteen specific drugs and 4 medication classes of high-alert medications. Comparing this with the author's prescribing indicators shows that 10 of the individual drugs and three of the drug classes are duplicated. The four high-alert drugs not identified in the author's prescribing indicators are all infusions commonly used in intensive care areas, such as dopamine and noradrenaline. Reference to errors involving infusions was excluded from the present research because the reported incidents all related to errors occurring as a result of incorrect administration or infusion preparation rather prescribing. The high-alert drug class from the Masskant *et al*[120] report that is not included in the author's prescribing indicators relates to parenteral nutrition. Errors reported relating to parenteral nutrition concerned administration or preparation errors rather than prescribing. This possibly reflects UK practice in terms of these medications where standard prescriptions and electronic systems for parenteral nutrition have been developed to prevent errors at the prescribing stage.

Stockwell *et al*[121] published a list of paediatric triggers developed using an eDelphi technique and an international panel. From their list of 21 triggers relating to medicines, 11 also appear in the present paediatric prescribing indicator list. The triggers describe adverse events that could result from any

incorrect use of a medicine. For example the administration of Digibind® could be triggered by an error in the prescribing, dispensing, administration or monitoring of digoxin. This is an appropriate way of identifying an adverse event *after* it has occurred. The indicators identified in this research, however, are specific for the prescribing process and can be used to identify errors at the prescribing stage, which may be in advance of the medicine being administered. This can tell us whether quality improvement interventions such as ePrescribing can prevent the 'potential' for harm occurring.

Many of the paediatric indicators for the exploratory round were derived from the adult indicators previously published.[90] The final list of 41 paediatric indicators contains 28 indicators modified from the research conducted in adult medicine. Many of the remaining indicators were related to specific paediatric settings or medicines not usually classed as high risk in adults as such as meropenem, as discussed above.

Reports of the incidence of prescribing errors in the paediatric setting vary between 7 and 13%.[30, 31] This is partly because there is no standard definition of what and how to collect information about errors. Studies use different data collection methods and different definitions of medication error.[122] This lack of standardisation makes comparison between reports difficult to assess.

Prescribing indicators can be used to assess the impact of a safety improvement intervention by standardising both pre- and post-implementation data collection. The objective nature of these data would allow comparisons and conclusions to be drawn and provide more robust evidence across healthcare settings. The standardisation means that for the first time, comparisons can be made between hospitals and different initiatives.

The indicators can also be used to optimise the capability of electronic prescribing systems, such as with the provision of complex clinical decision support to highlight and avert such errors at the point of prescribing. This also has the potential to focus alerts on high risk areas, with the advantage of reducing alert fatigue.[123]

While the paediatric indicators described here are focused on the secondary care setting, many could be applicable to general practice. There are currently no primary care related exclusive paediatric trigger tools published in the literature.

3.4.1 Limitations

The initial list of indicators was derived from an extensive literature search and therefore, unpublished cases of medication errors would not have been included. However, the author aimed to reduce this effect by including the exploratory round so panellists had the opportunity to propose indicators or errors they see in practice.

One of the limitations cited in the work by Thomas *et al*[90] was that the indicators provided to the expert panel in the exploratory round were already high risk indicators. In their work the initial list had been derived from a combination of personal experience and the literature. They did not have access to pharmacy interventions or NRLS data. Their initial list contained 210 indicators which was limited to 130 by the research team prior to the first exploratory round because they were neither prescribed at a reasonable frequency or considered to be sufficiently high risk. This review process meant that the list of indicators presented in their first exploratory round already contained high risk indicators. A similar process took place in this work but the majority of exclusions prior to the exploratory round were because the indicator drug was rarely prescribed in paediatric practice. This may account for the lower proportion of indicators that achieved consensus in this work when compared with the adult indicators.

The paediatric indicator work presented here is entirely UK based and as such, may not have applicability in other global settings. Lastly, as new evidence emerges and new drugs begin to be used, other potential indicators may become relevant. The adult indicators previously cited are currently under review and if the paediatric indicators described here become extensively utilised a program of periodic review will be necessary.

No specific definition of a prescribing error was provided to respondents, in fact the terminology used within the instructions used both the term indicator and error. It is possible that this lack of definition may have led to confusion in the way in which respondents scored the indicators. This was thought to be unlikely due to the fact that the respondents were involved in the development of the indicators in the first place and were able to clarify specific points with the author during the scoring process.

3.4.2 Conclusion

Paediatric prescribing errors with the potential to cause harm have been identified by an expert panel. The indicators provide an objective tool that can be used to test the ability of an EP system to prevent the prescribing errors described in the indicators. They could also be used to refine alerting systems used in electronic prescribing to target warnings and alleviate alert fatigue. A description of how the indicators were used to evaluate a range of EP systems is described in Chapter 4.

Chapter 4 Paediatric Prescribing Error Simulation

4.1 Introduction

It is clear from the literature that prescribing errors in secondary care are common and probably more frequent in paediatric patients.[28] The evidence relating to the effectiveness of electronic prescribing (EP) in reducing medication errors in children was reviewed in Chapter 1. The conclusion was that EP reduced medication errors however, the effectiveness of EP to reduce harm to patients from errors was not clear. Furthermore where studies have included harm within their analyses only those systems with clinical decision support (CDS) have been shown to have any impact. This programme of work has sought to identify a specific set of paediatric prescribing indicators that, by consensus, described errors that are highly likely to cause harm if they reach the patient. They can, therefore, be used prospectively to assess the impact of an EP implementation within a hospital. Indeed the All Wales Prescribing group has recently agreed to use both the paediatric indicators developed here together with the adult indicators developed elsewhere[90] to assess the impact of an EP system for Wales.[124] Pre- implementation data collection has recently started. The indicators can also potentially be used to test a system already in place for its ability to reduce the risk of the errors known to cause harm and, therefore, provide an understanding of the likelihood that a specific EP system will reduce harm. System administrators can review their systems in light of the results. Going forward, system vendors could use the indicators to show the relative safety of their system and even compare it to other systems, providing a degree of competition between vendors which may, in the longer term, increase patient safety.

This chapter describes the use of the paediatric prescribing indicators that were developed in the first part of this project (see Chapter 3) to ascertain the effectiveness of current EP systems in use in paediatric patients in NHS England Hospitals to help to prevent the errors described by the indicators.

4.2 Aim

The aim of this research was to ascertain the effectiveness of current EP systems to prevent a specific group of paediatric prescribing errors (identified using pre-defined indicators).

4.2.1 Objectives

- To develop a set of high risk paediatric prescribing indicators for use as an evaluation tool for EP systems (reported in Chapters 2 and 3)
- To establish the performance of a range of EP implementations in preventing specific prescribing errors identified using pre-defined indicators.
- To understand the attributes, level of clinical decision support (CDS) and general settings of an EP implementation that are able to trap the paediatric prescribing errors.

4.3 Background

CDS is functionality within an electronic prescribing system designed to help a prescriber's decision-making. This can occur in numerous ways including organisation of pertinent data, computerised resources or guidelines, alerts, treatment recommendations, dose range checking and co-morbidity data evaluation. There are a variety of different CDS functionalities ranging from simple allergy checking to complex guideline and co-morbidity data evaluation.[125] Stultz *et al*[64] reviewed a range of CDS functionalities and designs that were reported to be utilised within the paediatric setting. They concluded that certain CDS functionalities such as dose calculators had shown benefit in medication prescribing and others such as therapeutic duplication alerts had resulted in high override rates and inconsistent or unknown impact on patient care.

The paediatric prescribing indicators developed in the first part of this project[126] (Chapter 3) were agreed by an expert panel as having a high likelihood of causing harm should the described error occur. The phase of work described here was designed to test individual prescribing systems for their ability to trap or prevent the prescribing errors identified in the first part of the project. This process will be referred to as error simulation in this chapter.

There are several different EP systems available in the UK with others under development. As such there are a number of variables which may confer different abilities to trap the errors:

- The EP system (from different vendors);
- The level of decision support included within each system;
- The level of decision support invoked at a specific hospital based on local set up and preferences;

- The attributes of the hospital environment (teaching hospital, specialty hospital);
- The paediatric case mix for the hospital (age groups, specialties);

By simulating the prescribing errors in individual hospitals an assessment of the performance of the system to prevent harmful errors can be made.

4.4 Method

4.4.1 Study Design

A semi structured questionnaire/survey.

4.4.2 Identifying Participants/Sites

Hospitals were identified using data from the results of the digital maturity project undertaken by Digital Technology Dept, NHS England in 2015.[127] The local paediatric pharmacist was contacted via email by the author at each site to confirm whether or not the site was suitable based on the inclusion and exclusion criteria shown below.

4.4.3 Inclusion and Exclusion Criteria

Sites were included if they were in a secondary care setting that had implemented EP in a paediatric setting. Sites were excluded if they did not care for paediatric patients or did not have an EP system in place.

4.4.4 Research Approval

As no direct patient consent was required the research protocol was reviewed by the University of Portsmouth, Science Faculty Ethics Committee. It gave a favourable opinion on 16/2/2017. As a research project involving NHS staff, Health Research Authority (HRA) approval was required. The investigator completed the Integrated Research Application System (IRAS) on 3/3/2017 and received HRA approval on 4/4/2017.

4.4.5 Survey Development

A survey was designed which incorporated all the previously identified indicators (Appendix 15). An Excel spreadsheet was used as the most efficient and convenient way of collecting the data. The design mimicked the style used for the indicator consensus work and was reviewed by two colleagues; a previous collaborator on the eDelphi work and the NHS Digital Lead Pharmacist. In addition, the survey was piloted by the local e-

prescribing lead at UHS and the local lead paediatric pharmacist. This provided an estimate of the time needed to complete the survey and additional comments to include in the explanatory notes. In the final version participants were asked to simulate each of the errors in the prescribing process in their own EP systems and provide the following information:

- Was the error prescription permitted? – Y/N. The participant recorded whether or not the error could be prescribed.
- Was any decision support triggered during the prescribing process?
- A description of the decision support, if triggered, descriptors for the five possible levels of CDS are shown in Table 4.1.
- Explanatory notes – to enable the participant to give further comments if needed.

The descriptors for the levels of decision support were derived from work that was being undertaken at the time by a research team which included one of the previously cited collaborators, at the University of Birmingham and subsequently reported[128]. In Chapter 1 of this report, CDS was described as either basic or advanced. This was to allow a simple comparison of the literature being reviewed. In this part of the work a more detailed description of CDS was required to allow respondents to choose the option that best described the CDS they invoked when attempting to prescribe the errors. The descriptions used (Table 4.1) have a natural hierarchy in terms of their ability to prevent an error from occurring. This ranges from “restricted” where an incorrect entry or prescription cannot be entered, to “none” where no CDS is present.

In addition to providing details about the decision support, the participant was also asked to give their view on two further points using a five point likert scale. Firstly the likelihood of the prescribing error being prescribed and secondly, if it was successfully prescribed, whether or not it could reach the patient. While it is clear EP with CDS has the ability to prevent some errors, there are also practical post-prescribing steps which could trap or prevent an error. These include regular prescription monitoring by a clinical pharmacist and double checking by nursing staff prior to administration. The specific questions posed were:-

- Using your current EP system what, in your opinion, is the likelihood of THIS prescribing error occurring i.e. passing through any alerts or

barriers and being available for administration? On a scale of 1-5 where 1 is never and 5 certain

- Using your EP system if THIS prescribing error occurs, what in your opinion, is the likelihood of it reaching the patient i.e. passing through the current system of post-prescribing checks? On a scale of 1-5 where 1 is never and 5 is certain

Each participant was also asked to complete a series of questions related to their EP system and how some of the basic prescribing processes took place (Appendix 16)

Table 4.1 Clinical decision support levels and descriptions

Decision Support Level	Description
Restricted	Error is prevented by the system as prescriber cannot proceed
Guided	Default fields are pre-populated encouraging the prescriber to accept and continue
Permitted (with input)	An alert where a reason needs to be given to override
Alert (without input)	An alert where no reason needs to be given
None	No interruptive Clinical Decision Support

Five of the original 41 indicators were split into two or more questions to enable the question posed to participants to be unambiguous. For example the original indicator for domperidone stated:

Domperidone prescribed at > 1.2mg/kg/day max 20mg (prolongation of QT interval, sudden cardiac death)

This was split into two discrete questions for the simulation exercise relating to having a dose greater than 1.2mg/kg/day and having a dose exceeding 20mg.

This resulted in a total of 49 discrete errors relating to the original 41 indicators.

4.4.6 Data Analysis

There was no specific hypothesis in relation to the expected data, rather an explorative approach to the data that was obtained to identify trends and themes using descriptive statistics. The numbers of errors allowed and type of CDS alert by each EP system were calculated and compared using descriptive statistics. Comparisons of the responses for different types of error and therapeutic class of the target drug were also made using descriptive statistics. Qualitative responses were used to clarify answers and provide detail as well a basic analysis for any emerging themes.

4.5 Results

4.5.1 Response Rate

Twenty-two NHS trusts were identified as having electronic prescribing in paediatric patients. Responses were received from 15 of these sites giving a response rate of 68%. Table 4.2 summarises the types of hospital sites that responded. One site did not provided 13 responses to the simulation questions and three sites did not provide responses to the Likert scale questions.

4.5.2 Sites

Table 4.2 details the basic attributes of the participating sites

Table 4.2 Attributes of participating sites

Attribute	Result
Hospital Type	
General Hospital	10(67%)
General Teaching	3 (20%)
Specialist Children's	2 (13%)
Mean number of beds	80 (range = 11-355)
Mean spread of EP within paediatrics (% of beds using EP)	91% (range = 70-100%)
Mean length of use(yrs)	4.4 (range = 0.7 – 22)

In five of the sites there was 100% spread of EP. In sites where spread was less than 100% the most common area where EP was not in use were intensive care areas with neonatal intensive care being the most common (5 sites).

4.5.3 Electronic Prescribing Systems

Seven different EP systems were in use across the 15 sites. Table 4.3 details the name of the EP system in use and the number of sites using that system as well as a code letter for use during the remainder of this thesis.

Table 4.3 Electronic prescribing systems tested

EP System	System Code	Number of sites (%)
Epic	A	1 (7)
JAC	B	7 (47)
Cerner Millennium	C	2 (13)
Meditech	D	2 (13)
iCM	E	1 (7)
Medichart	F	1 (7)
CSC	G	1 (7)

4.5.4 System Settings

Sites were asked a range of questions designed to obtain an understanding of the basic system settings and safety features within their EP system; results are shown in Table 4.4

Table 4.4 Details of system setting responses

	System Setting	Yes (%)	No (%)
1	Does the system use abbreviations to describe drugs (e.g. AZT) rather than approved names?	0	15 (100)
2	Does the system allow prescribers to enter drugs as free-text prescriptions?	8 (53)	7(47)
3	Can doses be entered by the prescriber using a trailing zero after a decimal point (e.g. 5.0mg)?	7 (47)	8 (53)
4	Does the system require a weight to be entered before any prescribing can take place?	5 (33)	10 (67)
5	Does the system check if a weight is out of date based on internal rules?	8 (53)	7 (47)
6	Does the system allow a drug that is usually prescribed by weight to be prescribed without the presence of an up-to-date weight (defined by internal rules if present).	12 (80)	3 (20)

7	Does the system calculate BSA if so please describe how?	13 (87)	2 (13)
8	For drugs that are prescribed by BSA does the system allow the drug to be prescribed without the presence of an up to date BSA value (based on internal rules if present).	13	2
9	Does the system round doses to measurable amounts.	4 (27)	11 (73)
10	Does the system abbreviate units by using "u" or "iu"	0	15 (100)
11	Does the system support 18 hr or 36 hr dosing	13 (87)	2 (13)
12	Does the system abbreviate microgram and nanogram?	1 (7)	14 (93)

BSA = Body Surface Area,

None of the EP systems used abbreviations to describe drugs rather than their approved names; one system, however allowed a search by abbreviation.

Eight of the systems allowed the entry of a free text drug; in seven of these sites this occurred by utilising a “dummy drug” which allowed the user to prescribe a dose and frequency and describe the drug within a note assigned to the dummy drug.

Trailing Zeros – in all sites that allowed the entry of a trailing zero the final displayed dose or numeral had the trailing zero truncated i.e. entry of 5.0mg would display as 5mg.

Entry of Patent’s Weight – in five sites a weight was mandatory prior to any prescribing taking place. There were six sites where the weight was used to calculate a small range of doses and if the original weight was not already entered, then the prescriber would be prompted for a weight in these cases. Five of these sites used drug bundles in which the weight was used to calculate the dose. In one of these sites there was an option for the prescriber to enter a dose in mg/kg and the system would perform the calculation based on the weight. In nine sites a weight was not required prior to prescribing.

Weight checking – in eight sites there were internal rules within the system that would check if a weight was out of date. In most cases this was based on internal rules which changed with increasing age i.e. for patients between 0 and 6 months old, the weight would need to be recorded weekly; from 6 months to 2 years the weight would be recorded monthly.

Body Surface Area (BSA) – the majority of sites had EP systems that would calculate BSA if the weight and the height were entered – thereby using the

Dubois formula.[129] In one site the system used weight only to calculate BSA based on the work by Sharkey *et al.*[130]

Rounding doses – three systems performed dose rounding and in all cases this only occurred for specific groups of drugs such as injections or those where a bundle had been pre-programmed. Worryingly in one site the dose rounding was based on adult rules where some antibiotic injections were rounded to the nearest 200mg (Site 8).

None of the systems abbreviated "units" to "u." or "i.u."; this is extremely important for drugs such as insulin and heparin where doses are expressed in units. If handwritten these abbreviations have been miss-read as a zero resulting in 10 times the dose of insulin being administered.[131] Maintaining this convention within an EP system might help to reinforce incorrect practice in handwritten records.

Support of 18 hourly and 36 hourly dosing intervals was reported in the majority of systems; this is important when prescribing gentamicin for neonatal patients or those with severely diminished renal function where extended dosing is required to achieve appropriate plasma concentrations. In the two sites that answered no for this question, one stated it would use "stat" doses for these drugs and paper prescriptions; the other had a system that could support 36 hourly dosing but not 18 hourly.

Abbreviation of microgram and nanogram – all but one site had systems that did not abbreviate these terms. In the site where abbreviation did occur (Site 3) the abbreviations that were displayed were "mcg" and "ng". There are several reported cases of prescribing errors where handwritten abbreviations have been misread resulting in large overdoses.[132, 133] While there are no reports of this occurring with electronically displayed abbreviations the concern would be that handwritten records in, for example, medical notes would mimic the electronic abbreviations and increase the likelihood of error.

4.5.5 Error Simulation Permittedness

In the context of this work the term permittedness is used to describe whether or not an EP system allows (or permits) a prescribing error to be made. The more errors the EP system permits the more likely a prescribing error is to be made. A total of 699 responses to the 49 simulation questions were received. Fourteen sites answered all 49 simulations and one site answered 13 simulations.

A total of 629 errors were permitted i.e. the errors were able to be prescribed on the EP system and 29 were prevented. In 41 instances the question was not applicable to the individual site; the common reason being the error related to an intravenous drug that was prescribed on a paper chart rather than the EP system. Table 4.5 summarises these results. Appendix 17 contains a table with full detailed answers for each error.

Table 4.5 Number of errors permitted by the systems studied

Error Permitted	Number (%)
Yes	629 (90.0%)
No	29 (4.1%)
Not Applicable	41 (5.8%)
Total	699

Table 4.6 shows the number of errors permitted by each EP system using the designations described in Table 4.3. This shows that all systems had errors that were permitted; one system (G) had no errors that were prevented. System A had the largest proportion of errors that were not permitted (8.2%). System B, used by the largest number of sites (7) had only a 2.6% non-permissible rate.

Table 4.6 Number of errors permitted by specific electronic prescribing systems

EP System (No)	Error Permitted		
	Y (%)	N (%)	N/A (%)
A (1)	45 (91.8%)	4 (8%)	0 (0%)
B (7)	277 (90.2%)	8 (2%)	22 (7%)
C (2)	90 (91.8%)	7 (7%)	1 (1%)
D (2)	88 (89.8%)	6 (6%)	4 (4%)
E (1)	40 (81.6%)	3 (6%)	6 (12%)
F (1)	44 (89.8%)	1 (2%)	4 (8%)
G (1)	45 (91.8%)	0 (0%)	4 (8%)
Total	629	29	41

Figure 4.1 show the errors by error type and whether they were permitted by the EP systems investigated.

A proportion of each of the error types was permitted by the EP systems. The one drug name error in the study was most commonly prevented by the EP systems that were studied. Allergy and therapeutic duplication errors were the next most commonly prevented errors followed by dosing errors. Figure 4.1 shows the differences between the error types and the ability of the EP system to prevent them. None of the systems were able to prevent any of the

following error types: duration, omission, intravenous rate, and drug-drug interactions.

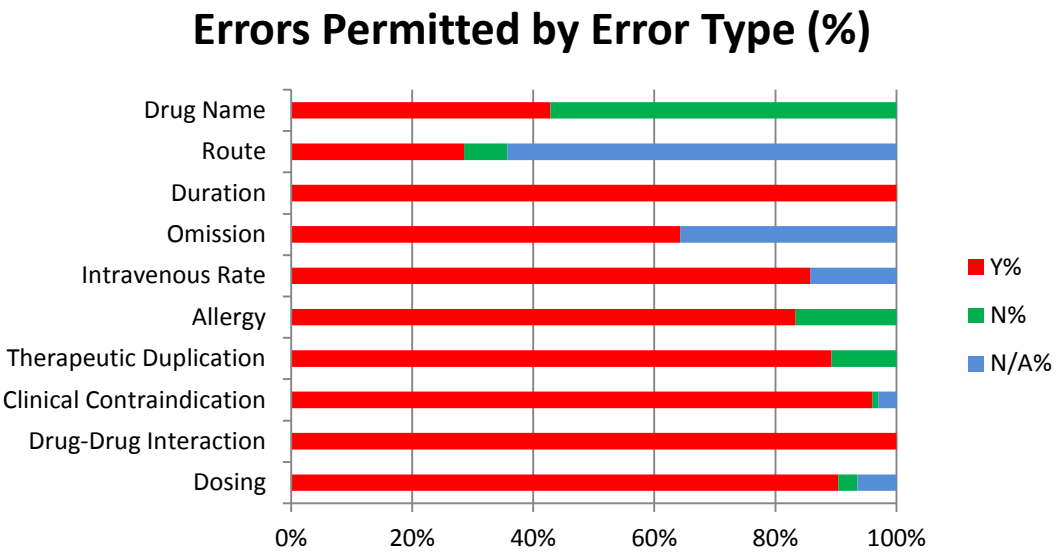


Figure 4.1 Error type and level of permittedness

Table 4.7 shows the errors by therapeutic area and whether they were permitted or not. The most commonly prevented errors were those related to anaesthetic agents and the general error which described the prescribing of a drug (excluding penicillin) to which the patient was allergic. Antimicrobial and immunosuppressant errors featured most commonly with 14 and 12 errors respectively. For both of these categories there were errors that were prevented by the EP systems. For four of the categories: gastrointestinal, cardiovascular, respiratory and musculoskeletal, none of the errors were prevented.

Table 4.7 Therapeutic area of error and number permitted by the electronic prescribing systems studied

Therapeutic Area (no of errors of that type)	errorPermitted		
	Y (%)	N (%)	N/A (%)
Gastrointestinal (2)	30 (100)	0	0
Cardiovascular (8)	108 (91)	0	11 (9)
Respiratory (1)	6 (40)	0	9 (60)
Central Nervous System (5)	67 (94)	4 (6)	0
Antimicrobial (14)	184 (93)	9 (5)	4 (2)
Endocrine (2)	24 (86)	1 (4)	3 (10)
Immunosuppressant (12)	157 (94)	6 (4)	5 (3)
Nutrition (2)	18 (64)	1 (4)	9 (32)
Anaesthetic (1)	10 (71)	4 (29)	0
General (1)	11 (73)	4 (27)	0
Musculoskeletal (1)	14 (100)	0	0

4.5.6 Detail of Errors Prevented and Not Applicable

Table 4.8 details all the errors where at least one system prevented them from being prescribed. Out of the 49 errors, only 9 (18.3%) were prevented by at least one EP system. The error which was most commonly prevented was error 22 which relates to the way in which amphotericin is prescribed.

Table 4.8 Detail of errors prevented

Error Ref	Error	Error Type	No. of sites at which error prevented (%)
10	Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)* e.g. morphine 10mg IV/PO/SC	Therapeutic Duplication	3 (20%)
12	Penicillin containing compound prescribed to a penicillin allergic patient (please describe in the notes whether symptoms of reaction can be added and hence whether a reason for prescribing can be made clear)	Allergy	1 (7%)
22	Amphotericin B prescribed without additionally stating both brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid*)	Drug Name	8 (53%)
24	Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Clinical Contraindication	1 (7%)
28	Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	Dosing	6 (40%)
33	Potassium chloride infusions exceeding 40 mmol/litre prescribed to be administered via the peripheral route (peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)	Route	1 (7%)
35	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration (e.g. oral dose prescribed via buccal route)	Dosing	4 (27%)
36	A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)* excluding penicillin	Allergy	4 (27%)
37	Dose of paracetamol prescribed inappropriate for route of administration	Dosing	1 (7%)

Table 4.9 lists the errors where there was at least one site where the error was deemed not applicable. There were various reasons cited as to why these errors were not applicable. Errors 7,8 and 33 were intravenous

infusions with variable dosing, i.e. the dose is altered based on the response of the patient. This type of treatment represents a complicated prescribing process which many systems are not able to achieve in a safe way. In all these sites, prescribing was performed using paper charts commonly cross referenced within the EP system.

Error 26 was deemed not-applicable in 5 sites; in all of these cases this specific treatment was not given at these sites. The use of high dose IV methotrexate in oncology patients only occurs in specialist centres.

In the sites where these errors were relevant, there were only two instances where the error was prevented. In one site error 24 was prevented by the system not allowing the insulin to be prescribed in a “PRN” fashion. In the second case error 33, potassium infusions, was prescribed using a pre-defined order sentence where the concentration and route of potassium infusion was stipulated and not editable.

Table 4.9 Errors deemed "Not Applicable" in at least one site

Error Ref No	Error	Error Type	Number of sites where deemed not applicable (%)
7	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*	Dosing	11 (73%)
8	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	Dosing	9 (60%)
16	Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment according to local policy *(increased risk of toxicity)*	Dosing	1 (7%)
17	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	Dosing	1 (7%)
21	Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	Intravenous Rate	2 (13%)
24	Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Clinical Contraindication	3 (20%)
26	Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*	Omission	5 (33%)
33	Potassium chloride infusions exceeding 40 mmol/litre prescribed to be administered via the peripheral route (peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)	Route	9 (60%)

4.5.7 Error Simulation – Degree of Clinical Decision Support

Sites were asked about the levels of clinical decision support offered to prescribers when simulating each of the errors. The range of CDS options are listed above in Table 4.1. There were a total of 699 responses across all 49 errors. Totals for each CDS level are shown in Table 4.10 and Figure 4.2. In the majority of cases (74.2%) no decision support was offered to the prescriber. Conversely in 25.8% of errors across all 15 sites, some form of CDS was provided to the prescriber. The most common level of CDS was

"permitted (with input)" where the prescriber is warned of a potential error and must provide some form of input to either acknowledge this or override it.

Table 4.10 Total clinical decision support level responses

CDS Level	Responses n=699 (%)
Restricted	25 (3.6%)
Guided	23 (3.3%)
Permitted (with input)	97 (13.9%)
Alert (without input)	35 (5.0%)
None	519 (74.2%)

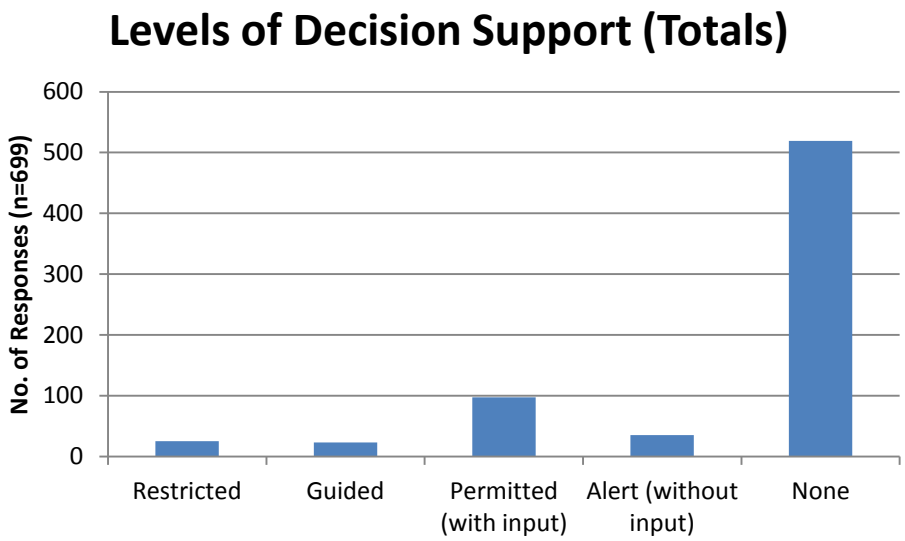


Figure 4.2 Frequency of various levels of clinical decision support

Table 4.11 shows the level of CDS offered by the different systems. Systems A and E offered the largest number of restricted errors and system C utilised the highest proportion of guided CDS. In terms of alerting CDS, system A utilised the highest proportion of CDS requiring input and systems F and G had the highest proportion of alerts without input. System C recorded the highest proportion of errors where no CDS was presented. Interestingly system B which is the most popular system in use across the sites did not utilise CDS in 77.9% of cases which was the second highest proportion.

Table 4.11 Level of clinical decision support offered by each system

EP System	Restricted (%)	Guided (%)	Permitted(with Input) (%)	Alert (without Input) (%)	None (%)	Total Responses
A	3 (6)	4 (8)	15 (30)	0 (0)	27 (55)	49
B	10 (3)	1 (0.3)	41 (13)	16 (5)	239 (77)	307
C	3 (3)	9 (9)	5 (5)	0 (0)	81 (82)	98
D	5 (5)	4 (4)	17 (17)	1 (1)	71 (72)	98
E	3 (6)	1 (2)	11 (22)	0 (0)	34 (69)	49
F	1 (2)	3 (6)	5 (10)	9 (18)	31 (63)	49
G	0 (0)	1 (2)	3 (6)	9 (18)	36 (73)	49

Table 4.12 shows the levels of CDS provided by the systems based on the error types. The allergy errors had some form of CDS in all cases and were the only error type where this was the case. In most cases prescribers were presented with a warning which requires an input to either acknowledge or override. This shows that all systems have at the very least, a basic level of CDS which includes allergy checking. Drug-Drug interactions and therapeutic duplications were the error types most commonly associated with some form of CDS. In the case of therapeutic duplication only 21.4% of responses indicated that there was no CDS for this error type. The types of error where there was least likely to be any CDS were: dosing (90.4%), omission (100%), duration (100%) and clinical contradiction (94%).

Table 4.12 Levels of clinical decision support based on error type

Error Type (No of Errors)	Restricted (%)	Guided (%)	Permitted (with Input) (%)	Alert (without Input) (%)	None (%)	Total
Dosing (24)	9 (2)	11 (3)	10 (3)	3 (1)	310 (90)	343
Drug-Drug Interaction (9)	0 (0)	0 (0)	47 (37)	27 (21)	54 (42)	128
Clinical Contraindication (7)	1 (1)	3 (3)	2 (2)	0 (0)	94 (94)	100
Therapeutic Duplication (2)	2 (7)	3 (11)	14 (50)	3 (11)	6 (21)	28
Allergy (2)	3 (10)	1 (3)	24 (80)	2 (7)	0 (0)	30
Intravenous Rate (1)	0 (0)	3 (21)	0 (0)	0 (0)	11 (77)	14
Omission (1)	0 (0)	0 (0)	0 (0)	0 (0)	14 (100)	14
Duration (1)	0 (0)	0 (0)	0 (0)	0 (0)	14 (100)	14
Route (1)	1 (7)	1 (7)	0 (0)	0 (0)	12 (86)	14
Drug Name (1)	9 (64)	1 (7)	0 (0)	0 (0)	4 (28)	14

Table 4.13 shows the levels of CDS reported from all sites using the most common system tested (system B). The variation in both the number of errors permitted and the types of CDS invoked between different sites using the same EP system.

Table 4.13 Levels of clinical decision support reported from all sites using electronic prescribing system B

Site	Restricted	Guided	Permitted (with Input)	Alert (without Input)	None
10	0	0	3	0	46
5	2	1	3	0	43
9	2	0	10	2	35
15	2	0	11	0	36
18	2	0	0	0	11
12	2	0	1	13	33
22	0	0	13	1	35

Table 4.14 lists all the dosing errors in detail and the level of decision support invoked for each one. The errors shaded are the ones where at least one site has CDS for that specific error. This, therefore, shows the detail of the dosing errors where no CDS was invoked.

Table 4.14 Detail of all dosing errors and level of clinical decision support. (Dosing errors with at least one level of CDS response are shaded).

Error Ref	Error Description	Restricted	Guided	Permitted (with input)	Alert (no input)	None (%)
1a	Domperidone prescribed at > 1.2mg/kg/day *(prolongation of QT interval, sudden cardiac death)*	0	1	1	0	13
1b	Domperidone prescribed at a dose exceeding 20mg per *day (max BNFC dose)*	0	1	1	0	13
2	Digoxin dose not reviewed in light of reduced renal function (less than 50ml/min/1.73m^2)	0	0	0	0	15
5	Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment (<30ml/min/1.73m2) (*increased risk of bleeding)*	0	1	0	0	14
7	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*	0	1	1	0	13
8	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	0	0	1	0	14
11	Phenytoin dose not reviewed in light of low albumin *(potential for toxicity)*	0	0	0	0	15
13	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	0	0	0	0	14
14	Ceftriaxone prescribed at a total daily dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis in a patient > 1 month of age *(risk of under dosage)*	0	0	0	0	14
15	Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or respiratory exacerbation of CF *(potential under treatment)*	0	0	0	0	14
16	Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment according to local policy (*increased risk of toxicity)*	0	0	0	0	14
17	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	0	0	1	0	13

Table 4.14 Detail of all dosing errors and level of clinical decision support. (Dosing errors with at least one level of CDS response are shaded). Continued

Error Ref	Error Description	Restricted	Guided	Permitted (with input)	Alert (no input)	None (%)
23	Failure to adjust dose or frequency of ganciclovir in the presence of altered renal function (less than 70ml/min/1.73m^2) *(risk of toxicity or treatment failure)*	0	0	0	0	14
25a	Dose reduction of ciclosporin not made despite low white cell count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*	0	0	0	0	14
25b	Dose reduction of tacrolimus not made despite low white cell count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*	0	0	0	0	14
25c	Dose reduction of mycophenolate not made despite low white cell count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*	0	0	0	0	14
25d	Dose reduction of azathioprine not made despite low white cell count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*	0	0	0	0	14
25e	Dose reduction of mercaptopurine not made despite low white cell count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*	0	0	0	0	14
28	Oral methotrexate prescribed to a patient with an inappropriate frequency (*increased risk of toxicity)*	6	2	2	2	2
34	Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m^2)	0	0	0	0	14
35	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration (e.g. oral dose prescribed via buccal route)	3	3	0	0	8
37	Dose of paracetamol prescribed inappropriate for route of admin.	0	2	3	1	8
39	Aciclovir prescribed at a dose of 250mg/m2 instead of 500mg/m^2 for herpes simplex encephalitis in patients aged between 3 months and 12 years	0	0	0	0	14
41	Failure to increase of hydrocortisone to “sick day doses” from “maintenance” doses in those adrenally suppressed	0	0	0	0	14

Table 4.15 shows the CDS responses related to the therapeutic class of the error. All the therapeutic types had some form of CDS in at least one of the sites. No specific conclusions could be drawn form these results.

Table 4.15 Therapeutic class of errors and level of clinical decision support response

Therapeutic Class (number of errors)	Restricted (%)	Guided (%)	Permitted (with Input) (%)	Alert (without Input) (%)	None (%)	Total Responses
Gastrointestinal (2)	0 (0)	2 (7)	2 (7)	0 (0)	26 (87)	30
Cardiovascular (8)	0 (0)	2 (2)	20 (17)	7 (6)	90 (76)	119
Respiratory (1)	0 (0)	0 (0)	1 (7)	0 (0)	14 (93)	15
Central Nervous System (5)	2 (3)	5 (7)	17 (24)	4 (6)	43 (61)	71
Antimicrobial (14)	10 (5)	4 (2)	34 (17)	15 (8)	134 (68)	197
Endocrine (2)	1 (4)	3 (11)	0 (0)	0 (0)	24 (86)	28
Immunosuppressant (12)	6 (4)	2 (1)	12 (7)	8 (5)	140 (93)	168
Nutrition (2)	1 (4)	1 (4)	0 (0)	0 (0)	26 (93)	28
Anaesthetic (1)	3 (21)	3 (21)	0 (0)	0 (0)	8 (57)	14
General (1)	2 (13)	1 (7)	11 (73)	1 (7)	0 (0)	15
Musculoskeletal (1)	0 (0)	0 (0)	0 (0)	0 (0)	14 (100)	14

4.5.8 Error Likelihood Scoring

In addition to simulating the errors within their EP system, respondents were asked two questions relating to the likelihood of the error occurring. Firstly, how likely they thought a prescriber would make the error using the EP system; this gives an indication of the respondents view of the likely knowledge and experience of the prescriber and therefore, the likelihood they may make the prescribing errors described. Secondly respondents were asked to consider how likely the error would then reach the patient; the intention here was to gain an understanding of the likelihood that post-prescribing checks might prevent an error from reaching the patient. All of the respondents were paediatric pharmacists using the system in their hospitals.

The median Likert scores with inter-quartile ranges for each error for both of these questions are shown in Figures 4.3 and 4.4. For reference the error descriptions and full results are tabulated in Appendix 17.

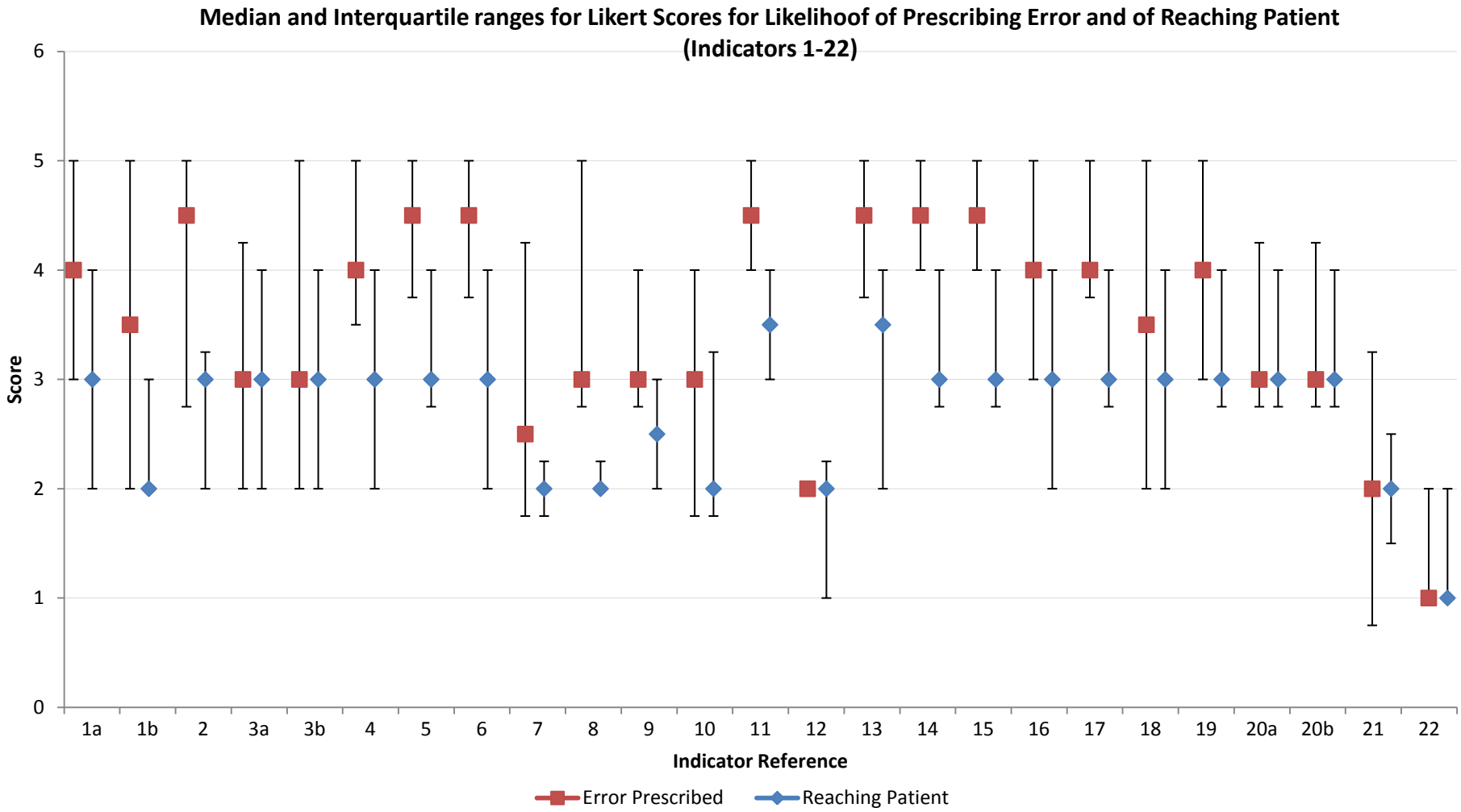


Figure 4.3 Median and interquartile ranges for Likert scores for likelihood of prescribing error and of reaching the patient (Errors 1 - 22)

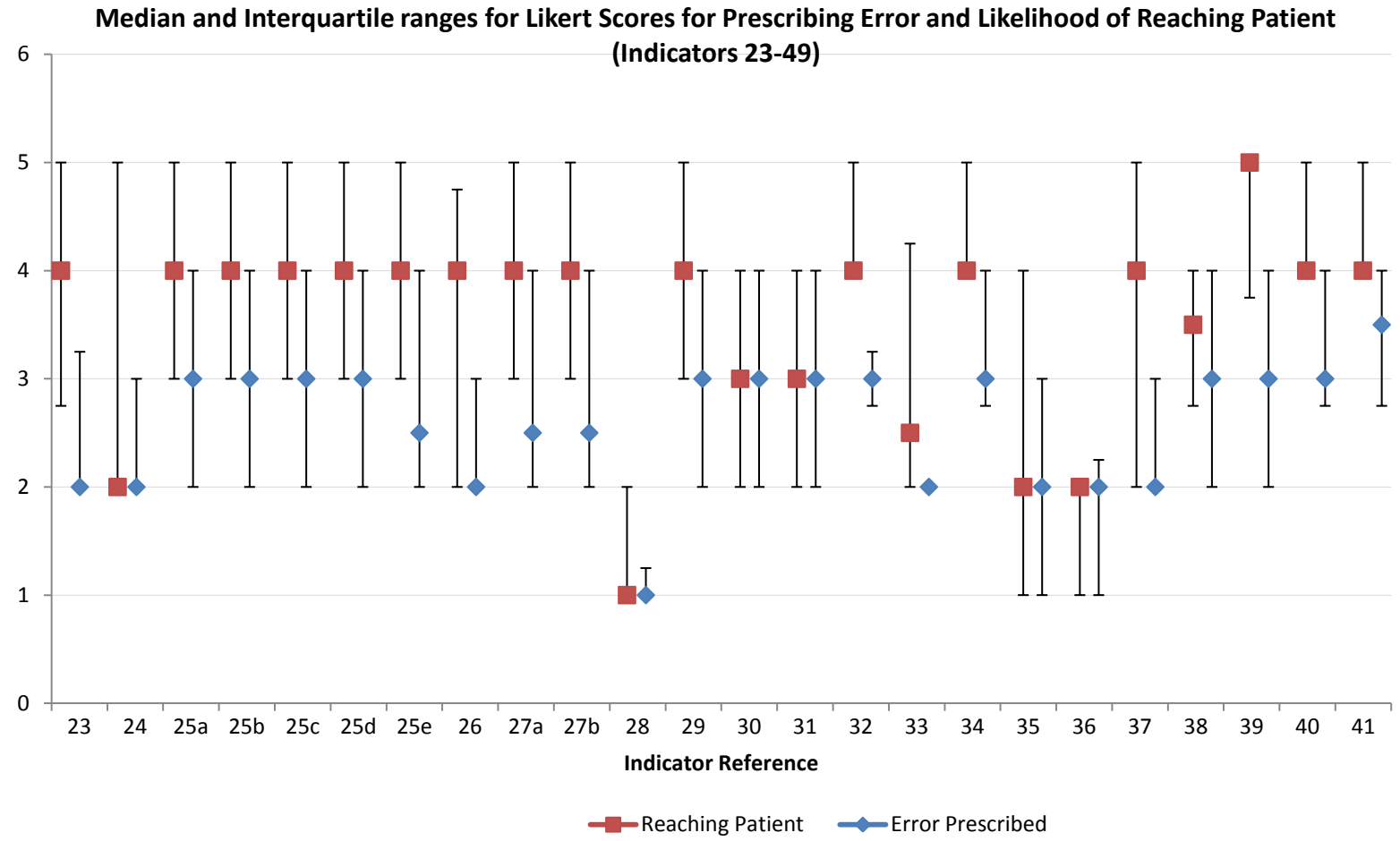


Figure 4.4 Median and interquartile ranges for Likert scores for likelihood of prescribing error and of reaching patient (Errors 23-41)

Figures 4.5 – 4.8 take the results shown in Fig 4.4 and 4.5 above specifically relating to the likelihood of the prescribing error to be made and attempt to show a relationship between this and the levels of CDS. Four specific errors have been isolated to help illustrate this. In each case the x-axis in each figure shows the level of CDS followed by a Likert score option. The natural hierarchy of CDS is maintained from left to right with the highest possible level "restricted" on the left and "none" on the right. For example "Guided/2" denotes the number of responses where the error offered Guided CDS (left hand bar) and the number of respondents who scored "2" on the Likert scale (right hand bar) for this error. In each figure the number of responses for the left hand bar varies according to the number of responses received.

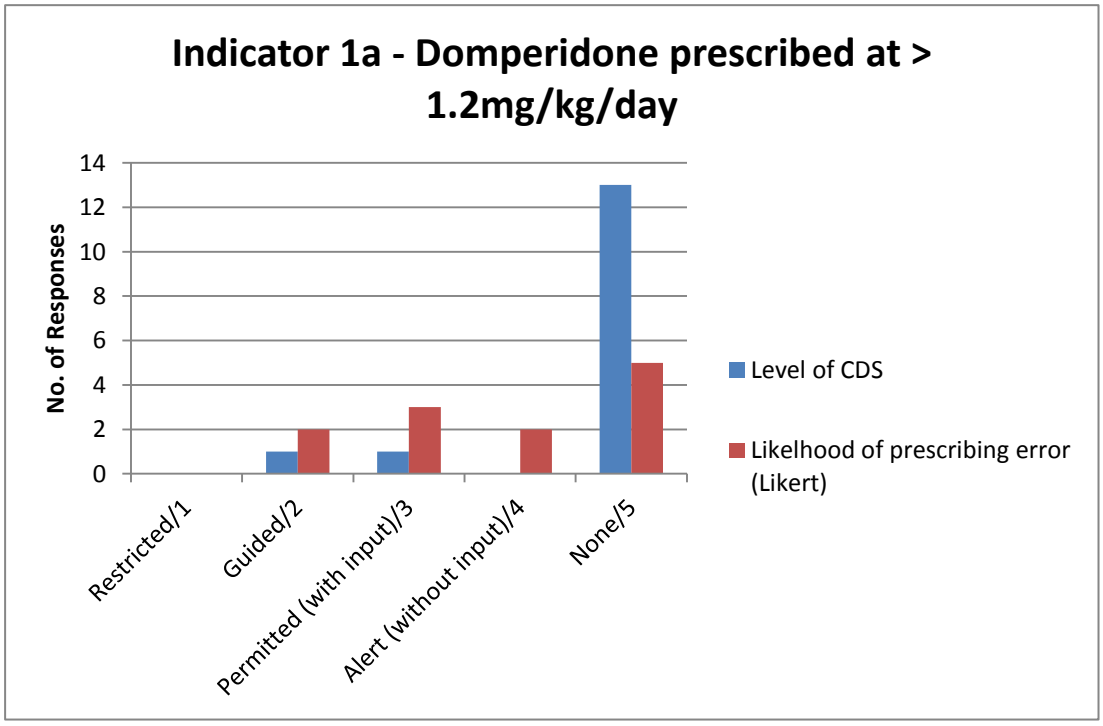


Figure 4.5 Level of clinical decision support and Likert responses for error 1a

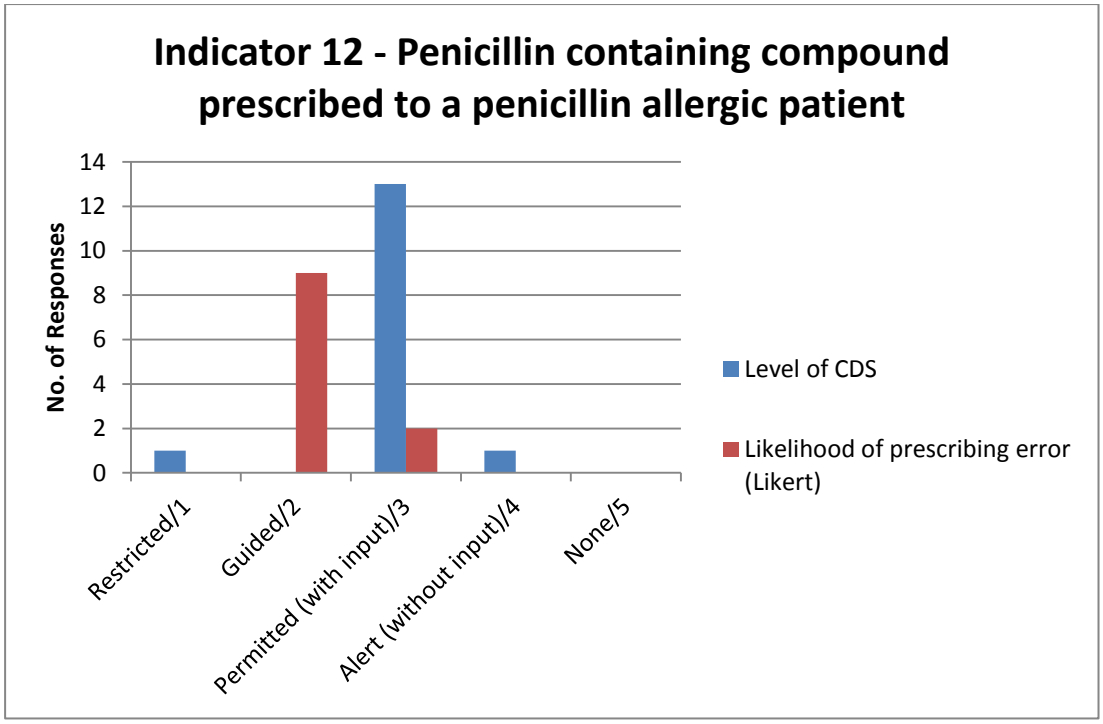


Figure 4.6 Level of clinical decision support and Likert responses for error 12

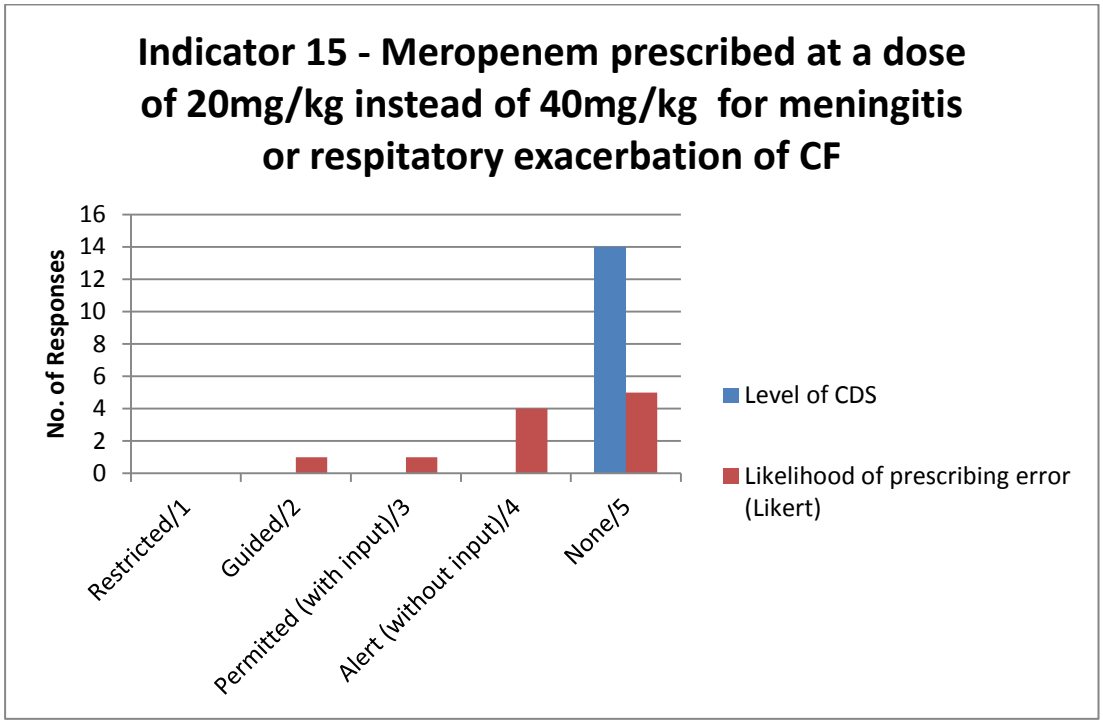


Figure 4.7 Level of clinical decision support and Likert responses for error 15

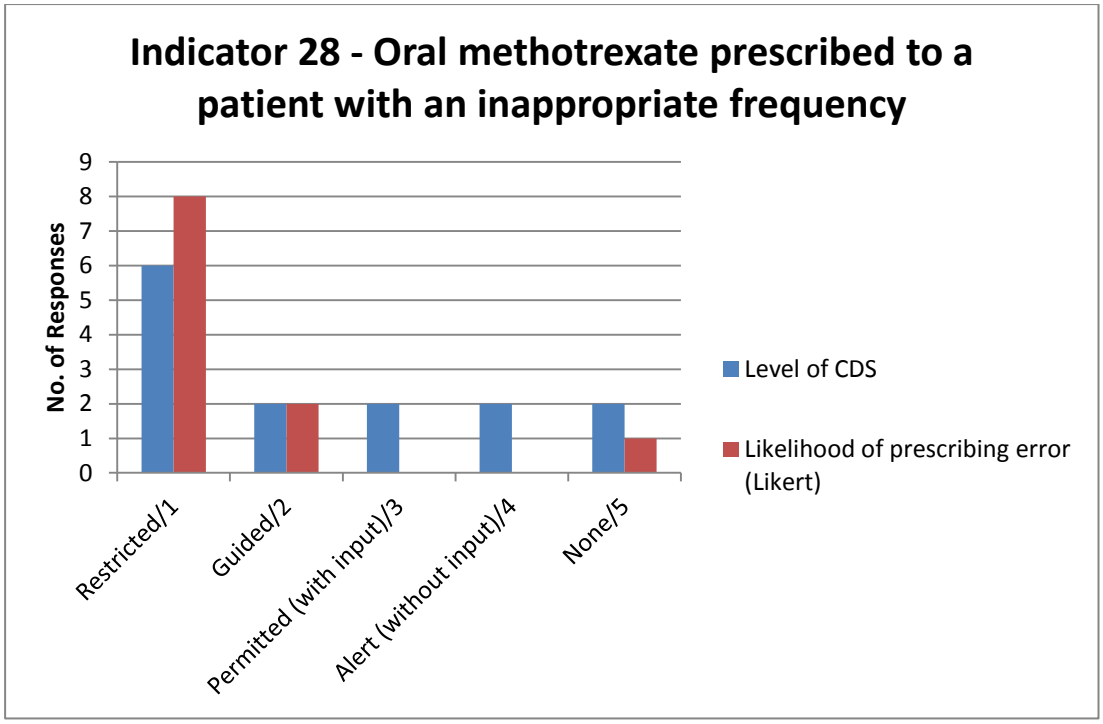


Figure 4.8 Level of clinical decision support and Likert responses for error 28

These Figures (4.5 – 4.8) were chosen to illustrate the relationship between the levels of CDS and the perceived likelihood of the error being prescribed. Out of the 49 simulated errors they represent examples to illustrate possible relationships between the Likert scoring and CDS. In the case of errors 1a and 15 there was very little CDS offered to the prescriber; indeed for error 15 there was none. In both these cases the perceived likelihood of the error being prescribed was high possible linked to greater numbers of answers at level 5 (no CDS) on the Likert scale.

Errors 12 and 28 had the greatest level of CDS invoked during the simulation. In both these cases the Likert scoring is at a lower level with increased frequency of scores 1 and 2, possibly indicating a link to a reduction in the risk of the error being prescribed and the higher levels of CDS.

4.6 Discussion

In this research a range of EP systems were tested using a set of errors previously developed as part of this project. The errors were agreed by consensus to have a high likelihood of causing harm should they reach the patient. Development of the errors is fully described in Chapter 2 and published by Fox *et al*.[126] The tests showed that in only 4.1 % of cases the

error was prevented by the EP system, and that in 74.2% of cases no warning or support was presented to the prescriber.

Fifteen sites conducted the simulations using a variety of different EP systems. None of the systems prevented or indeed provided warning to the prescriber about all the errors.

Responses to the system settings questions were varied but in general provided a positive view of the way systems had been set up to accommodate paediatric prescribing. Probably the most concerning finding was that in nine sites, there was no requirement for a weight to be entered prior to prescribing. The majority of prescribing for infants and children is based on weight and in the case of infants, weight increases rapidly over time. For chronic medicines this can result in under dosing (in mg/kg) as the weight increases.

Out of the 49 errors, only 9 (18.3%) were prevented by at least one EP system. The error which was most commonly prevented was error 22 which relates to the way in which amphotericin is prescribed. In 2007 the NPSA issued an alert highlighting incidents that had caused harm due to confusion between non-lipid and lipid based formulations of injectable amphotericin.[134] It is encouraging to see that the potential risk of this specific error has been reduced by the use of EP. Certainly EP lends itself well to preventing this type of error with the minimum of CDS, as the naming conventions can be agreed during system set up, which precludes the use of ambiguous names. In all cases where explanatory notes were provided from sites, this error was prevented by only having the lipid formulation listed on the system. However, the availability of a "Free-Text" drug entry option, allowing a prescriber to type any drug into the system together with a dose could override this safety feature. In this case only one site where this error was prevented also disallowed "free-text" prescriptions.

Error 28 had six sites where it was prevented. This specific error is included in the NHSE Never Event framework[135] and was the subject of an NPSA alert in 2004.[136] So despite a relatively high level of professional and public awareness of the potential harm from oral methotrexate, there were 9 sites where this error was permitted within the EP system. Indeed the risk to these sites of triggering a "Never Event" is higher, as the definition was altered in 2015 whereby only those sites using EP were considered having the ability to prevent the error. Sites that were able to prevent this error utilised pre-filled

frequencies as part of a prescribable bundle which were not editable, leaving the prescriber just to enter the dose.

When considering all the errors in Table 4.9, with the exception of error 35 they are all adult based errors and were originally identified in the eDelphi study described previously.[90] Error 35 relates to a situation most commonly encountered in the paediatric population where midazolam is used by different routes for procedural sedation. Only four of the sites were able to prevent this specific error, in the most part by use of pre-filled order sentences where the route of administration could not be altered. It could of course be argued that the wrong order sentence could be selected for a route that was not intended; however, the dose for this route would still be correct within the order sentence meaning the patient would receive the correct dose if the prescription is followed.

This result also suggests that systems have not been developed with paediatric patients in mind; several of the errors were paediatric specific and only one was prevented.

Error 22 was not permitted in eight of the sites and as such is the most likely of the tested errors to be prevented. This error lends itself well to being prevented by EP because the drug names are pre-populated in the system. The prescriber does not have to remember to add detail to the drug name about the formulation because it is already included. However, EP systems can contribute to drug choice errors because the usual prescribing process involves picking the required drug from a drop down list. Errors have been reported where the wrong drug is selected, particularly where they begin with similar letters[137] and specifically with Slow-K® and Slow Na®.[138]

CDS was available in all systems being tested and in 25.8% of the error simulations, some form of CDS was triggered to provide a warning to the prescriber. All of the CDS invoked could be described as basic i.e. allergy, drug-drug interaction and therapeutic duplication checking.

Along with drug-drug interactions; therapeutic duplications were the most commonly provided CDS and represented a basic level of CDS. These two types of error require a similar level of information within a system in order for them to present a warning to the prescriber. Commonly, EP systems have drug interaction databases included as part of the installation. These databases are usually provided and updated by a third party under licence by

the vendor of the EP system. This means that if a drug is prescribed that has a link within the database to a drug with which it interacts or is therapeutically similar, an alert can be presented to the prescriber. The results show that this type of CDS was common among the systems investigated. However, in the case of drug-drug interactions, not all systems alerted the prescribers to all interactions. This is because interactions are assigned a level of severity, usually between 1 and 4, where 4 is the most likely to cause harm. System administrators can set a system to show alerts for interactions of certain levels and above. This is illustrated in Table 4.14 which shows the results of the CDS levels from all sites using the same system (B). There was variation in the number of "permitted with input" and "alert no input" warnings that were presented to the prescriber between different sites. This was because some sites chose to switch drug-drug interactions alerting off completely, while others had only alerts for levels 3 and 4 presented to the prescriber. The balance that system administrators must keep is between providing useful and meaningful alerts while not providing too many and risking alert fatigue.

Where dosing errors did have CDS there was a range of CDS levels (Table 4.15). In the case of dosing errors prevented by guided CDS (1a, 1b, 5, 7, 28, 35, 37), the systems all utilised a pre-filled order that provided the prescriber with default doses, calculated using the weight of the patient. One site accounted for five of these responses, utilising a particular EP system which allowed this kind of CDS to be set up easily. Two sites used this system and interestingly, the other site did not provide similar responses. This again would indicate differences in system level set up options. Error 37 had three sites (20%) where guided CDS was used; this probably reflects both the ease of set up and the high frequency of paracetamol prescribing, where the time required setting up guided CDS, if available, has the greatest potential impact.

Out of the 24 dosing error types, nearly a third of them (15/62.5%) had no CDS. Closer scrutiny revealed a difference within the dosing error types. Those where CDS was present, lend themselves to a level of decision support that could be described as internal, i.e. an attribute directly related to the inputs made at the time of entering the prescription in the system. For example, errors 1a and 1b relate to the dose of domperidone that the prescriber would enter or have calculated based on the patient's weight. This prescription does not require any information from outside of the prescribing system. However, the errors where no CDS was available all required

information generally outside of a prescribing system, such as clinical condition, renal function and blood cell counts. To enable warnings to be provided to the prescriber for example, about a patient's renal function, data including serum creatinine and urea are required. This information is often held on a different electronic system within the hospital used by the pathology dept and without an interface, the ability to present these data is reduced.

Furthermore, simple presentation of this data, whilst clearly an improvement, would not necessarily lead to any CDS being triggered. For this to happen the system would need to recognise that, for example, an estimated creatinine clearance of 30ml/min in an adult is classed as mild renal failure; the system would then need to assimilate this and present an appropriate dose to the prescriber. In some cases it can be more complicated than a single value. When reviewing liver function tests for a patient on methotrexate (Error 29), a trend in the results over time might need to be considered rather than a single result. There may also be a requirement to compare these results with the patient's baseline results rather than a recognised normal value. This represents an advanced level of CDS which has not been shown in any of the systems used by the sites in this study.

Clinical contraindication error types also require external information, relating to co-morbidities, to enable CDS to be provided to the prescriber. There were seven error types of this nature and only six instances of any level of decision support across the 15 sites, involving errors 4 and 24. In two sites, error 4 triggered the "permitted with input" CDS level; in both cases this occurred only if the patient was also prescribed salbutamol and, therefore, the alert was triggered by virtue of a drug-drug interaction. In one of these sites it was possible to set a rule that reviewed the co-morbidities of the patient and provided "notices" which could work for this error; however, this was not currently utilised. Error 24 had three responses of guided CDS and one response of restricted CDS. In these cases insulin was prevented from being prescribed "when required" by system restrictions on this type of prescribing for this specific drug.

There was only one error type each for duration and omission where none of the systems provided any CDS. The omission error 26 relates to the co-prescribing of folinic acid for patients receiving high dose methotrexate. High dose methotrexate was not used in all sites, and in other sites, chemotherapy was prescribed on a separate, dedicated prescribing system. In some cases

the folinic acid was prescribed on the chemotherapy system in others the prescribing was separate. During the eDelphi work, previously described (see Chapter 2), most doses of omission were removed during the exploratory round because they were not preventable by the use of EP. This specific error was included because of its potential severity and the need for folinic acid being directly related to high dose methotrexate; therefore making it preventable by EP. However, it is clear from the responses that this particular error is unlikely to be resolved while different systems are in use without any interface.

The most advanced CDS that was described was the use of "quicklists" or "bundles". These are pre-programmed order sets which guide the prescriber to the correct dose by virtue of the patient's weight and choice of route. The ability to set these up is dependent on the EP system; not all systems have this functionality. One system utilised maximum dose checking and this was based on weight, however, this was not set up for all drugs within the errors. Order sets can be developed to include more than one drug. An example of this would be a post-operative pain order set which might contain morphine, paracetamol, an anti-emetic and naloxone. These allow prescribers a short cut to the most commonly used combinations. CDS will present alerts for individual drugs within an order set or bundle.

Similar work has been published by Schiff *et al*[139] and Slight *et al*[140] They reviewed 10,060 medication errors reported to the national database in the US which had CPOE as a contributory factor in the error. From these mainly adult errors they identified 21 error scenarios. These scenarios were then tested on a range of EP systems available in the US. The testing was carried out by prescribers who were asked to undertake the prescribing and were observed by an investigator. In their attempts to prescribe the prescribers were allowed to use any workaround they were aware of in order to prescribe the erroneous scenario. The ability of the system to prevent the error and the level of workarounds used were recorded. Interestingly, as in the work presented here, not all errors were able to be tested, mainly due to formulary constraints or other design limitations. Similarly all the testers were familiar with the systems in use; indeed in the work reported here two original contacts passed the tests on to staff that were more familiar with the system.

The results showed that 79.5% of the erroneous orders could be prescribed on the EP systems. This is comparable to the 90% permitted errors in the

work presented here. Schiff *el al*[139] reported that 28.0% of the errors were placed "easily" where the order was accepted with no extra steps or warnings. This is far better than the results reported here where 74.2% of the errors had no CDS and therefore, could be placed without extra steps or warnings, or in the terminology used by Schiff *et al* "easily".[139]

The test patients used in this study were adults and the majority of the test scenarios related to adult specific drugs. However, the error types described in the tests were similar to those used here. In addition, the errors were identified purely from spontaneously reported medication errors making it difficult to draw conclusions about the relative frequency of the specific problems. The work described here specifically relates to errors that are likely to cause harm in children and the errors were derived from not only spontaneous reports but pharmacist interventions and the expertise and experience of the expert panel.

Importantly this work identifies the importance of other post prescribing barriers which prevent prescribing errors from reaching the patient. The potential for the errors described to reach the patient should it be prescribed, was assessed by the respondents and results shown in Figures 4.3 and 4.4. The prescribing error score gives an indication of how likely a prescriber using the system might make the error. It is not just a consideration of the EP system but also the interaction of the prescriber with the system and that prescriber's knowledge of the patient, drug and indication. In other words the whole of the prescribing process as described previously (Chapter 1).

Eight errors achieved a score of greater than 4 for this question suggesting these are the most likely prescribing errors (errors 2,5,6,11,13,14,15 and 39). In all cases these errors had no CDS in any of the systems. In addition they are all errors which refer to information that would either be in another system or part of the knowledge of the prescriber. For example error 39 which had the highest score, relates to the wrong dose of IV aciclovir for herpes simplex encephalitis. In order for an EP system to provide an alert or warning it would need to know the indication being treated. A low level CDS could warn prescribers that if they are prescribing for encephalitis, then a specific dose must be chosen; however, this would need to be presented for every prescription for aciclovir, possibly reducing its overall impact of the warning.

Four errors (23, 24, 37 39) had the greatest drop in score between the likelihood of the error being prescribed and the likelihood of it reaching the patient. This suggests that these were most likely to be detected by post-prescribing checks. Two cases, IV ganciclovir (23) and folinic acid (24) relate to drugs which are routinely prepared in the pharmacy rather than at ward level; this may provide a higher level of local scrutiny. In the case of paracetamol (37), probably the most common prescription for children in a hospital setting, nursing staff will routinely check and re-calculate doses. Error 39 relates to IV aciclovir and is discussed above.

Seven errors received low scores of 2 or less. These were errors 12, 21, 22, 24, 28, 35 and 36. All of these errors had relatively high levels of CDS when compared to other errors. In all cases the likelihood of the error reaching the patient also scored low, which suggests the CDS is helping to prevent the error from reaching the patient.

In all cases the scores for the likelihood of the error reaching the patient are less than or equal to the prescribing error scores. This is reassuring as it would suggest that all sites utilise post prescribing checks to reduce the risk of errors reaching the patient.

It is clear from the results that there are few barriers within the EP systems in use in the UK to prevent errors that are known to cause harm and therefore, the post-prescribing checks remain vital to prevent it. Four examples of errors had their Likert response scores combined with the CDS level scores in an attempt to see if there was a possible relationship. These results illustrate that there were errors that were, in the opinion of the respondents, likely to be prescribed on an EP system. Where these errors invoked a higher level of CDS there was a suggestion from these examples that the error was less likely to be prescribed.

4.7 Limitations

There are a number of possible limitations to consider with this work. Firstly, not all of the original 21 sites identified completed the survey. This may mean that a unique EP system in use in the UK was not subjected to the test.

Error simulation was performed by paediatric pharmacists rather than prescribers. In the Schiff *et al*[139] work, prescribers were asked to try and

prescribe the error for a test patient using any means possible including work-arounds. It could therefore, be argued that this work did not simulate the true electronic prescribing process. However, the results do give an insight into the ability for the EP systems, currently in use, to help prevent a specific group of errors. Future work should take this into account.

The Likert scoring was performed only by pharmacists originally contacted to complete the survey. It is possible that their views of whether a prescribing error is likely to occur are different from prescribers. It was assumed that all sites had a clinical pharmacy service to the paediatric specialties and therefore, the respondents would be familiar with the prescribing practices in their sites.

A proportion of the errors were deemed not applicable as paper prescribing was used. This reduced the number of responses for these errors making specific conclusions difficult. In most sites the use of a paper prescription is usually cross referenced within the EP system by using a dummy drug file, e.g. “Heparin Infusion – see paper chart” which was quoted by some sites for error 7. While the use of a dummy drug on the EP system was not fully investigated, the author’s experience is that they can be tagged within the EP system to a target drug and therefore, provide appropriate warning where applicable. So in the heparin example, if a patient was already prescribed an oral anticoagulant, the prescriber would be presented with a therapeutic duplicate warning when prescribing the heparin dummy drug. Of course this does assume that the prescriber will prescribe on both EP and paper, which in the prescriber’s eyes could be construed as a duplication of effort. This presents its own challenges in terms of the prescribing process.

4.8 Conclusion

The EP systems in use in the UK do not prevent the majority of harmful errors from being prescribed to paediatric patients. Levels of CDS and warning provided to prescribers vary considerably.

None of the systems were specifically designed for use with paediatric patients and they were all commercially available systems rather than home-grown developments. The author is aware of a system which, at the time of writing, has gone live. It has been designed specifically for a Children’s Hospital. So as part of further work it will be fascinating to compare this system with those already studied.

Chapter 5 Overall Discussion and Conclusions

5.1 Introduction

To the author's knowledge, this is the first work undertaken in the UK to test electronic prescribing systems that are used for paediatric patients in hospital, for their ability to prevent errors likely to cause harm. The work described in this thesis has created new knowledge concerning the way electronic prescribing systems are utilised in the paediatric setting in UK hospitals. The original aims and objectives have been achieved and the work has stimulated and identified the need for further research. This chapter brings together the research and reviews and makes conclusions. Limitations of the work will also be discussed and ideas for further work postulated.

5.2 Literature Review

A review of the literature pertaining to the use of EP in paediatric hospital settings was undertaken. This showed that EP systems could clearly reduce the incidence of prescribing errors and in some cases, a reduction in errors that could cause harm. However, it also highlighted a range of definitions for medication errors and different methods for identifying them. This makes comparison of data very difficult and does not allow researchers to make any clear conclusions.

5.3 Prescribing Indicators

Prescribing indicators were chosen as a means of providing a clear definition of a prescribing error, i.e. by describing a set of very specific errors. These could then form the basis of an easily reproducible method of evaluating an EP system. Other tools such as the trigger tool have been used to identify errors, but they currently rely on retrospective analysis of notes.[61, 141]

A set of 41 paediatric prescribing errors was developed using an eDelphi methodology to gain consensus from an expert panel. The eDelphi method allowed an electronic transfer of a large amount of information to each of the expert panel members. This was an efficient way of conducting multiple rounds of scoring in order to gain consensus. It was used in the development of the adult prescribing indicators[90] on which this work was based.

There are three common methodologies for determining consensus within healthcare: nominal group processes, consensus development panels and the Delphi technique. The nominal group process involves four phases, three of

which involve face to face presentation and discussion about a set of solutions to the proposed problem. The solutions to the problem under discussion are generated anonymously by the panel members for subsequent discussion. It has been used particularly for the appropriateness of interventions in health care.[92] Consensus development panels are organised conferences or events specifically planned to discuss a topic. They are commonly used to formulate policy and strategic plans. It is a multidisciplinary approach involving a great deal of face to face discussion. Specific methodology is not agreed and the logistics and cost involved make it unfeasible for most researchers.[93]

A recent review of the three methods by Waggoner *et al*[118] outlined the advantages and disadvantages of each method. It made recommendations specifically on Delphi studies in terms of panel size, number of rounds, definition of "expert" and statistical analysis. The recommended panel size was 5-11 members; however, this is based on face to face discussion rather than the electronic process used in this work. The optimal number of rounds was two, which was also used in the work (excluding the exploratory round). A definition of expert was not considered in this work. The panel was identified through the author's own professional networks within paediatrics and paediatric pharmacy. It might have been prudent to insist on a minimum number of years' experience during the selection process. However, the resulting panel of 21 members had a total of 424 years of paediatric experience, with the minimum being nine.

The initial list of indicators was developed from a range of sources including the expert panel itself. Consensus was achieved on a group of 41 indicators which had the potential to cause harm if they were prescribed and subsequently reached the patient. This work was subsequently published in the British Journal of Clinical Pharmacology.[126]

The indicators, while relating to potential errors for a specific drug, also included a range of error types such as wrong dose, contraindication and allergy. They therefore, can provide not just a measure relating to specific drugs but also general measures to reduce the risk of these error types.

The second phase of this research involved the identification of hospitals currently using EP for their paediatric patients. The paediatric pharmacist at each of the sites was asked to simulate the prescribing indicators and provide a description as to whether the indicator was permitted by their system and

what level of clinical decision support (CDS), if any, was provided to the prescriber. A detailed description of this work is provided in Chapter 4.

In summary, the majority of the errors described in the indicators could be prescribed on the eight different EP systems that were studied (90%). In addition, in only 28.2% of cases was a warning provided to the prescriber to help prevent the error from being prescribed.

While warnings and alerts were provided to the prescriber for specific drugs, the results suggest that only basic levels of CDS are in place. This did not come as a surprise as it is the experience of the author in his local centre.

There are a number of reasons for this, some of which have already been discussed in Chapter 4.

5.4 Paediatric *Versus* Adult.

At all sites the EP system had been designed for use in a general clinical setting rather than specifically for paediatric prescribing. There is a clear organisational advantage of having a single EP system across a single organisation, such as a reduction in licence costs and administrative support. However, this means that compromises in the way the system works across all patient types may have to be made. Cordero *et al*[71] showed the benefit of having a system specifically designed for paediatric and neonatal patients where, despite having a basic EP system there were significant decreases in errors.

The dual setting issue was highlighted specifically in one site (site 8) where adult based dose ranges and rounding were present in the system. Specifically, for indicator 14 the dose was rounded to the nearest 200mg. This is perfectly acceptable for this drug in adult patients and indeed some older children, as ceftriaxone has a relatively wide therapeutic range. It also means that drug preparation for nursing staff is made simpler. However, ceftriaxone is licensed for use in children from as young as 4 weeks who may only weigh 4kg. A 200mg dose adjustment for a 4kg patient represents a dose change of 50mg/kg which is far in excess of the normal dosing limits for this drug. One of the studies reviewed in Chapter 1[75] used a system designed for adults with adult dosing ranges and this was cited as one of the reasons the reduction in prescribing errors in the paediatric setting was not as great as that seen with adults.

There were a number of indicators that were not specific to the paediatric setting; for example indicator 28 which relates to the frequency of dosing of methotrexate. This indicator was originally identified during indicator development from an NPSA alert[136] and the Never Event framework[135] it was also included in the adult indicators previously published.[90] Methotrexate is prescribed for children but not as commonly as for adults and one could argue that it does not represent a common prescribing error in children. It was included in the original list because of the high potential for harm and because the frequency error should lend itself to being prevented by EP. Following the eDelphi process it did become one of the final 41 indicators. It was reassuring to see that this indicator, which has had a relatively high level of publicity, had one of the highest rates of CDS.

5.5 Acclimatisation

The literature review also highlighted the importance of taking into account an acclimatisation period following implementation of an EP system. Users need time to become accustomed to their system, understand how it works and get used to changes in their work flows. This can itself contribute to more errors in the initial period after implementation. All of the sites which undertook indicator simulation had been using their system for enough time for acclimatisation (mean: 4.4 years; range: 8 months – 22 years). The pharmacists who undertook the simulation, therefore, were familiar with the systems, removing any concern about unfamiliarity.

5.6 Use of Indicators

The indicators are suitable for continued assessment of an EP system over time. Kadmon *et al*[78] showed the impact of the evolution of an EP system over time. With increasing levels of CDS added to their system, there were further reductions in prescribing errors. As the use of EP systems in the UK develops, hospitals will be looking to change or upgrade their systems. The indicators can be used to evaluate any upgrade either prospectively within a test environment, or prospectively in real prescribing situations. To aid evaluation of either a first implementation or an upgrade, both the adult and paediatric indicators have been incorporated into a web based data collection tool.[142] This is available free for any UK trust wishing to undertake an evaluation. Data from sites using the tool will be collected centrally by the University of Birmingham. This will allow data to be analysed nationally to

compare systems and sites as implementation occurs. The author will be involved in the analysis of paediatric data in the future.

It would be tempting to compare systems by virtue of the number of indicators that were permitted. This represents a very simplified and crude measure of what is actually happening. Rather, the presence or absence of some form of CDS for each of the indicators represents a more nuanced way of comparing systems.

It could be argued that three of the indicators should not be permitted: allergy, methotrexate frequency and amphotericin preparation. These indicators lend themselves easily to a basic level of CDS. Indeed, the results show that these indicators commonly triggered warnings to the prescriber. However, it is necessary, in some cases to be able to override the system constraints. This is particularly the case in relation to allergies. Patients often cite an allergy to penicillin but this is not always a true allergic reaction; it may have been an adverse effect such as nausea or diarrhoea which is miss-construed as an allergy. If one of these patients requires a penicillin containing antibiotic, the prescriber is faced with a decision. Penicillin and penicillin containing antimicrobials are contra-indicated in patients with a true allergy. The EP system, however, may not be advanced enough to distinguish between a true allergy and a sensitivity or previous adverse effect. Furthermore, the EP system may not have a field in which the symptom or severity of the allergic reaction can be recorded. In this case it may be acceptable to override any alerts provided to the prescriber.

This highlights the impact and importance of the underlying information that becomes part of a patient's record within an EP system.

In the case of amphotericin the need to distinguish between plain and lipid formulations is vital and there are no clinical situations in which this needs to be overridden. Not all EP systems in the study were able to prevent this specific indicator – indeed some of the sites had taken a policy decision to remove plain amphotericin from the hospital completely, thereby preventing the potential, for this error.

5.7 Alert Variation

There was a wide variation between sites in the number and type of warnings presented to prescribers in an attempt to prevent the prescribing errors. Drug-drug interactions and therapeutic duplications were the most common error

types that invoked a warning. The reasons for this have previously been discussed in Chapter 4 along with the differences between sites. A wide variation in high priority drug interaction alerts was also reported in the US by McEvoy *et al*.[143] Variety in the use of order sets or "bundles" has also been described.[144]

The inference is that all the indicators should invoke at least some form of alert to the prescriber. However, this is likely to result in an increase in the number of alerts shown to prescribers, which raises the spectre of alert fatigue.

5.8 Alert Fatigue

Alert fatigue is the phenomenon whereby a prescriber gets used to certain levels of alerts and begins to ignore them or regard them as a nuisance. Prescribers will try and find a work-around in their processes, which may or may not result in fewer alerts. A study of medication dose alerts presented to prescribers in a US hospital was published in 2013.[145] It reported an 8.5% acceptance rate for dose range alerts and 5.5% for informational alerts. In addition to the direct consequences of ignoring alerts,[146] there are indirect consequences of the impact of distractions on clinical decision making.[147]

Horsky *et al*[148, 149] have reviewed best practices for CDS, specifically for prescribing interventions. They made several recommendations specifically about alerts such as tiered severity levels, concise text and meaningful use of colour. Just as importantly they described desirable system attributes such as consistent terminology, workflow integration and density of information on the screen. They also highlighted the importance of integrating contextual patient data into the decision logic. The results of the work presented here clearly show that these elements are lacking in the EP systems in use in the UK. The poor specificity of alerts leads to a lowering of the perceived signal to noise ratio and therefore, increases the risk of critical or dangerous prescribing errors.

One possible solution would be to build a system which alerted the prescriber only when prescribing the errors described in the paediatric prescribing indicators developed in this research. In order to achieve this, a very high degree of specificity would need to be included in the system. For example, the system would need to alert the prescriber only when the specific drug interactions involved in the list of indicators were being prescribed, and ignore

all other interactions. The same argument would apply to the other error types. While it could be possible to program a system only to alert the prescriber when the drugs in the indicators are being prescribed at the wrong dose; would this make the system safe? The indicators were developed in order to identify errors likely to cause harm, in an effort to develop a tool to measure the effectiveness of an EP system to prevent harm. They represent errors likely to cause significant harm. However, there are, of course, numerous other specific wrong dose errors that could cause harm in children (see Chapter 1). It was impossible to include all of them in the indicator list. By including a range of error types such as dosing errors, interactions and contra-indications, it has been possible to obtain a general sense of how safe a system is. More specifically, in the case of wrong dose errors, the ability to prevent the indicator errors gives an indication of the ability of the system to identify dosing errors generally by using a form of dose range checking. Very few of the systems tested in the study had the ability to do this. In the ones that did, the dose range checking was used in only a limited number of drugs.

5.9 "Free-text" Prescriptions

All EP systems rely on a database of drugs and medications from which the prescriber can choose. Not all medicines will be included in this list. In this case the prescriber may be able to use a free-text option when prescribing. If so it is likely that none of the CDS available in the system will be applied to this prescription, including allergy checking. This clearly has safety implications and, in general free-text prescribing, should be kept to a minimum, by maintaining the drug database within the system. A recent review by Tolley *et al*[150] identified the need to use free-text prescriptions due to the lack of available dosing options as a system design attribute linked to prescribing errors in paediatrics In the simulation work described in this report, it was assumed that the prescriber would not choose to write each drug up using a free-text option. In the author's experience this process requires several extra key strokes which means prescribers are more inclined to search for the correct drug. Conversely, having a long list of similar products to choose from in a drop-down list can increase the likelihood of picking errors.[137]

5.10 Organisational aspects

One organisational aspect of EP is the general IT strategy adopted by the organisation. Some sites, as in the researcher's own, adopt a "best of breed" approach, whereby systems specifically developed to undertake a function within a hospital setting, are purchased or commissioned. This results in discrete systems for prescribing: pharmacy, pathology, radiology and critical care for example. While these systems individually may be excellent and achieve the original specification, there may not be appropriate interfaces between them. This was highlighted in Chapter 4 with indicators that related to information about the patient's blood tests and co-morbidities. There was no CDS in any of the systems that warned the prescriber the patient may have a low white blood cell count. This would have required a link to the blood tests for that patient.

Some organisations (particularly in the US) adopt a single hospital-wide system that does everything. Implementation of these systems is much more arduous and expensive than individual systems. While links between departments and information can easily be made, the specifications for each area may not be fully met. The systems tend to be cumbersome and are less likely to be customisable for a specific organisation. Support from the vendor may also be a consideration.

5.11 Post- Prescribing Checks

As previously discussed, the indicators represent prescribing errors which are likely to cause harm. As such they provide a measure of the level of harm that can be avoided if the errors are prevented by an EP system. However, as we have seen, a large number of the errors are not prevented or their risk mitigated by CDS. The respondents were asked to give their opinion on whether a specific prescribing error was likely to be made and then if made, how likely it would be to reach the patient. The results show that even if prescribed, in many cases the error would be picked up before it reached the patient. For the EP systems seen in this work, with relatively basic CDS, the importance of these post prescribing checks is clear. It is reassuring to see that these checks are in place and it highlights the importance of other health care professionals in the system and their contribution to keeping patients safe.

5.12 Limitations of this Research

The prescribing indicators were developed with the express intention of evaluating whether or not an EP system would prevent them. They included a range of error types and as we have seen, EP systems showed a variety of performance in the tests.

As EP systems become more widely used in secondary care, and certainly in the US where they are in more common use, there is an increasing interest in errors that occur as a result of EP or where EP is a contributory factor. The vulnerability testing by Schiff *et al*[139] discussed in Chapter 4 was designed to evaluate EP systems against a test formulated from incident reports that cited EP as a contributory factor.

In addition to the testing detailed by Schiff *et al*[139] the Leapfrog group also has a CPOE testing process used in the US.[151] The Leapfrog system requires hospitals to register and attempt to order a series of test prescriptions for a group of test patients. The results are recorded online and the hospital given a score. The test is used for benchmarking hospitals across the US.[152]

The prescribing indicators described in this work were not designed specifically to identify errors caused by EP systems. However, they do describe errors which could be prevented by an EP system that took into account the issues described in the review. Apart from the adult nature of the tests developed by Schiff *et al*[139] the range of error types are the same. Future work could include reference to the impact of EP as a contributory factor to the error to ensure the indicators provide a comprehensive test of a system.

The researcher who conducted this work is an experienced paediatric pharmacist. It is important to consider what effect he may have had on the research. The simulation exercise was carried out by a different paediatric pharmacist in the researcher's own local centre. As a paediatric pharmacist with 24 years' experience, the researcher is well aware of the risk of medication errors in children and indeed the wider population. The evidence of the impact of medication errors in paediatrics has been presented and is clear. Despite that, it is possible that a bias towards paediatric care could have had an impact on the way the research was carried out and reported. However, it is precisely because of this experience that the research was focussed on the paediatric population and has enabled the conclusions to be

made from the data collected. The results have been presented to show the specific concerns around prescribing errors in children, but reference to the impact of this with adult patients has been alluded to. The researcher's experience has meant that the data can be analysed and reviewed in the context of paediatric prescribing and appropriate conclusions made.

5.13 Future Research

The use of the indicators to assess the impact of the implementation of an EP system has already been alluded to. Data are currently being collected by the All Wales Quality and Patient Safety Group (AWQ&PS) using both adult and paediatric indicators.[124] The author has been involved in the development of an electronic data collection tool which includes the paediatric indicators developed in this work. The tool allows ward based pharmacists to collect information on prescribed medicines and possible triggers related to the indicators. This is in advance of the implementation of the Welsh Hospital Electronic Prescribing, Pharmacy and Medicines Administration (WHEPPMA) system. The implementation of WHEPPMA is likely to be at least two years away, so this gives ample opportunity to collect data on both paediatric and adult prescribing errors. The researcher will remain involved in the data analysis for this work.

Brown *et al*[153] published a systematic review of prescribing errors generated from computerised provider order entry systems in primary and secondary care. They included 34 studies from a range of countries. Eight themes associated with EP related prescribing errors emerged from this review: computer screen display, drop-down menus and auto-population, wording, default settings, non-intuitive or inflexible ordering, repeat prescriptions and automated processes, users' work processes and CDS systems. While CDS was cited as one of the themes which has been explored in the work presented here, the importance of the other themes must not be overlooked. It is possible that vendors apply a greater level of emphasis on CDS to prevent prescribing errors rather than taking into account the design and flexibility of a system.

In this work the indicators were simulated by the paediatric pharmacist at the site. One possible option for the future would be to get prescribers to undertake the simulation as in the work reported by Schiff *et al*.[139] The advantages of this would be that observing the prescribers would allow a

better understanding of how they interact with the EP system and the workarounds that might be used. In addition an assessment as to how easy it is to prescribe the errors could be made. Socio-technological issues could then be qualitatively analysed using the themes described by Brown *et al*[153]

The indicators may need to be updated as both the range of drugs used in the paediatric population changes, and EP systems become more advanced. However, this is unlikely to be required in the next five years. Paediatric drug therapy does not alter as rapidly as adult drug therapy. New treatments are rarely licensed for the paediatric population. In addition, the prescribing indicators cover a range of prescribing error types which in themselves, are unlikely to change.

Errors can occur at any point in the drug use process. Administration errors are also a concern and have been reported to occur at higher rates than prescribing errors in the paediatric setting.[30] EP systems, certainly in the UK, are combined with an electronic administration record as well, often termed electronic prescribing and medicines administration (EPMA) systems. Currently, methods to evaluate administration errors rely on observational techniques or spontaneous event recording, as discussed in Chapter 1. It may be feasible to develop and test a set of administration indicators that could be used in a similar way to test EPMA systems for their ability to prevent such errors.

5.14 Future Practice

The results of this work clearly show that EP systems do not currently prevent the majority of potentially harmful paediatric prescribing errors. In terms of future practice there are two workstreams that could be undertaken as a consequence.

Firstly, it is possible that prescribers faced with using a new EP system have a specific set of expectations in the system's ability to prevent prescribing errors. Managing these expectations is vital throughout the whole of the implementation and ongoing management of an EP system. A recent report by Puaar *et al*[154] detailed a qualitative evaluation of the impact of an inpatient prescribing system on prescribing errors. One of the themes detailed related to expectations of decision support. There was an expectation that the system would prevent certain errors such as duplications and incorrect doses, when it did not. A detailed understanding of the EP system and the CDS,

provided by use of the indicators, could help to provide detailed evidence and support to prescribers rather than allowing them to find out during training or routine use.

Secondly, the results highlight the importance of the post prescribing check in preventing errors from reaching patients. Hospital staff involved in these processes such as pharmacists, nurses and midwives also need an understanding of the constraints within their EP system. This will allow them to target their activity in such a way as to make the most of their, possibly limited, resources.

5.15 Conclusion

The aim of this programme of research was to evaluate the ability of electronic prescribing systems to prevent prescribing errors known to cause harm in the secondary care paediatric setting. In order to achieve this, a set of 41 paediatric prescribing indicators were developed by consensus with an expert panel.[126] The indicators were subsequently used in a simulation test of eight different EP systems across 15 different NHS trusts in the UK.

The majority of errors were not prevented by the EP system under test. Post prescribing checks by pharmacy and nursing staff were identified as barriers to the error reaching the patient.

Suggestions for the development of EP and CDS systems and the way they are set up within care settings can be made from these results; for EP systems specifically, the need for warnings relating to the dose based on the diagnosis, and the functionality to link or provide other clinical data at the point of prescribing. For system set up, the utilisation of functionality to assist prescribers to prevent prescribing errors, while providing an appropriate level of meaningful warnings during the prescribing process. Lastly, there is a clear requirement to understand the differences in prescribing for children and for EP systems to have the appropriate functionality to accommodate these differences.

This is the first such work to be carried out in the paediatric patient population in the UK. It has highlighted the current shortcomings of EP and CDS systems and can influence and direct future work in this field to continue to help reduce the risk of prescribing errors in our paediatric hospital settings.

Appendix 1 – Literature Review Search Strategy

1. EMBASE; *MEDICATION ERROR/;
2. EMBASE; "prescribing error".ti,ab;
3. EMBASE; "dispensing error".ti,ab;
4. EMBASE; "administration error".ti,ab;
5. EMBASE; 1 OR 2 OR 3 OR 4; 6611
6. EMBASE; 5 [Limit to: Human and English Language and Publication Year 1999-2014];
7. EMBASE; *ELECTRONIC PRESCRIBING/;
8. EMBASE; "electronic prescribing".ti,ab;
9. EMBASE; "e-prescribing".ti,ab; 395 results.
10. EMBASE; *COMPUTERIZED PROVIDER ORDER ENTRY/;
11. EMBASE; 7 OR 8 OR 9 OR 10;
12. EMBASE; 11 [Limit to: Human and English Language and Publication Year 1999-2014];

Databases searched – Embase, Medline and CINAHL. Appropriate related terms used in Medline and CINHAL based on thesaurus.

Appendix 2 – Email Invitation

Email invitation to potential expert panel members

University of Portsmouth School of Pharmacy and Biomedical Sciences

University Hospital Southampton NHS
NHS Foundation Trust

Southampton Pharmacy Research Centre (SPRC)

An evaluation of the impact of electronic prescribing on paediatric prescribing errors in a secondary care setting.

Participant Information

Background

Prescribing safety indicators have been developed for primary and secondary care settings for the adult population[88, 90]. This project aims to develop a set of prescribing indicators for the paediatric population in secondary care by gaining consensus from a range of experts on the likelihood and chance of significant harm in secondary care. I will then use the indicators to evaluate the impact of electronic prescribing on the incidence of frequent or high risk prescribing errors likely to cause harm.

The eDelphi Process

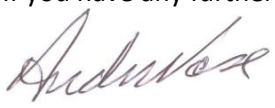
I am using electronic Delphi (eDelphi) technique to gain consensus on the opinions of experts through a series of questionnaires. The technique has been used previously in healthcare research to establish consensus. I have derived an initial list of 122 prescribing safety indicators through literature searching and clinical experience for consideration by the panel of experts.

The eDelphi will be conducted in three rounds and all data received and exchanged via email.

Round 1 (Exploratory)	A list of indicators will be sent out to participants, who will be asked to suggest critical indicators that they think are missing. Also to suggest any changes to wording or terminology.
Round 2	Responses from Round 1 will be analyzed and collated into a second revised, list of indicators, which will be sent by email to participants. This spreadsheet will have a scoring functionality, where participants will score the likelihood of the error occurring and the seriousness of the error should it occur using a 5-point Likert scale.
Round 3	Participants will receive a second spreadsheet containing their initial score and the median score for each indicator. Participants will be asked if they want to change their score in response to the groups median value. A comments section will allow respondents to justify/comment on their scoring decision.

Participants are asked to respond within two weeks for each round of the process.

If you have any further questions please do not hesitate to contact me.



Andy Fox
Director – Southampton Pharmacy Research Centre(023 8120 4201)
eDelphipaed@uhs.nhs.uk

References

1. Thomas SK, McDowell SE, Hodson J, Nwulu U, Howard RL, Avery AJ, *et al*. Developing consensus on hospital prescribing indicators of potential harms amenable to decision support. *British Journal of Clinical Pharmacology*. 2013;76(5):797-809.
2. Avery AJ, Dex GM, Mulvaney C, Serumaga B, Spencer R, Lester HE, *et al*. Development of prescribing-safety indicators for GPs using the RAND Appropriateness Method. *Br J Gen Pract*. 2011 Aug;61(589):e526-36.

Appendix 3 – Participant Details Form

University of Portsmouth School of Pharmacy and Biomedical Sciences

University Hospital Southampton NHS
NHS Foundation Trust

Southampton Pharmacy Research Centre (SPRC)

An evaluation of the impact of electronic prescribing on paediatric prescribing errors in a secondary care setting using prescribing indicators

Participant Application Information

If you would like to take part in the research project please complete the following details

Name	
Hospital Address	
Email	
Job Title	
Qualifications	
Years of clinical experience (post qualification)	
Years of experience with electronic prescribing systems (does not have to be paediatric)	

If you require any further information please do not hesitate to contact me.

Andy Fox
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023 8120 4201

Appendix 4 – Adult Indicators

Adult indicators previously published[90] – results of review for consideration as paediatric indicators.

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Proton-pump inhibitors prescribed at the same time as antacid formulations *(therapeutic effect of the proton-pump inhibitor reduced)*	Timing of antacid and proton-pump inhibitor dosing should be separated	N	Rare use in paediatrics
Diphenoxylate, loperamide, or codeine phosphate prescribed as antidiarrhoeal agents for treatment of diarrhoea of unknown cause *(increased risk of exacerbating constipation with overflow diarrhoea)*	Risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis	N	Rare indication in paediatrics
Diphenoxylate, loperamide, codeine phosphate prescribed as antidiarrhoeal agents for treatment of severe infective gastroenteritis (e.g. bloody diarrhoea, high fever, or severe systemic toxicity) *(increased risk of exacerbation or protraction of infection)*	Risk of exacerbation or protraction of infection	N	Rare indication in paediatrics
Digoxin prescribed at a dose >125 micrograms daily to a patient with renal impairment *(increased risk of digoxin toxicity)*	Risk of digoxin toxicity when given at doses >125 micrograms in patients with renal impairment	M	Combined into single digoxin indicator (4)
Digoxin prescribed at a dose of >125 micrograms daily to a patient with heart failure who is in sinus rhythm *(increased risk of digoxin toxicity)*	Risk of digoxin toxicity when given at doses >125 micrograms in patients with heart failure	M	Combined into single digoxin indicator(4)
Digoxin prescribed concomitantly with a diuretic *(risk of hypokalaemia and subsequent digoxin toxicity)*	Risk of potassium below 4 mmol/litre - increased risk of sensitising the myocardium to digoxin	N	Rare use in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Statins prescribed concomitantly with macrolide antibacterials *(increased risk of myopathy)*	Macrolide antibacterials can increase the concentration of statins	N	Rare use in paediatrics
Thiazide diuretic prescribed to a patient with a history of gout *(increased risk of exacerbating symptoms in pre-existing gout)*	Thiazide diuretics can cause hyperuricaemia and gout, and can therefore exacerbate symptoms in pre-existing gout	N	Rare use in paediatrics
Two loop diuretics prescribed concomitantly *(increased risk of adverse effects)*	Increased risk of adverse effects	N	Rare use in paediatrics
Thiazide prescribed to a patient with chronic kidney disease (CKD) stage 3 (eGFR< 45/ml/min/1.73m^2) or above *(increased risk of side effects)*	No clinical benefit and may get adverse effects	N	Rare use in paediatrics
Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*	Increased risk of severe hyperkalaemia	Y	(5)
Amiodarone prescribed to a patient with abnormal thyroid function tests *(increased risk of thyroid disorders)*	Amiodarone can cause thyroid disorders	Y	(6)
Amiodarone prescribed concomitantly with simvastatin 40 mg or above *(increased risk of myopathy)*	Stain concentration increased by amiodarone, increasing risk of myopathy	N	Rare use in paediatrics
Non-cardioselective beta-adrenoceptor blocking drug prescribed to a patient with COPD *(increased risk of bronchospasm)*	Beta-adrenoceptor blocking drugs can cause bronchospasm. A cardio-selective form should be prescribed if one is essential for a co-existing condition	N	Indication not applicable in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*	Beta-adrenoceptor blocking drugs are known to cause bronchoconstriction in asthmatics, and can cause acute deterioration	Y	(7)
ACE inhibitor or angotensin-II receptor antagonist prescribed to a patient with a potassium level ≥5.0 mmol/litre *(can cause or exacerbate hyperkalaemia)*	ACE inhibitors and angiotensin-II receptor antagonists can cause hyperkalaemia and are contraindicated in patients with a potassium concentration about the desired reference range	Y	(8)
Aliskiren prescribed concomitantly with ACE inhibitors or angiotensin-II receptor antagonists *(increased risk of serious adverse cardiovascular and renal outcomes)*	The combination of aliskiren with ACE inhibitors or ARBs has been associated with serious adverse cardiovascular and renal outcomes	N	Rare use in paediatrics
Aliskiren prescribed to a patient with severe renal impairment - GFR< 30ml/min/1.73m^2 *(risk of hyperkalaemia)*	Use of aliskiren (either as monotherapy or in combination with other medicines) is no longer recommended in patients with severe renal impairment (ie, eGFR <30mL/min per 1.73 m^2)	N	Rare use in paediatrics
Verapamil prescribed to a patient with NYHA Class III or IV heart failure *(risk of precipitating heart failure, exacerbating conduction disorders and causing significant deterioration)*	Diltiazem and verapamil can precipitate heart failure, exacerbate conduction disorders and cause significant deterioration	N	Rare indication in paediatrics
Verapamil prescribed to a patient concomitantly a with beta-adrenoceptor blocking drug *(increased risk of adverse cardiovascular effects)*	Asystole, severe hypotension and heart failure when verapamil and beta-blockers prescribed concomitantly	N	Rare indication in paediatrics
Low molecular weight heparin omitted to be prescribed for prophylaxis *(increased risk of thrombosis)*	All patients should be assessed for VTE risk on admission to hospital and prophylaxis prescribed if indicated	N	Error of omission

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Low molecular weight heparin prescribed without the patient's weight being used to calculate the treatment dose *(risk of subtherapeutic or supratherapeutic dosing)*	The patient's weight should be used as the basis for calculating the required treatment dose	M	Too drug specific modified for documentation error (D)
Low molecular weight heparin prescribed at a dose exceeding the maximum as stated in the product literature *(risk of bleeding increased)*	Increased risk of bleeding when the dose is prescribed above the recommended limit for the indication	M	Too drug specific modified for documentation error(D)
Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment *(increased risk of bleeding)*	Increased risk of bleeding with the dose of low molecular weight heparin is not adjusted for renal function	Y	(11)
Warfarin prescribed concomitantly with a NSAID *(increased risk of bleeding)*	Concomitant anticoagulants and NSAIDs increase the risk of bleeding	Y	(14)
Warfarin prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	High risk of bleeding when warfarin prescribed to patients with a past medical history of bleeding disorders	Y	(13)
Aspirin prescribed to a patient with a past medical history of peptic ulcer disease without antisecretory drugs or mucosal protectants *(increased risk of peptic ulceration, and risk of bleeding)*	Increased risk of peptic ulceration, and risk of bleeding	N	Rare co-morbidity
Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	High risk of bleeding when antiplatelets prescribed to patients with a past medical history of bleeding disorders	Y	(17)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Clopidogrel prescribed to a patient concomitantly with a NSAID (excluding aspirin)*(increased risk of bleeding)*	Increased risk of bleeding when clopidogrel prescribed concomitantly with NSAIDs	N	Rare use in paediatrics
Clopidogrel prescribed to a patient concomitantly with omeprazole or esomeprazole *(antiplatelet effect of clopidogrel potentially reduced)*	Antiplatelet effect of clopidogrel potentially reduced	N	Rare use in paediatrics
Cholestyramine prescribed to a patient at the same time as any other medication *(risk of poor clinical effect owing to reduced absorption of medications)*	Absorption of concomitant medication can be impaired, causing a lack of efficacy	N	Rare use in paediatrics
Long-acting beta-2-agonist inhaler prescribed to a patient who is not also on an inhaled corticosteroid *(evidence base - not in line with British Thoracic Society guidelines)*	Not in line with British Thoracic Society (BTS) guidelines	M	Modified according to paediatric BTS guidance (20)
Long-acting inhaled antimuscarinic prescribed concomitantly with a short acting nebulised antimuscarinic *(increased risk of additive adverse effects)*	Long-acting antimuscarinics should be omitted during short courses of nebulised therapy to avoid additive adverse effects	N	Rare use in paediatrics
Benzodiazepines prescribed long-term (i.e. more than 2–4 weeks) *(risk of dependence and withdrawal reactions)*	Dependence and withdrawal reactions after long-term use; duration of use 2-4 weeks, incl. Dose tapering phase	N	Rare use in paediatrics
Benzodiazepine or benzodiazepine-like drug prescribed long-term to a patient with depression *(risk of dependence and withdrawal reactions)*	Risk of dependence after long-term use; duration of use 2-4 weeks	N	Rare use in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Benzodiazepine or benzodiazepine-like drug prescribed to a patient with COPD *(risk of respiratory depression)*	Risk of respiratory depression	N	Rare co-morbidity
Benzodiazepine-like drug (e.g. Zopiclone) prescribed long-term (i.e. more than 2–4 weeks) *(risk of dependence reactions)*	Risk of dependence after long-term use; duration of use 2–4 weeks	N	Rare use in paediatrics
Antipsychotic, other than risperidone, prescribed to a patient for the management of the behavioural and psychological symptoms of dementia *(increased risk of stroke)*	Antipsychotics, other than risperidone, should be avoided in patients with dementia owing to the increased risk of stroke	N	Rare use in paediatrics
Antipsychotic prescribed long-term (i.e. > 1 month) to a patient with parkinsonism *(increased risk of worsening of extra-pyramidal side effects)*	Likely to worsen extra-pyramidal side effects	N	Rare use in paediatrics
Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (> 1.0 mmol/litre) *(risk of lithium toxicity)*	Risk of lithium toxicity	N	Rare use in paediatrics
Lithium therapy prescribed in conjunction with newly prescribed NSAIDs without dose adjustment or increased monitoring (*increased risk of toxicity)*	Risk of lithium toxicity with concomitant prescribing of NSAIDs even within the usual normal therapeutic range	N	Rare use in paediatrics
Lithium therapy prescribed in conjunction with newly prescribed loop or thiazide diuretics without dose adjustment or increased monitoring (*increased risk of toxicity)*	Risk of lithium toxicity with concomitant prescribing of loop and thiazide diuretics even within the usual normal therapeutic range	N	Rare use in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Tricyclic antidepressant prescribed to a patient with dementia *(increased risk of worsening cognitive impairment)*	Risk of worsening cognitive impairment	N	Rare co-morbidity
Tricyclic antidepressants prescribed at the same time as monoamine oxidase inhibitors *(increased risk of serotonin syndrome)*	Risk of serotonin syndrome when tricyclic antidepressants and monoamine oxidase inhibitors prescribed concomitantly	N	Rare use in paediatrics
Tramadol prescribed concomitantly with monoamine oxidase inhibitors *(increased risk of serotonin syndrome)*	Risk of serotonin syndrome when tramadol and monoamine oxidase inhibitors prescribed concomitantly	N	Rare use in paediatrics
Selective serotonin re-uptake inhibitor prescribed to a patient with epilepsy *(increased risk of seizure threshold being reduced)*	Selective serotonin re-uptake inhibitors lower the seizure threshold	N	Rare use in paediatrics
Selective serotonin re-uptake inhibitor prescribed to a patient with a history of clinically significant hyponatraemia (non-iatrogenic , sodium <130mmol/litre in the previous 2 months) *(increased risk of hyponatraemia)*	Selective serotonin re-uptake inhibitors can cause syndrome of inappropriate ADH secretion - exacerbating hyponatraemia	N	Rare use in paediatrics
SSRI prescribed concomitantly with tramadol *(increased risk of serotonin syndrome)*	Drugs with serotonergic properties can increase the risk of CNS toxicity (serotonin syndrome)	N	Rare use in paediatrics
SSRI prescribed concomitantly with pethidine *(increased risk of serotonin syndrome)*	Drugs with serotonergic properties can increase the risk of CNS toxicity (serotonin syndrome)	N	Rare use in paediatrics
SSRI prescribed concomitantly with aspirin without appropriate prophylaxis with antisecretory drugs or mucosal protectant *(increased risk of gastrointestinal bleeding)*	Concomitant use of selective serotonin re-uptake inhibitors and aspirin can increase the risk of gastrointestinal bleeding	N	Rare use in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Selective serotonin re-uptake inhibitors prescribed at the same time as monoamine oxidase inhibitors *(increased risk of serotonin syndrome)*	Risk of serotonin syndrome when selective serotonin re-uptake inhibitors and monoamine oxidase inhibitors prescribed concomitantly	N	Rare use in paediatrics
Citalopram prescribed concomitantly with other QT prolonging drugs *(increased risk of arrhythmias)*	Increased risk of arrhythmias	N	Rare use in paediatrics
SSRI prescribed concomitantly with aspirin without appropriate prophylaxis with antisecretory drugs or mucosal protectant (increased risk of gastrointestinal bleeding)	Concomitant use of Selective serotonin re-uptake inhibitors and aspirin can increase the risk of gastrointestinal bleeding	N	Rare use in paediatrics
Orlistat prescribed at the same time of day as antiepileptics *(orlistat can reduce the absorption of antiepileptics, leading to loss of seizure control)*	Orlistat can reduce the absorption of antiepileptics, leading to loss of seizure control. Dose adjustment of antiepileptic may be required	N	Rare use in paediatrics
Prochlorperazine prescribed to a patient with parkinsonism *(risk of exacerbating parkinsonism symptoms)*	Risk of exacerbating parkinsonism symptoms	N	Rare co-morbidity
Metoclopramide prescribed to a patient with parkinsonism *(risk of exacerbating parkinsonism symptoms)*	Risk of exacerbating parkinsonism symptoms	N	Rare co-morbidity
Metoclopramide prescribed to a patient <20 years (except in cases of severe intractable vomiting of known cause, or due to cytotoxics/radiotherapy)(i*ncreased risk of extrapyramidal side-effects)*	Increased risk of extrapyramidal side-effects in children and young adults (especially 15-19 years old)	N	Rare use in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Domperidone prescribed at a total daily dose exceeding 30mg/day or in adults >60yrs old *(increased risk of QTc prolongation, serious ventricular arrhythmia and sudden cardiac death)*	QTc prolongation, increase risk of serious ventricular arrhythmia and sudden cardiac death	M	Amended to reflect paediatric maximum doses (1)
Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates)*	Injudicious use of two opiates	Y	(26)
Aspirin prescribed to a child ≤ 16 years (except in Kawasaki's disease) *(increased risk of Reye's syndrome)*	Risk of Reye's syndrome	M	Amended for to include other appropriate indications (18)
More than one paracetamol- containing product prescribed to a patient at a time *(maximum dose exceeded)*	Concomitant prescribing of more than one paracetamol containing product that can enable a dose of > 4g to be administered in 24 hours	Y	(23)
Paracetamol prescribed at a dose of 1g over a 24 hour to a patient under 50kg *(risk of hepatocellular toxicity)*	Risk of heptaocellular toxicity	N	Adult specific dose
Tramadol prescribed concomitantly with antiepileptics *(increased risk of seizures in patients with uncontrolled epilepsy)*	Increased risk of seizures	Y	(25)
Nefopam prescribed concomitantly with antiepileptics *(increased risk of seizures in patients with uncontrolled epilepsy)*	Increased risk of seizures	N	Rare use in paediatrics
Regular opiates prescribed without concurrent use of laxatives *(risk of severe constipation)*	Risk of severe constipation	Y	(27)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)*	Oral and intramuscular doses are not equivalent	Y	(28)
Phenytoin and enteral feeds prescribed to a patient concomitantly *(reduced absorption of phenytoin)*	Enteral feeds prevent the absorption of phenytoin. The feed should be stopped for at least 2 hours before the dose is given, and then a further 2 hours before it is re-started	Y	(31, 42)
Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a mild or non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) *(risk of hypersensitivity reactions)*	Penicillin containing products are contraindicated in patients with an allergy	Y	(36)
Cephalosporin antibacterial prescribed to an older adult (except under the direction of Microbiology or for suspected meningitis) *(increased risk of antibiotic-associated infections)*	Cephalosporins should be avoided in older adults where possible owing to the increased risk of antibiotic-associated infections	N	Rare co-morbidity
Gentamicin prescribed to a patient with renal impairment without dose adjustment *(increased risk of toxicity)*	Increased risk of toxicity if dose regimens are not adjusted for renal function	Y	(48)
Gentamicin prescribed to an adult patient with normal renal function in a dose exceeding 7mg/kg/day *(increased risk of toxicity)*	Doses should not exceed 7mg/kg/day owing to the risk of toxicity	M	Amended to reflect paediatric doses (49, 51)
Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	Risk of excessive dosing and toxicity	Y	(50)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*	Macrolide antibacterials can reduce the metabolism of warfarin, causing an increase in the INR and an increased risk of bleeding	Y	(52)
Vancomycin prescribed intravenously at a rate of less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	Rapid infusion of vancomycin can cause severe reactions, such as "red man syndrome"	Y	(59)
Vancomycin prescribed to a patient with renal impairment without dose adjustment *(increased risk of toxicity)*	Vancomycin dosing should be adjusted in renal impairment to avoid toxicity	Y	(58)
Vancomycin prescribed intravenously for the treatment of *Clostridium difficile* infection *(intravenous vancomycin has limited therapeutic effect)*	Intravenous vancomycin is not effective for the treatment of *Clostridium difficile* infection	N	Rare co-morbidity
Quinolone antibacterial prescribed to a patient with epilepsy *(increased risk of seizure threshold being reduced)*	Quinolone antibacterials lower the seizure threshold	Y	(40)
Quinolone prescribed to a patient who is also receiving theophylline *(possible increased risk of convulsions)*	Possible increased risk of convulsions	y	(39)
Oral quinolone antibacterial prescribed at the same time as iron *(reduced absorption of quinolones)*	Iron reduces the absorption of quinolone antibacterials. At last 4 hours should separate the administration of a quinolone and iron	Y	(41)
Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	Risk of peripheral neuropathy and reduced therapeutic effect	Y	(44)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Triazole antifungal prescribed at the same time as fentanyl *(increased risk of opiate toxicity)*	Increased risk of opiate toxicity	N	Rare use in paediatrics
Amphotericin B prescribed without stating the brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid formulations)*	Brand name should be specified, along with the dose calculation	Y	(64)
Atazanavir prescribed concomitantly with proton-pump inhibitors *(concentration of atazanavir potentially reduced, reducing therapeutic effect)*	Proton-pump inhibitors can reduce the plasma concentration of atazanavir	N	Rare use in paediatrics
Rifampicin prescribed concomitantly with ritonavir *(ritonavir concentration can be potentially be reduced, reducing its effect)*	Plasma concentration of ritonavir can be reduced by rifampicin	N	Rare use in paediatrics
Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) *(increased risk of hypoglycaemia)*	Insulin should be prescribed at meal times to avoid the risk of hypoglycaemia	Y	(67)
Soluble insulin prescribed to a patient on a when required *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia especially if given more than 1 stat dose. Not managing the long-term condition	Y	(66)
Glibenclamide prescribed to an older adult with Type 2 diabetes mellitus *(increased risk of hypoglycaemia)*	Risk of prolonged hypoglycaemia	N	Rare indication in paediatrics
Metformin prescribed to a patient with eGFR < 30 mls/min *(increased risk of lactic acidosis)*	Metformin should be avoided in patients with an eGFR < 30 mls/min owing to the risk of lactic acidosis	N	Rare use in paediatrics

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Pioglitazone prescribed to a patient with heart failure *(risk of exacerbation of heart failure)*	Risk of exacerbation of heart failure	N	Rare use in paediatrics
Bisphosphonate prescribed to a patient with an inappropriate timing *(increased risk of adverse effects and possible reduced absorption if given after food)*	Doses should be prescribed in the morning, at least 30 minutes before breakfast - the times on the prescription should be endorsed as such to ensure this	N	Rare use in paediatrics
Bisphosphonate prescribed to a patient at the same time of day as calcium *(bisphosphonate absorption reduced by calcium salts)*	Doses of calcium should be delayed, administered at least 4 hours after the bisphosphonate dose (or completely omitted on the day of the weekly dose)	N	Rare use in paediatrics
Weekly dose of an oral bisphosphonate prescribed daily *(risk of hypocalcaemia)*	Risk of hypocalcaemia when prescribed at doses exceeding the recommended range	N	Rare use in paediatrics
Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	Oral methotrexate should be dosed ONCE WEEKLY, and the prescription clear as to which day of the week this should be	Y	(76)
Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count *(risk of bone marrow suppression)*	Methotrexate should be stopped immediately if significantly low white cell count or platelet count due to risk of abrupt bone marrow suppression	Y	(75)
Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*	Risk of liver toxicity	Y	(77)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*	Trimethoprim suppresses activity of dihydrofolate reductase - potential for additive effect to produce folate deficiency. Increased risk of haematological toxicity when methotrexate given with trimethoprim (including trimethoprim containing compound - co-trimoxazole)	Y	(78)
Methotrexate prescribed on the same day as folic acid *(reduced efficacy of methotrexate)*	Concomitant administration of folic acid with methotrexate will reduce efficacy of methotrexate	Y	(79)
Allopurinol prescribed concomitantly with azathiorpine *(allopurinol enhances effect of azathioprine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of azathioprine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Y	(80)
Allopurinol prescribed concomitantly with mercaptopurine *(allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of mercaptopurine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Y	(81)
Calcium resonium prescribed when the potassium concentration is within the desired reference range (3.5–5.3 mmol/litre) *(risk of hypokalaemia)*	Calcium resonium should be stopped when the potassium concentration is within the desired reference range, as it continues to work for a few days once discontinued	Y	(83)
Potassium chloride supplements continued for longer than is required (reference range 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*	Failure to act on potassium chloride monitoring and continuing treatment for longer than required risks hyperkalaemia	Y	(84)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Potassium chloride infusions exceeding 40 mmol/litre given via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*	Intravenous administration of potassium chloride solutions exceeding 40mmol/litre should be prescribed via the central route to avoid arrhythmias	Y	(86)
NSAID prescribed to a patient with chronic renal failure *(increased risk of deteriorating renal function)*	Sodium and water retention may occur. Risk of deteriorating renal function.	Y	(15)
NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without antisecretory drugs or mucosal protectants *(increased risk of peptic ulceration and bleeding)*	Risk of peptic ulcer relapse or gastrointestinal bleeding	Y	(16)
NSAID prescribed to a patient with a history of heart failure *(risk of exacerbation of heart failure)*	Risk of exacerbation of heart failure	N	Rare use in paediatrics
Selective COX-2 inhibitor NSAID prescribed to a patient with cardiovascular disease *(increased risk of thrombotic events)*	Increased risk of thrombotic events	N	Rare use in paediatrics
More than one NSAID prescribed to a patient at a time *(increased risk of bleeding)*	Increased risk of bleeding when more than one NSAID is prescribed.	Y	(89)
Allopurinol prescribed at a dose exceeding 100 mg in a patient with renal impairment *(risk of accumulation and subsequent toxicity)*	Prolonged half-life of allopurinol can lead to accumulation causing gastrointestinal adverse-effects	N	Rare indication in paediatrics
Brand specific prescribing of tacrolimus preparations (*brands vary in their dosing and pharmacokinetics)*	Tacrolimus prescriptions should clearly state the brand name and formulation as switching between brands requires close medical supervision	Y	(82)

Adult indicators previously published[90] – results of review for consideration as paediatric indicators. continued

Indicator	Original Adult Descriptor	Include Y=Yes N=No M=Modified	Notes and cross reference to final list
Live vaccine prescribed to an immunosuppressed patient, including those on corticosteroids *(increased risk of reaction or infection)*	Risk of reaction/infection	Y	(91)

Appendix 5 – Indicator Identification Search Strategy

1. MEDLINE; *MEDICATION ERRORS/; 7056 results.
2. MEDLINE; "prescribing error".ti,ab; 103 results.
3. MEDLINE; "prescribing errors".ti,ab; 413 results.
4. MEDLINE; "dispensing error".ti,ab; 68 results.
5. MEDLINE; "dispensing errors".ti,ab; 166 results.
6. MEDLINE; "administration error".ti,ab; 90 results.
7. MEDLINE; "administration errors".ti,ab; 381 results.
8. MEDLINE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; 7418 results.
9. MEDLINE; 8 [Limit to: English Language and Humans and Publication Year 1999-2014]; 4992 results.
10. MEDLINE; exp ELECTRONIC PRESCRIBING/; 551 results.
11. MEDLINE; exp MEDICAL ORDER ENTRY SYSTEMS/ OR exp DECISION SUPPORT SYSTEMS,
CLINICAL/; 6225 results.
12. MEDLINE; "electronic prescribing".ti,ab; 388 results.
13. MEDLINE; "eprescribing".ti,ab; 35 results.
14. MEDLINE; "e-prescribing".ti,ab; 287 results.
15. MEDLINE; 10 OR 11 OR 12 OR 13 OR 14; 6923 results.
16. MEDLINE; 15 [Limit to: English Language and Humans and Publication Year 1999-2014]; 5493 results.
17. MEDLINE; 16 [Limit to: English Language and Humans and Publication Year 1999-2014 and (Age Groups All
Infant birth to 23 months or All Child 0 to 18 years or Newborn Infant birth to 1 month or Infant 1 to 23 months or
Preschool Child 2 to 5 years or Child 6 to 12 years or Adolescent 13 to 18 years)]; 452 results.
18. MEDLINE; "prescribing indicator".ti,ab; 13 results.
19. MEDLINE; *PEDIATRICS/; 29479 results.
20. MEDLINE; 15 AND 19; 57 results.
21. MEDLINE; "The impact of hospitalwide computerized physician order entry".ti; 1 results.

Appendix 6 – Indicators from Literature Search

Indicators considered from literature search sources

Possible indicator drug/subject	Outcome	Reason (Cross Reference to Initial Indicator List)
Ten times overdose prescribed[155-157]	Included	Specific indicator for opioid Included as part of documentation error review (29, Doc)
Parenteral Nutrition[158]	Excluded	Too complicated to collect data, stand alone EP systems for PN in use in most centres
Lamotrigine - Overdose[159]	Included	Specifically relating to starting dose and combination with Sodium Valproate (33)
Flecainide – overdose due to incorrect labelling of liquid strength[160]	Excluded	Dispensing error rather than prescribing. Rarely used drug.
Vitamin D – case reports of high doses[161-163]	Excluded	Administration errors.
Propofol – Case reports of overdose[164, 165]	Excluded	Administration errors
Heparin dose[166, 167]	Included	High risk drug also involved in local ME and local pharmacy interventions and NPSA Alert (19)
Alfacalcidol 10 times overdoses[168]	Included	Specific documentation error (Doc).
Anticonvulsants – Errors relating to transition of care and changes in weight[169-171]	Included	High risk medicines, picked up in local data (30,31,32,33)
Ketotifen overdose[172]	Excluded	Rarely used drug.
Chemotherapy medication errors[173-176]	Included	High risk medicine. Specific indicators relating to immunosuppressants and methotrexate (72,75,76)
Polyethelene glycol – case report of inadvertent infusion[177]	Excluded	Administration error
Paracetamol – prescribing and administration errors relating to duplicate paracetamol preparations and IV dosing[178-180]	Included	High risk drug also involved in local ME and local pharmacy interventions (23)
Anti depressants – Surveillance report of medication errors relating to antidepressants[181]	Excluded	Rare indication in secondary care paediatrics
Obesity – reports of dosing errors for antimicrobials and analgesics in obese patients[182]	Included	Theme for specific drugs (37, 50)

Indicators considered from literature search sources continued

Possible indicator drug/subject	Outcome	Reason (Cross Reference to Initial Indicator List)
Clonidine – case report of 100 times overdose of caudal clonidine[183]	Excluded	Rare indication in paediatrics
Labetolol – Case report of overdose in 8-month old infant[184]	Excluded	Rare use in paediatrics
Metoprolol – Case report of prescribing error relating to use of decimal points[185]	Excluded	Rare use in paediatrics, general documentation error included (Doc)
Di sodium Edetate – case reports of deaths relating to hypocalcaemia and chelation therapy[186]	Excluded	Rare indication in paediatrics
Adrenaline – case report of overdose[187]	Excluded	Administration error
Haloperidol. Case reports of two patients with toxic levels following prescribing error[188]	Excluded	Rare indication in paediatrics
Xanthine – Case report of overdose[189]	Excluded	Rare use in paediatrics. Caffeine included as specific documentation error (Doc)
Salbutamol – Case report of oral overdose[190]	Excluded	Rare use of oral formulation in UK. IV infusion indicator included (21)
Fluoxetine – Case report of dispensing error[191]	Excluded	Dispensing error and rare use in secondary care paediatrics.
Amlodipine – Case report of poisoning[192]	Excluded	Administration error
Risperidone – Review of accidental poisonings in France[193]	Excluded	Rare use in paediatrics

Appendix 7 – Indicators from National Reporting and Learning System

Indicators identified from NRLS[95] reports considered for the paediatric indicators

Possible indicator drug/subject	Outcome	Reason (Cross Reference to Initial Indicator List)
Failure to prescribe or prescribe incorrect vaccinations for childhood immunisation	Included	Common area of concern/intervention (92). Adult indicator also included in relation to the use of a live vaccine in an immunosuppressed patient (91)
Ten times overdose – incorrect calculation or use of decimal point resulting in ten times overdose	Included	Some specific overdose indicators included, as well as different descriptions of overdoses (95,96, 100)
Administration of penicillin containing product to a patient with penicillin allergy	Included	Duplicated from other sources (36, 99)
Lamotrigine and sodium valproate – prescribing of incorrect starting dose of lamotrigine when patient already on sodium valproate	Included	Complicated initial dose regime results in possible errors. (33)
Dose of meropenem too low for indication	Included	Duplicated in local interventions (46)

Appendix 8 – Indicators from Interventions and Incident Reports

Indicators identified from intervention and incident reports

Indicator	Outcome	Reason (Cross Reference to Initial Indicator List)
Common drugs with interaction including macrolides, rifampicin, ivacaftor, quinolones	Included	Range of interacting drugs included (22,39, 41,47,52-60)
Dose of ganciclovir prescribed without reference to renal function	Included	High risk drug, more common in paediatric use in secondary care. (65)
Potassium supplements prescribed for longer than required based on serum potassium levels	Included	Common reason for pharmacy intervention. (84)
Midazolam prescribed at incorrect dose for preparation	Included	Numerous formulations and routes with different doses causes confusion (93)
Co-prescription of trimethoprim prophylaxis with treatment antimicrobials	Included	Regularly encountered problem (35)
Propranolol Concentration – Wrong strength propranolol liquid prescribed or dispensed resulting in dosing error	Excluded	Dispensing error rather than prescribing error
Failure to prescribe and/or administer folinic acid rescue therapy following high dose methotrexate therapy	Included	High risk error (73)
Failure to prescribe and/or administer mesna therapy following cylophosphamide/Iphosphamide therapy	Included	High risk error (74)
Wrong dose or rate of salbutamol infusion	Included	Complicated calculation required to prescribe high risk indication/drug (21)
Confusion between clonazepam/clobazam	Included	Common confusion between two anti-convulsants (34)
Changing dose frequencies with increasing age	Included	Several antimicrobials require an increase in frequency with increasing age (e.g. flucloxacillin) as a result of changing pharmacokinetics. (43,61,62,63,98)
Specific dose of antimicrobial related to indication	Included	Specific indications require specific doses for some antimicrobials e.g. Meropenem for sepsis. (45, 46)
IV to oral switch using requiring different dose	Included	Some antimicrobials require different doses when switching from IV to oral therapy. E.g. Ciprofloxacin. (38, 97)

Indicators identified from intervention and incident reports continued

Indicator	Outcome	Reason (Cross Reference to Initial Indicator List)
IV Vancomycin prescribed to run over less than 60 minutes	Included	Increased risk of red man syndrome with rapid infusion (59)
Prescribing steroids concomitantly by different routes	Included	Risk of overdose when inhaled, oral IV steroids prescribed at the same time (68,69)
Prescription for enteric coated prednisolone in a patient with inflammatory bowel disease.	Included	Reduced absorption from enteric coated formulation (70)
Incorrect volume of maintenance fluid prescribed	Included	Complex calculation required for prescribing maintenance fluid (87)
Dose of baclofen not reduced in the presence of renal failure	Included	Rare but serious overdose can occur, often due to limited knowledge of baclofen.(90)
Incorrect dose/dilution of IV acetylcysteine for the treatment of paracetamol poisoning	Included	Complex calculation required to prescribe acetylcysteine (94)
Desmopressin prescribed for nocturnal enuresis at any other time other than bedtime.	Included	Common cause of concern with desmopressin, must be taken at the correct time in relation to bedtime to avoid fluid overload. (71)
Phenytoin prescribed to be administered at the same time as an enteral feed.	Included	Local interventions and recognised interaction (31)
Co-prescribing of drugs that could cause QT prolongation	Included	Several adult indicators included this issue, revised to include reference to medicines commonly used in children e.g. macrolides. (53, 54)
Common drugs requiring dose changes as a result of reduced renal function	Included	Several specific cases included (62)
Digoxin loading and maintenance doses	Included	Complicated regimens based on age and weight (2,3)
Drug food interactions	Included	Quinolones and enteral feed specifically (42)
Allopurinol prescribed to a patient concomitantly with azathioprine or 6-mecaptopurine	Included	Recognised interaction with severe consequence (80,81)
Gentamicin overdose and under dose due to calculation error or reduced clearance	Included	Modified for both neonates and paediatrics (49, 51)

Appendix 9 – Indicators from National Alerts

Indicators identified from national alerts

Possible indicator drug/subject	Outcome	Reason (Cross reference to Initial Indicator List)
Metoclopramide risk of neurological adverse effects[194]	Excluded	Rare use outside of paediatric oncology, general dosing errors included under documentation
Codeine for analgesia: restricted use in children because of reports of morphine toxicity[114]	Included	High risk medicine/group (24)
Caffeine for apnoea of prematurity. Possible confusion over use of base and salt[195]	Included	Specific documentation error included relating to use of salt when prescribing (Doc)
Maintenance Fluid – use of incorrect fluid can cause cerebral oedema[113, 196]	Included	High risk issue nationally reported (85,87)
Parenteral amphotericin B: fatal overdose risk due to confusion between lipid-based and non-lipid-based formulations[197]	Included	High risk medicine (64)
Oral tacrolimus products: prescribe and dispense by brand name only, risk of toxicity and graft rejection[198]	Included	High risk medicine (82)
Domperidone: risks of cardiac side effects[119]	Included	Highly publicised issue within paediatrics (1)
Oral Methotrexate prescribed or administered at an inappropriate frequency.[199]	Included	High risk medicine (76). Other adult indicators also included (75.77,78,79)
Phenytoin dose not reviewed in light of low albumin level[95]	Included	Serious incident reported via the national reporting system (30)
Vincristine administered by the incorrect route[200]	Excluded	Administration error rather than prescribing
Low molecular weight heparin[201]	Included	Modified to relate to paediatrics (10, 11,12)

Appendix 10 – Documentation Errors

Documentation errors. Shaded lines indicate errors identified by expert panel during round 1

Code	Potential Indicator	Supporting Information	Source	Error Type	Outcome	Reason For Exclusion
D1	Use of an unapproved abbreviation to indicate the drug required such as NaOH, NaPO4, AZT, CPL etc	Ambiguous prescription with the potential for wrong drug or wrong dose	Prescribing Standard	Other	Include	
D2	Use of a trailing zero following a decimal point when expressing a dose	Risk of ten times overdose	Prescribing Standard	Dose	Include	
D3	Strength of steroid inhaler or combination steroid inhaler not prescribed	Risk of sub or supratherapeutic doses	Pharmacist Interventions	Therapeutic Duplication	Include	
D4	Presence of a prescription based on the weight of a child without a record of the weight on the prescription	Risk of over/under dose	Ghaleb *et al* [202]	Dose	Include	
D5	Prescription for an intermittent intravenous infusion with no indication of the duration of the infusion (risk of adverse reaction)	Risk of adverse reaction from rate	Ghaleb *et al*[202]	Pharmaceutical	Include	
D6	Absence of a leading zero before a decimal point when expressing dose	Risk of overdose	Prescribing Standard	Dose	Include	
D7	Total daily dose prescribed for each dose during the day	Overdose	Pharmacist Interventions	Dose	Include	
D8	Tenfold overdose prescribed	Overdose	Pharmacist Interventions	Dose	Include	

Documentation errors. Shaded lines indicate errors identified by expert panel during round 1 continued

Code	Potential Indicator	Supporting Information	Source	Error Type	Outcome	Reason For Exclusion
D9	Use of weight instead of BSA to calculate the dose of drug where BSA is meant to be used (e.g. aciclovir)	Risk of sub or supratherapeutic doses increasing risk of adverse effects	Prescribing Standard	Dose	Include	
D10	Prescribing of dose per/kg value instead of required dose	Risk of subtherapeutic doses decreasing efficacy	NRLS[95]	Dose	Include	
D11	Inappropriate rounding of dose resulting in a clinically significant over or under dose based on the therapeutic range of the drug	Risk of supratherapeutic doses increasing risk of adverse effects	Pharmacist Interventions	Dose	Include	
D12	Dose of liquid preparation expressed in ml rather than mg for a drug where the dose is expressed in mg in the BNFC	Risk of supratherapeutic doses increasing risk of adverse effects	Prescribing Standard	Dose	Include	
D13	Dose value of alfacalcidol in nanograms expressed as micrograms	Risk of 1000 time overdose	NPSA[168]	Dose	Include	
D14	Prescription containing an abbreviation for units (risk of misreading u/iu resulting in overdose)	Risk of insulin/heparin/other overdose	NPSA[9]	Dose	Include	
D15	Use of ml instead of mg resulting in dose outside normal recommendations (severity drug dependent - need to record drug and severity rating)	Risk of sub or supratherapeutic doses	Prescribing Standard	Dose	Remove	Too complex to collect due to lack of standard interpretation

Documentation errors. Shaded lines indicate errors identified by expert panel during round 1 continued

Code	Potential Indicator	Supporting Information	Source	Error Type	Outcome	Reason For Exclusion
D16	Use of incorrect weight resulting in dose outside normal recommendations (severity drug dependent - need to record drug and severity)	Risk of sub or supratherapeutic doses	NRLS[95]	Dose	Include	
D17	Prescribing Caffeine using base rather than salt i.e. Caffeine rather than Caffeine Citrate (risk of sub-therapeutic dosing)	Risk of subtherapeutic dosing	MHRA[195]	Other	Remove	Added as a specific prescribing indicator (94)
D18	18 or 36 hourly gentamicin frequency prescribed in a way that could result in a different frequency of administration (risk of toxicity)	Risk of supratherapeutic doses increasing risk of adverse effects	Maaskant JM *et al*[120] and NPSA	Dose Frequency	Include	
D19	Doses calculated using weight in pounds instead of kilograms	Significant risk of overdose severity dependent on specific drug (will specify drug and severity score) Severity will also depend on actual weight Should we specific an upper weight limit for this indicator?	NRLS[95]	Dose	Include	
D20	Strength of steroid inhaler or combination steroid inhaler not prescribed	Risk of sub or supratherapeutic doses	Pharmacist Interventions	Therapeutic Duplication	Remove	
D21	Prescription without indication of dose form	Increased risk of error			Include	

Documentation errors. Shaded lines indicate errors identified by expert panel during round 1 continued

Code	Potential Indicator	Supporting Information	Source	Error Type	Outcome	Reason For Exclusion
D22	1000 fold by overwriting mg with g	Possible dose error if units not correctly indicated			Include	
D23	Working weight/dosing weight neonate	Possible does error due to use of incorrect weight			Remove	Captured by D16
D24	Use of unapproved abbreviation to describe dose e.g. mcg, ng.	Potential for dosing error			Include	
D25	using a decimal point for doses < 1mg	Potential 10 fold errors			Include	
D26	Drug prescribed where dose exceeds standard adult dose	Risk of supratherapeutic doses			Include	
D27	Dose prescribe which is impossible to measure accurately (not rounded appropriately)	Increase risk of inappropriate rounding of dose			Include	
D28	When required medication prescribed without indication	Clarity over reason for medicine provides information about correct dose.			Include	

Appendix 11 – Indicators and Source Used for Rounds 1 and 2

Indicator sent to expert panel members with reference code and source

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
1	Domperidone prescribed at > 1.2mg/kg/day max 20mg *(prolongation of QT interval, sudden cardiac death)*	Increased risk of arrhythmias and sudden cardiac death	Y		Y		
2	Digoxin Loading dose or frequency prescribed incorrectly according to BNFC	Risk of supratherapeutic doses increasing risk of adverse effects					Y
3	Digoxin maintenance dose started too soon or too late after completion of loading doses.	Risk of supratherapeutic doses increasing risk of adverse effects					Y
4	Digoxin dose not reviewed in light of reduced renal function	Risk of supratherapeutic doses increasing risk of adverse effects	Y				
5	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*	Increased risk of severe hyperkalaemia	Y				
6	Amiodarone prescribed to a patient with abnormal thyroid function tests *(increased risk of thyroid disorders)*	Amiodarone can cause thyroid abnormalities	Y				
7	Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*	Beta-adrenoceptor blocking drugs are known to cause bronchoconstriction in asthmatics, and can cause acute deterioration	Y				

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
8	ACE inhibitor or angotensin-II receptor antagonist prescribed to a patient with a potassium level >5.0 mmol/litre *(can cause or exacerbate hyperkalaemia)*	ACE inhibitors and angiotensin-II receptor antagonists can cause hyperkalaemia and are contraindicated in patients with a potassium concentration about the desired reference range	Y				
9	Low molecular weight heparin prescribed to be administered concomitantly with unfractionated heparin *(increased risk of bleeding)*	Increased risk of bleeding	Y				
10	Low molecular weight heparin not adjusted based on factor 10a levels *(risk of inappropriate dose)*	Risk of sub or supratherapeutic doses			Y		
11	Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment *(increased risk of bleeding)*	Increased risk of bleeding with the dose of low molecular weight heparin is not adjusted for renal function			Y		
12	Enoxaparin prescribed at the wrong frequency according to the BNFC or product literature	risk of subtherapeutic levels of enoxaparin			Y		
13	Warfarin prescribed to a patient with a concurrent bleeding problem *(risk of bleeding)*	High risk of bleeding when warfarin prescribed to patients with a past medical history of bleeding disorders	Y				
14	Warfarin prescribed concomitantly with a NSAID *(increased risk of bleeding)*	Increased risk of bleeding when co-prescribed with NSAID	Y				

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
15	NSAID prescribed to a patient with chronic renal failure *(increased risk of deteriorating renal function)*	Sodium and water retention may occur risk of decreasing renal function	Y				
16	NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without antisecretory drugs or mucosal protectants *(increased risk of peptic ulceration and bleeding)*	Risk of GI ulcer / reflux	Y				
17	Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	High risk of bleeding when antiplatelets prescribed to patients with a past medical history of bleeding disorders	Y				
18	Aspirin prescribed to pt <16 without appropriate indication *(risk of Reye's syndrome)*	Risk of Reye's Syndrome	Y				
19	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	Risk of supratherapeutic or subtherapeutic dose of heparin		Y	Y		
20	Long-acting beta-2-agonist inhaler prescribed to a patient who is not also on an inhaled corticosteroid *(evidence base - not in line with British Thoracic Society guidelines)*	Not in line with British Thoracic Society guidelines)	Y				
21	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	Risk of supratherapeutic or subtherapeutic dose of salbutamol					Y

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
22	Ivacaftor co-prescribed with an interacting drug with no dose adjustment of interacting drug *(risk of subtherapeutic levels of interacting drug)*	Risk of supratherapeutic or subtherapeutic levels of ivacaftor due to enzyme induction or inhibition					Y
23	More than one paracetamol-containing product prescribed to be administered concomitantly *(maximum dose exceeded)*	Concomitant prescribing of more than one paracetamol containing product can result in doses over the daily limit for the age group		Y			
24	Codeine phosphate prescribed to a patient under the age of 12 *(contraindicated)*	MHRA guidance restrict use of codeine in children due to risk of fatal toxicity			Y		
25	Tramadol prescribed concomitantly with antiepileptics *(increased risk of seizures in patients with uncontrolled epilepsy)*	Increased risk of seizures	Y				
26	Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates risk of toxicity)*	Injudicious use of two opiates	Y				
27	Regular opiates prescribed without concurrent use of laxatives *(risk of severe constipation)*	Risk of severe constipation	Y				
28	Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)*	Oral and intramuscular doses are not equivalent	Y				
29	Ten times overdose of opioid *(overdose/respiratory arrest)*	Risk of supratherapeutic doses increasing risk of adverse effects		Y		Y	
30	Phenytoin dose not reviewed in light of low albumin *(potential for toxicity)*	Increased risk of toxicity		Y	Y		

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
31	Phenytoin and enteral feeds prescribed to a patient concomitantly *(reduced absorption of phenytoin)*	Enteral feeds prevent the absorption of phenytoin. The feed should be stopped for at least 2 hours before the dose is given, and then a further 2 hours before it is re-started	Y	Y	Y		
32	Failure to increase dose of anticonvulsant in line with weight for epilepsy *(increased risk of seizure)*	Increased risk of seizures		Y			
33	Prescribing an incorrect starting dose of lamotrigine when used in combination with sodium valproate *(increased risk of ADR)*	Increased risk of adverse reaction in paritcualr rashes		Y		Y	
34	Clonazepam prescribed when clobazam required or vice versa	Risk of incorrect dose of the wrong drug					Y
35	Prophylactic Trimethoprim and treatment antimicrobials for urinary tract infection prescribed to be administered concomitantly *(increased risk of resistance)*	Risk of antimicrobial resistance					Y
36	Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a mild or non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) *(risk of hypersensitivity reactions)*	Contraindicated in pts with history of penicillin allergy. Risk of hypersensitivity reaction	Y			Y	
37	More than 400mg per dose of oral or intravenous metronidazole prescribed to a patient weighing > 54kg *(risk of toxicity)*	Risk of supratherapeutic doses increasing risk of adverse effects		Y			

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
38	Dose change for metronidazole not made when switching from IV to oral *(risk of overdose)*	risk of toxicity					Y
39	Quinolone antibiotic prescribed to a patient who is also receiving theophylline *(possible increased theophylline level)*	Possible increased theophylline level	Y				Y
40	Quinolone antibiotic prescribed to a patient with epilepsy *(increased risk of seizure threshold being reduced)*	Quinolone antibacterials lower the seizure threshold	Y				
41	Oral quinolone antibacterial prescribed at the same time as iron *(reduced absorption of quinolones)*	Iron reduces the absorption of quinolone antibacterials. At last 4 hours should separate the administration of a quinolone and iron	Y				
42	Oral Quinolones and enteral feeds prescribed concomitantly *(risk of treatment failure with quinolone)*	Reduced absorption of quinolone	Y				Y
43	Intravenous ciprofloxacin prescribed twice daily instead of three times a day in children over 1 month old (*risk of therapeutic failure)*	Risk of subtherapeutic levels of antibiotic					Y
44	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	Risk of peripheral neuropathy and reduced therapeutic effect	Y				

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
45	Ceftriaxone prescribed at a dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis *(risk of under dosage)*	Potential subtherapeutic dose for severe infection/sepsis					Y
46	Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or exacerbation of CF (*potential under treatment)*	Potential subtherapeutic dose for severe infection/sepsis				Y	
47	Co-prescribing of meropenem with sodium valproate *(increased risk of seizure)*	Reduction in valproate levels leading to increased risk of seizure					Y
48	Gentamicin prescribed to a patient with at least mild renal impairment without dose adjustment *(increased risk of toxicity)*	Increased risk of toxicity	Y				
49	Gentamicin prescribed at a dose exceeding 7mg/kg/day to an child > 1month *(risk of toxicity)*	Increased risk of toxicity			Y		
50	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	Risk of excessive dosing and toxicity	Y	Y			
51	Gentamicin prescribed at a dose exceeding 5mg/kg/dose to a neonate *(risk of toxicity)*	Increased risk of toxicity			Y		
52	Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*	Macrolide antibacterials can reduce the metabolism of warfarin, causing an increase in the INR and an increased risk of bleeding					Y
53	Co-prescribing of macrolides with interacting drug *(QT prolongation)*	Risk of prolongation of QT interval and ventricular arrhythmia					Y

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
54	Co-prescribing of a macrolide with Domperidone *(QT prolongation)*	Risk of prolongation of QT interval and ventricular arrhythmia					Y
55	Co-prescribing of a macrolide with an anticonvulsant *(risk of toxicity or subtherapeutic levels)*	Risk of supratherapeutic or subtherapeutic levels of anticonvulsant					Y
56	Co-prescribing of a macrolide with ciclosporin or tacrolimus *(increases plasma levels of anti-rejection agent)*	Increased plasma concentration of ciclosporin					Y
57	Co-prescribing of a macrolide with Midazolam *(risk of sedation)*	Increased sedation					Y
58	Vancomycin prescribed intravenously to a patient with at least mild renal impairment without dose adjustment *(increased risk of toxicity)*	Increased risk of toxicity	Y				Y
59	Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	Increased risk of Infusion reactions	Y				Y
60	Rifampicin co-prescribed with an interacting drug with no dose adjustment of interacting drug *(risk of subtherapeutic levels of interacting drug)*	risk of subtherapeutic levels of interacting drug due to enzyme induction					Y
61	Fluconazole prescribed more frequently than every 72 hours for a neonate < 14 days old (*risk of toxicity)*	Increased risk of toxic effects, Neonates have a 72 or 48 hour frequency based on age.					Y

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
62	Fluconazole prescribed as standard dose from day 2 of treatment in a patient with a creatinine clearance of < 50 ml/min/1.73m2 *(risk of toxicity, normally halve dose after first day)*	Increased risk of toxic effects Patient with renal failure <50ml/min/1.73m2 have standard dose for one dose then halved.					Y
63	Fluconazole prescribed more frequently than every 48 hours for a neonate between 14 and 28 days old *(risk of toxicity)*	Increased risk of toxic effects, neonates have a 72 or 48 hour frequency based on age.					Y
64	Amphotericin B prescribed without stating the brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid)*	Specification of brand name to reduce risk of wrong formulation being administered and resulting toxicity	Y		Y		
65	Failure to adjust dose or frequency of Ganciclovir in the presence of altered renal function *(risk of toxicity or treatment failure)*	Risk of supratherapeutic or subtherapeutic levels of ganciclovir					Y
66	Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia especially if given more than 1 stat dose. Not managing the long-term condition	Y				
67	Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) *(increased risk of hypoglycaemia)*	Insulin should be prescribed at meal times to avoid the risk of hypoglycaemia	Y				
68	Oral prednisolone and intravenous hydrocortisone prescribed to be administered concomitantly simultaneously *(risk of toxicity)*	Increased risk of adverse effects					Y

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
69	Oral prednisolone and steroid inhalers prescribed to be administered concomitantly *(risk of toxicity)*	Increased risk of adverse effects					Y
70	Prednisolone EC prescribed for patient with Inflammatory Bowel Disease *(reduced absorption of prednisolone)*	Reduced absorption of predinsolone					Y
71	Desmopressin prescribed for nocturnal enuresis at any other time than at bedtime *(risk of fluid overload)*	Risk of over hydration					Y
72	Dose reduction of immunosuppressant not made despite low white cell count *(risk of neutropenia)*	Increased risk of neutropenia and subsequent infection		Y			
73	Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*	Risk of methotrexate toxicity					Y
74	Failure to prescribe mesna for patients receiving alkylating agents *(risk of toxic symptoms)*	Risk of bladder toxicity					Y
75	Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count *(risk of bone marrow suppression)*	Risk of bone marrow suppression	Y	Y			Y
76	Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	Oral methotrexate should be dosed ONCE WEEKLY, and the prescription clear as to which day of the week this should be	Y	Y			Y

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
77	Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*	Risk of liver toxicity	Y		Y		
78	Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*	Trimethoprim suppresses activity of dihydrofolate reductase - potential for additive effect to produce folate deficiency. Increased risk of haematological toxicity when methotrexate given with trimethoprim (including trimethoprim containing compound - co-trimoxazole)	Y		Y		
79	Methotrexate prescribed to be administered on the same day as folic acid *(reduced efficacy of methotrexate)*	Concomitant administration of folic acid with methotrexate will reduce efficacy of methotrexate	Y		Y		
80	Allopurinol prescribed concomitantly with azathiorpine *(allopurinol enhances effect of azathioprine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of azathioprine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Y				Y
81	Allopurinol prescribed concomitantly with mercaptopurine *(allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of mercaptopurine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	Y				Y
82	Tacrolimus not prescribed using brand name *(variation in pharmacokinetics and dosing)*	Risk of subtherapeutic levels due to differences in pharmacokinetics	Y		Y		

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
83	Calcium resonium prescribed when the potassium concentration is within the desired reference range (3.5–5.3 mmol/litre) *(risk of hypokalaemia)*	Calcium resonium should be stopped when the potassium concentration is within the desired reference range, as it continues to work for a few days once discontinued	Y				
84	Potassium chloride supplements continued for longer than is required (reference range 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*	Failure to act on potassium chloride monitoring and continuing treatment for longer than required risks hyperkalaemia	Y				Y
85	Prescribing of hypotonic sodium solutions as post-operative intravenous fluid *(risk of cerebral oedema)*	Rick of cerebral oedema			Y		
86	Potassium chloride infusions exceeding 40 mmol/litre given via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*	Intravenous administration of potassium chloride solutions exceeding 40mmol/litre should be prescribed via the central route to avoid arrhythmias	Y				
87	Incorrect volume of maintenance fluid prescribed	Risk of fluid overload or inadequate hydration			Y		Y
88	Incorrect stock parenteral nutrition bag prescribed	Risk of inappropriate nutrition				Y	
89	More than one NSAID prescribed to a patient at a time *(increased risk of bleeding)*	Increased risk of bleeding when more than one NSAID is prescribed.	Y				

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
90	Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m^2)	Increased risk of toxic effects					Y
91	Live vaccine prescribed to an immunosuppressed patient, including those on corticosteroids *(increased risk of reaction or infection)*	Risk of reaction/infection	Y				
92	Failure to prescribe or prescribing the incorrect vaccines for childhood immunisation *(risk of serious childhood infection)*	Lack of immunity for serious childhood infections				Y	
93	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration	Risk of supratherapeutic or subtherapeutic dose of midazolam					Y
94	Acetylcysteine prescribed at a dose inconsistent with the product literature for paracetamol poisoning	Risk of sub or supratherapeutic doses					Y
95	Prescribing of a dose exceeding standard adult dose of any drug *(risk of overdose)*	Overdose				Y	
96	Prescribing a drug at a frequency not recommended for that formulation *(risk of sub or supratherapeutic dose)*	Risk of supratherapeutic doses increasing risk of adverse effects				Y	
97	Dose change for ciprofloxacin not made when switching from IV to oral *(risk of overdose)*	risk of toxic dose					Y
98	Failure to increase frequency of antibiotic with increasing age of neonate over first 28 days of life *(risk of subtherapeutic dose)*	Risk of subtherapeutic dosing and treatment failure					Y

Indicator sent to expert panel members with reference code and source continued

Code	Potential Indicator	Supporting Information	Adult	LIt	Nat Report	NRLS	Pharm Int
99	A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)*	Risk of anaphylaxis				Y	
100	Prescribing of a dose that is not within +/- 25% of the recommended dose for the indication *(risk of subtherapeutic or toxic effects)*	Risk of supratherapeutic doses increasing risk of adverse effects				Y	

Appendix 12 – New Indicator Suggestion Form

New indicator suggestion form

University Hospital Southampton NHS
NHS Foundation Trust

University of Portsmouth
School of Pharmacy and Biomedical Sciences

Southampton Pharmacy Research Centre (SPRC)

eDelphiPaed – New Indicator Form

Exploratory Round : Identifying essential missing prescribing safety indicators

Participant response to round 1

☐ Having read the list of 100 paediatric prescribing safety indicators, I do not have any additional indicators to add.

☐ Having read the list of 100 paediatric prescribing safety indicators, I wish to add the indicators described below:

Proposed prescribing safety indicator title	BNF class	Source	Supporting information

Please complete this form and return to:-

Andy Fox
Director – Southampton Pharmacy Research Centre(023 8120 4201)
eDelphipaed@uhs.nhs.uk

Appendix 13 – Indicator Scoring Instructions

University Hospital Southampton NHS
NHS Foundation Trust

University of Portsmouth
School of Pharmacy and Biomedical Sciences

Southampton Pharmacy Research Centre (SPRC)

An evaluation of the impact of electronic prescribing on paediatric prescribing errors in a secondary care setting.

Round 1 scoring the indicators

In this round of the process, I wish to obtain each participant's view on the severity and likelihood of the error occurring in secondary care. Please note that I am only considering prescribing safety in paediatric/neonatal practice, and are not considering errors relating to monitoring, administration, or dispensing. These indicators will be used to evaluate whether the introduction of electronic prescribing systems results in a reduction in clinically important errors.

I have considered the suggested additional indicators provided by all of the participants some of which are now included. Following your comments I have removed some original indicators and amended others.

Round 2 therefore includes a total of 125 prescribing indicators (91 indicators from round 1 and 34 additional indicators).

Please score each indicator, each using a scale from 1–5 based on both the severity of the prescribing error and the likelihood of the prescribing error occurring. We acknowledge that your previous clinical practice (e.g. oncology, paediatrics) may influence your scoring, but please try to take a more general view in your interpretation of each indicator.

Severity Scoring

The severity score is defined as the consequence of the prescribing error to the patient should it occur.

Severity Score	1	2	3	4	5
Description	**Insignificant** No risk of patient injury or harm and no intervention required	**Minor** Minor injury or illness requiring minor intervention	**Moderate** Moderate injury requiring intervention	**Major** Major injury or illness leading to long-term incapacity / disability	**Catastrophic** Leads to death, multiple permanent injuries or irreversible health effects

Likelihood Scoring

The likelihood score is defined as the probability of the *prescribing error occurring* **not** the likelihood of an adverse outcome should the error occur

Likelihood Score	1	2	3	4	5
Description	**Rare** This will probably never occur	**Unlikely** Do not expect it to occur but it is possible it may do so	**Possible** This might occasionally occur	**Likely** This will probably occur	**Almost Certain** This will undoubtedly occur, possibly frequently

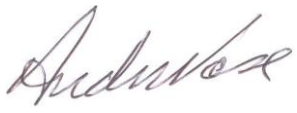
General Error Monitoring

Many of the indicators that have been removed relate to general prescribing errors or legibility issues. These will be included as part of the evaluation process but are not specific enough to be able to score for round 2. E.g. inappropriate use of abbreviations or ten times overdoses. Please be assured that these type of error will be included in an evaluation of electronic prescribing as part of the data collection tool.

Round 3

Participants will receive a second spreadsheet containing their initial score and the median score for each indicator. Participants will be asked if they want to change their score in response to the median value. A comments section will allow respondents to justify/comment on their scoring decision.

If you have any further questions please do not hesitate to contact me.



Andy Fox
Director – Southampton Pharmacy Research Centre(023 8120 4201)
eDelphipaed@uhs.nhs.uk

Appendix 14 – Results of Consensus Scoring

Full list of indicators and levels of consensus after 2 rounds of eDelphi

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
1	Domperidone prescribed at > 1.2mg/kg/day max 20mg *(prolongation of QT interval, sudden cardiac death)*	Increased risk of arrhythmias and sudden cardiac death	3	86%	Y
2	Digoxin Loading dose or frequency (Oral or IV) prescribed incorrectly according to BNFC	Risk of supratherapeutic doses increasing risk of adverse effects	3	71%	
3	Digoxin maintenance dose started too soon or too late after completion of loading doses.	Risk of supratherapeutic doses increasing risk of adverse effects	3	67%	
4	Digoxin dose not reviewed in light of reduced renal function	Risk of supratherapeutic doses increasing risk of adverse effects	3	95%	Y
5	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*	Increased risk of severe hyperkalaemia	3	90%	Y
6	Amiodarone prescribed to a patient with abnormal thyroid function tests *(increased risk of thyroid disorders)*	Amiodarone can cause thyroid abnormalities	2	71%	
7	Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*	Beta-adrenoceptor blocking drugs are known to cause bronchoconstriction in asthmatics, and can cause acute deterioration	3	81%	Y
8	ACE inhibitor or angotensin-II receptor antagonist prescribed to a patient with a potassium level >5.0 mmol/litre *(can cause or exacerbate hyperkalaemia)*	ACE inhibitors and angiotensin-II receptor antagonists can cause hyperkalaemia and are contraindicated in patients with a potassium concentration about the desired reference range	3	71%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
9	Low molecular weight heparin prescribed to be administered concomitantly with unfractionated heparin *(increased risk of bleeding)*	Increased risk of bleeding	2	62%	
10	Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment *(increased risk of bleeding)*	Increased risk of bleeding with the dose of low molecular weight heparin is not adjusted for renal function	3	86%	Y
11	Low molecular weight heparin prescribed at the wrong frequency according to the BNFC or product literature	Risk of supra or subtherapeutic levels of low molecular weight heparin	3	62%	
12	Warfarin prescribed to a patient with a concurrent bleeding problem *(risk of bleeding)*	High risk of bleeding when warfarin prescribed to patients with a past medical history of bleeding disorders	3	71%	
13	Warfarin prescribed concomitantly with a NSAID *(increased risk of bleeding)*	Increased risk of bleeding when co-prescribed with NSAID	3	75%	
14	NSAID (excluding low dose aspirin) prescribed to a patient with chronic renal failure *(increased risk of deteriorating renal function)*	Sodium and water retention may occur risk of decreasing renal function	3	76%	
15	NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without antisecretory drugs or mucosal protectants *(increased risk of peptic ulceration and bleeding)*	Risk of GI ulcer / Reflux	3	71%	
16	Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	High risk of bleeding when antiplatelets prescribed to patients with a past medical history of bleeding disorders	3	81%	Y
17	Aspirin prescribed to pt <16 without appropriate indication *(risk of Reye's syndrome)*	Risk of Reye's Syndrome	1	95%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
18	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*	Risk of supratherapeutic or subtherapeutic dose of heparin	3	86%	Y
19	Long-acting beta-2-agonist inhaler prescribed to a patient who is not also on an inhaled corticosteroid *(evidence base - not in line with British Thoracic Society guidelines)*	Not in line with British Thoracic Society guidelines)	2	100%	
20	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*	Risk of supratherapeutic or subtherapeutic dose of salbutamol	3	81%	Y
21	Ivacaftor co-prescribed with an interacting drug with no dose adjustment of interacting drug *(risk of subtherapeutic levels of interacting drug)*	Risk of supratherapeutic or subtherapeutic levels of ivacaftor due to enzyme induction or inhibition	2	76%	
22	More than one paracetamol-containing product prescribed to be administered concomitantly *(maximum dose exceeded)*	Concomitant prescribing of more than one paracetamol containing product can result in doses over the daily limit for the age group	3	71%	
23	Codeine phosphate prescribed to a patient under the age of 12 *(contraindicated)*	MHRA guidance restrict use of codeine in children due to risk of fatal toxicity	3	57%	
24	Tramadol prescribed concomitantly with antiepileptics *(increased risk of seizures in patients with uncontrolled epilepsy)*	Increased risk of seizures	3	71%	
25	Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates risk of toxicity)*	Increased risk of opioid toxicity	3	86%	Y
26	Regular opiates prescribed without concurrent use of laxatives *(risk of severe constipation)*	Risk of severe constipation	2	52%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
27	Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)*	Oral and intramuscular doses are not equivalent, risk of therapeutic failure or toxicity	3	81%	Y
28	Phenytoin dose not reviewed in light of low albumin (potential for toxicity)	Increased risk of phenytoin toxicity	3	86%	Y
29	Failure to increase dose of anticonvulsant in line with weight for epilepsy *(increased risk of seizure)*	Increased risk of seizures	3	52%	
30	Prescribing an incorrect starting dose of lamotrigine when used in combination with Sodium Valproate *(increased risk of ADR)*	Increased risk of adverse reaction in particular rashes	2	71%	
31	Clonazepam prescribed when clobazam required or vice versa	Risk of incorrect dose of the wrong drug and subsequent toxicity or therapeutic failure	3	76%	
32	Prophylactic antimicrobials and treatment antimicrobials prescribed to be administered concomitantly *(increased risk of resistance)*	Risk of antimicrobial resistance	3	67%	
33	Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) *(risk of hypersensitivity reactions)*	Contraindicated in pts with history of penicillin allergy. Risk of hypersensitivity reaction	3	81%	Y
34	Dose change for metronidazole not made when switching from an IV dose >400mg to oral *(risk of overdose)*	Increased risk of supratherapeutic dose of metronidazole	2	75%	
35	Quinolone antibiotic prescribed to a patient who is also receiving theophylline *(possible increased theophylline level)*	Possible increased theophylline level	2	81%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
36	Quinolone antibiotic prescribed to a patient with epilepsy *(increased risk of seizure threshold being reduced)*	Quinolone antibacterials lower the seizure threshold	3	57%	
37	Oral quinolone antibacterial prescribed at the same time as iron *(reduced absorption of quinolones)*	Iron reduces the absorption of quinolone antibacterials. At last 4 hours should separate the administration of a quinolone and iron	2	76%	
38	Oral quinolones and enteral feeds prescribed concomitantly *(risk of treatment failure with quinolone)*	Reduced absorption of quinolone	2	76%	
39	Intravenous Ciprofloxacin prescribed Twice daily instead of three times a day in children over 1 month old *(risk of therapeutic failure)*	Risk of subtherapeutic levels of ciprofloxacin	3	55%	
40	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	Risk of peripheral neuropathy and reduced therapeutic effect	3	80%	Y
41	Ceftriaxone prescribed at a total daily dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis in a patient > 1 month of age *(risk of under dosage)*	Potential subtherapeutic dose for severe infection/sepsis	3	90%	Y
42	Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or respiratory exacerbation of CF *(potential under treatment)*	Potential subtherapeutic dose for severe infection/sepsis	3	86%	Y
43	Co-prescribing of meropenem with sodium valproate *(increased risk of seizure)*	Reduction in valproate levels leading to increased risk of seizure	3	71%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
44	Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment *(increased risk of toxicity)*	Increased risk of toxicity	3	81%	Y
45	Gentamicin prescribed at a dose exceeding maximum stated in local protocol e.g. 7mg/kg/day to a child > 1month *(risk of toxicity)*	Increased risk of toxicity	2	62%	
46	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	Risk of excessive dosing and toxicity	3	100%	Y
47	Gentamicin prescribed at a dose exceeding 5mg/kg/dose to a neonate *(risk of toxicity)*	Increased risk of toxicity	2	67%	
48	Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*	Macrolide antibacterials can reduce the metabolism of warfarin, causing an increase in the INR and an increased risk of bleeding	3	90%	Y
49	Co-prescribing of macrolides with interacting drug *(QT prolongation)*	Risk of prolongation of QT interval and ventricular arrhythmia	3	86%	Y
50	Co-prescribing of a macrolide with domperidone *(QT prolongation)*	Risk of prolongation of QT interval and ventricular arrhythmia	3	76%	
51	Co-prescribing of a macrolide with an anticonvulsant *(risk of toxicity or subtherapeutic levels)*	Risk of supratherapeutic or subtherapeutic levels of anticonvulsant	3	70%	
52	Co-prescribing of a macrolide with ciclosporin or tacrolimus *(increases plasma levels of anti-rejection agent)*	Increased plasma concentration of ciclosporin	3	86%	Y

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
53	Co-prescribing of a macrolide with midazolam *(risk of sedation)*	Increased risk of sedation	2	76%	
54	Vancomycin prescribed intravenously to a patient with at least mild renal impairment without dose adjustment *(increased risk of toxicity)*	Increased risk of toxicity	3	76%	
55	Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	Increased risk of infusion reactions	3	81%	Y
56	Rifampicin co-prescribed with an interacting drug with no dose adjustment of interacting drug *(risk of subtherapeutic levels of interacting drug)*	Risk of subtherapeutic levels of interacting drug due to enzyme induction	2	52%	
57	Fluconazole prescribed more frequently than every 72 hours for a neonate < 14 days old *(risk of toxicity)*	Increased risk of toxic effects, Neonates have a 72 or 48 hour frequency based on age.	3	52%	
58	Fluconazole prescribed as standard dose from day 2 of treatment in a patient with an estimated GFR of < 50 ml/min/1.73m2 *(risk of toxicity, normally halve dose after first day)*	Increased risk of toxic effects. Patients with renal failure <50ml/min/1.73m2 have standard dose for one dose then halved.	3	76%	
59	Fluconazole prescribed more frequently than every 48 hours for a neonate between 14 and 28 days old *(risk of toxicity)*	Increased risk of toxic effects. Neonates have a 72 or 48 hour frequency based on age.	3	62%	
60	Amphotericin B prescribed without additionally stating both brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid)*	Specification of brand name to reduce risk of wrong formulation being administered and resulting toxicity	3	90%	Y

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
61	Failure to adjust dose or frequency of ganciclovir in the presence of altered renal function *(risk of toxicity or treatment failure)*	Risk of supratherapeutic or subtherapeutic levels of ganciclovir	3	80%	Y
62	Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia especially if given more than 1 stat dose. Not managing the long-term condition	3	85%	Y
63	Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) *(increased risk of hypoglycaemia)*	Insulin should be prescribed at meal times to avoid the risk of hypoglycaemia	3	76%	
64	Oral prednisolone and intravenous hydrocortisone prescribed to be administered concomitantly simultaneously *(risk of toxicity)*	Increased risk of adverse effects	2	86%	
65	Oral prednisolone and steroid inhalers prescribed to be administered concomitantly *(risk of toxicity)*	Increased risk of adverse effects	3	57%	
66	Prednisolone EC Prescribed for patient with Inflammatory Bowel Disease *(reduced absorption of prednisolone)*	Reduced absorption of predinsolone	2	76%	
67	Desmopressin prescribed for nocturnal enuresis at any other time than at bedtime *(risk of fluid overload)*	Risk of over hydration	2	81%	
68	Dose reduction of immunosuppressant not made despite low white cell count *(risk of neutropenia)*	Increased risk of neutropenia and subsequent infection, (list of common immunosuppressants will be included during data collection)	3	90%	Y

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
69	Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*	Risk of methotrexate toxicity	3	80%	Y
70	Failure to prescribe mesna for patients receiving alkylating agents *(risk of toxic symptoms)*	Risk of bladder toxicity	3	75%	
71	Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count *(risk of bone marrow suppression)*	Risk of bone marrow suppression	3	90%	Y
72	Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	Oral methotrexate should be dosed ONCE WEEKLY, and the prescription clear as to which day of the week this should be	3	100%	Y
73	Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*	Risk of liver toxicity	3	85%	Y
74	Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*	Trimethoprim suppresses activity of dihydrofolate reductase - potential for additive effect to produce folate deficiency. Increased risk of haematological toxicity when methotrexate given with trimethoprim (including trimethoprim containing compound - co-trimoxazole)	3	85%	Y
75	Methotrexate prescribed to be administered on the same day as folic acid *(reduced efficacy of methotrexate)*	Concomitant administration of folic acid with methotrexate will reduce efficacy of methotrexate	2	75%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
76	Allopurinol prescribed concomitantly with azathiorpine *(Allopurinol enhances effect of azathioprine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of azathioprine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	3	65%	
77	Allopurinol prescribed concomitantly with mercaptopurine *(allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*	Increased risk of toxicity and enhanced effects of mercaptopurine when given concomitantly. The dose of mercaptopurine should be one quarter of usual dose	3	80%	Y
78	Tacrolimus prescribed without reference to brand name *(variation in pharmacokinetics and dosing)*	Risk of subtherapeutic levels due to differences in pharmacokinetics	2	55%	
79	Calcium resonium prescribed when the potassium concentration is within the desired reference range (3.5–5.3 mmol/litre) *(risk of hypokalaemia)*	Calcium resonium should be stopped when the potassium concentration is within the desired reference range, as it continues to work for a few days once discontinued	2	85%	
80	Potassium chloride supplements continued for longer than is required (based on age appropriate local reference ranges approx 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*	Failure to act on potassium chloride monitoring and continuing treatment for longer than required risks hyperkalaemia	3	81%	Y
81	Prescribing of Sodium Chloride 0.18% with Glucose 4% solutions as post-operative intravenous fluid *(risk of cerebral oedema)*	Risk of cerebral oedema	3	62%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
82	Potassium chloride infusions exceeding 40 mmol/litre prescribed to administered via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*	Intravenous administration of potassium chloride solutions exceeding 40mmol/litre should be prescribed via the central route to avoid arrhythmias	3	86%	Y
83	Incorrect stock parenteral nutrition bag prescribed based on local protocol	Risk of inappropriate nutrition	2	62%	
84	More than one NSAID prescribed to a patient at a time *(increased risk of bleeding)*	Increased risk of bleeding when more than one NSAID is prescribed.	2	71%	
85	Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m2)	Increased risk of toxic effects	3	90%	Y
86	Live vaccine prescribed to an immunosuppressed patient, including those on corticosteroids *(increased risk of reaction or infection)*	Risk of reaction/infection	3	52%	
87	Prescribing the incorrect vaccines for childhood immunisation based on the current vaccination guidelines *(risk of serious childhood infection)*	Lack of immunity for serious childhood infections	2	90%	
88	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration	Risk of supratherapeutic or subtherapeutic dose of midazolam	3	81%	Y
89	Acetylcysteine prescribed at a dose inconsistent with the product literature for paracetamol poisoning	Risk of sub or supratherapeutic doses with treatment failure or toxicity	3	70%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
90	Dose change for ciprofloxacin not made when switching from IV to oral *(risk of overdose)*	Risk of supratherapeutic dose of ciprofloxacin	2	90%	
91	A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)*	Risk of anaphylaxis	3	100%	Y
92	Dose of paracetamol prescribed inappropriate for route of administration *(potential overdose due to change in route or misreading of BNFC)*	Risk of paracetamol overdose	3	81%	Y
93	Amiodarone prescribed to a patient on digoxin without review of the digoxin dose	Risk of digoxin toxicity	3	81%	Y
94	Caffeine Citrate maintenance dose prescribed to start too soon or too late after loading dose (should be 24 hours)	Risk of sub or supra therapeutic dose	2	90%	
95	Oral quinolone prescribed to be administered at the same time as an oral calcium	Risk of treatment failure	2	81%	
96	Ceftriaxone prescribed at a dose greater than 50mg/kg in a patient < 1month old	Risk of supratherapeutic dose of Ceftriaxone	2	90%	
97	Aciclovir prescribed to a patient with at least mild renal impairment without dose adjustment	Increased risk of toxicity	3	76%	
98	Desmopressin nasal formulation prescribed for nocturnal enuresis *(increased incidence of side effects)*	Risk of toxicity due to increased bioavailability of nasal formulation	2	95%	
99	Dose of cefotaxime exceeding 200mg/kg/day in patients <4 weeks old	Risk of toxicity	2	100%	
100	Amiodarone loading dose prescribed incorrectly according to BNFC	Risk of sub or supra therapeutic dose	3	62%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
101	Aciclovir prescribed at a dose of 250mg/m^2 instead of 500mg/m^2 for herpes simplex encephalitis in patients aged between 3 months and 12 years	Risk of treatment failure	3	90%	Y
102	Thiopurines (azathioprine and 6MP) prescription in presence of abnormal liver function tests (LFTs will be defined)	Increased risk of toxicity	3	76%	
103	Intravenous aminophylline prescribed without appropriate monitoring or adjustment of dose in relation to theophylline levels	Risk of sub or supra therapeutic levels	3	71%	
104	Ranitidine dose not altered when switching between oral and IV routes	Risk of sub or supra therapeutic doses	2	86%	
105	IV cefuroxime prescribed using the oral dose (20mg/kg/dose twice daily)	Subtherapeutic dose leading to potential treatment failure	3	52%	
106	Gabapentin prescribed without gradually increasing the dose	Increased risk of toxicity	2	71%	
107	Theophylline prescribed without reference to the brand	Risk of sub or supratherapeutic doses and subsequent treatment failure or toxicity	2	65%	
108	Furosemide prescribed twice daily in neonates < 31 weeks gestational age	Risk of toxicity	3	67%	
109	Prescription for beclometasone inhaler without reference to the brand	Difference in bioavailability between Qvar and Clenil brands. Risk of toxicity or treatment failure	2	62%	
110	Prescription for Intramuscular ceftriaxone without co-prescription of lidocaine for reconstitution	Lidocaine used to prepare ceftriaxone and reduce pain at injection site.	3	52%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
111	Concomitant prescription of ibuprofen/indometacin and hydrocortisone in neonatal patient	Risk of spontaneous gastrointestinal perforation	3	65%	
112	Co - prescribing of nebulised Tobramycin and intravenous tobramycin in CF patients	Risk of toxicity	3	67%	
113	Prescription of NSAIDS in suspected toxic shock syndrome *(contraindicated but patients are pyrexial)*	Risk of enhanced cytokine release contributing to shock, organ failure etc	3	81%	Y
114	Regular prescription of anti-pyretic in paediatric oncology patients	Risk of masking neutropenic sepsis	3	67%	
115	Maintenance fluids prescribed such that >3l of fluid would be administered in 24 hours	Exceeds maximum adult maintenance fluid	2	76%	
116	Failure to increase of hydrocortisone to “sick day doses” from “maintenance” doses in those adrenally suppressed	Reduces risk of shock	3	95%	Y
117	Prescription of mycophenolate with no reference to salt or brand	Risk of sub or supratherapeutic levels	3	68%	
118	Failure to increase dose of prophylactic trimethoprim with increasing weight	Risk of sub therapeutic levels and treatment failure	2	67%	
119	Failure to increase frequency of IV benzylpenicillin over the first 5 weeks of life	Risk of treatment failure	3	67%	
120	Failure to increase frequency of oral or IV Flucloxacillin over the first 4 weeks of life	Risk of treatment failure	3	67%	
121	Failure to increase the frequency of IV cefotaxime over the first 4 weeks of life	Risk of treatment failure	3	67%	

Full list of indicators and levels of consensus after 2 rounds of eDelphi continued

No	Indicator	Supporting Information	Median Risk Score	Consensus	Include
122	Sodium supplements continued for longer than is required (based on age appropriate local reference ranges approx 135 - 145 mmol/litre) *(increased risk of hypernatraemia)*	Risk of hypernatraemia	2	81%	
123	Prescribing caffeine using base rather than salt i.e. caffeine rather than caffeine citrate *(risk of sub-therapeutic dosing)*	Risk of subtherapeutic dosing	2	71%	
124	Dose value of alfacalcidol in nanograms expressed as micrograms	Risk of 1000 time overdose	3	71%	
125	Prescribing a fluid containing dextrose rather than glucose	Risk of confusion at drug selection/administration stage	2	100%	

Appendix 15 – Paediatric Indicator Simulation Survey

Instructions

A. For each indicator test whether your prescribing system would allow it to occur in paediatric patients.
B. For each indicator choose the level of decision support triggered during the prescribing process using the descriptions below, if more than one apply please state in the notes
C. Describe the warnings/alerts provided to the prescriber and the input required to continue prescribing if prescribing is possible
D. Provide explanatory notes as appropriate.
E & F. Provide a judgment of the likelihood for the questions posed using a scale of 1-5 where 1 = never and 5 = certain.

Definitions

Paediatric Patient:- Use your local definition of paediatric patient and please clarify how the system uses this e.g. a clearly defined global setting for age, ward based setting or combination.

Definitions of levels of clinical decision support (CDS):

Restricted: -Error was prevented by the system as prescribers could not proceed or were blocked
Guided:- -Default fields pre-populated to encourage the prescriber to accept and continue
Permitted (with input):-An alert where a reason needs to be given to override
Alert (without input):-An alert where no reason needs to be given for override
None:-No interruptive CDS present
NB- If more than one apply please state in the notes column (C/D)

Paediatric indicator simulation survey

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
1a	Domperidone prescribed at > 1.2mg/kg/day *(prolongation of QT interval, sudden cardiac death)*					
1b	Domperidone prescribed at a dose exceeding 20mg per day *(max BNFC dose)*					
2	Digoxin dose not reviewed in light of reduced renal function (less than 50ml/min/1.73m^2)					

Paediatric indicator simulation survey continued

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
3a	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor *(increased risk of severe hyperkalaemia)*					
3b	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*					
4	Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*					
5	Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment (<30ml/min/1.73m^2) *(increased risk of bleeding)*					
6	Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*					
7	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*					
8	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate *(risk of toxicity or therapeutic failure)*					
9	Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates risk of toxicity)*					

Paediatric indicator simulation survey continued

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
10	Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)* e.g. morphine 10mg IV/PO/SC					
11	Phenytoin dose not reviewed in light of low albumin *(potential for toxicity)*					
12	Penicillin containing compound prescribed to a penicillin allergic patient (please describe in the notes whether symptoms of reaction can be added and hence whether a reason for prescribing can be made clear)					
13	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*					
14	Ceftriaxone prescribed at a total daily dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis in a patient > 1 month of age *(risk of under dosage)*					
15	Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or respiratory exacerbation of CF *(potential under treatment)*					
16	Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment according to local policy *(increased risk of toxicity)*					
17	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*					

Paediatric indicator simulation survey continued

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
18	Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*					
19	Co-prescribing of macrolides with interacting drug (QT prolongation) Do not test with all possible drugs, please test with three appropriate drugs from the QT Drug worksheet and state which drugs in the notes column					
20a	Co-prescribing of a macrolide with tacrolimus *(increases plasma levels of anti-rejection agent)*					
20b	Co-prescribing of a macrolide with ciclosporin *(increases plasma levels of anti-rejection agent)*					
21	Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*					
22	Amphotericin B prescribed without additionally stating both brand name and the dose in mg/kg *(risk of fatal overdose due to confusion between lipid based and non-lipid)*					
23	Failure to adjust dose or frequency of Ganciclovir in the presence of altered renal function (less than 70ml/min/1.73m^2) *(risk of toxicity or treatment failure)*					
24	Soluble insulin prescribed to a patient on a when required basis *(increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*					
25a	Dose reduction of Ciclosporin not made despite low White Cell Count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*					

Paediatric indicator simulation survey continued

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
25b	Dose reduction of Tacrolimus not made despite low White Cell Count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*					
25c	Dose reduction of Mycophenolate not made despite low White Cell Count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*					
25d	Dose reduction of Azathioprine not made despite low White Cell Count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*					
25e	Dose reduction of Mercaptopurine not made despite low White Cell Count (Less than 3.5 x 10^9/L) *(risk of neutropenia)*					
26	Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*					
27a	Methotrexate prescribed to a patient with a clinically significant drop in white cell count (< 4 x10^9/L) *(risk of bone marrow suppression)*					
27b	Methotrexate prescribed to a patient with a clinically significant drop in platelet count (< 150 x 10^9/L) *(risk of bone marrow suppression)*					
28	Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*					
29	Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*					
30	Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*					

Paediatric indicator simulation survey continued

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
31	Allopurinol prescribed concomitantly with mercaptopurine *(allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*					
32	Potassium chloride supplements continued for longer than is required (based on age appropriate local reference ranges approx 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*					
33	Potassium chloride infusions exceeding 40 mmol/litre prescribed to be administered via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*					
34	Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m^2)					
35	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration (e.g. oral dose prescribed via buccal route)					
36	A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)* excluding penicillins					
37	Dose of paracetamol prescribed inappropriate for route of administration					
38	Amiodarone prescribed to a patient on digoxin, system prompts a review of digoxin dose					
39	Aciclovir prescribed at a dose of 250mg/m^2 instead of 500mg/m^2 for herpes simplex encephalitis in patients aged between 3 months and 12 years					

Paediatric indicator simulation survey continued

No	Indicator	Indicator Permitted Y/N	Level of Decision Support	Description of decision support	Likert 1	Likert 2
40	Prescription of NSAIDS in suspected toxic shock syndrome *(contraindicated but patients are pyrexial)*					
41	Failure to increase of hydrocortisone to “sick day doses” from “maintenance” doses in those adrenally suppressed					

Appendix 16 – Supplementary Questions

Supplementary questions for completion at sites undertaking paediatric indicator simulation

University of Portsmouth School of Pharmacy and Biomedical Sciences

University Hospital Southampton NHS NHS Foundation Trust
Southampton Pharmacy Research Centre (SPRC)

Paediatric Indicator Simulation - General Information

Instructions:
Please complete the answers to the first five questions in relation to the whole organisation
The subsequent questions relate to the way the ePrescribing system works when prescribing for children. Please use your local definition of children.
If you have any questions please contact Andy Fox at eDelphiPaed@uhs.nhs.uk or 02381204201
Once completed please go to the indicator worksheet next.

If you use more than one EPrescribing system for children please complete the questionnaire for each system.

	Your Contact Details here		
	Question	Response (use this column for your main response)	Notes (use this column to provide any explanatory notes you feel would be needed to interpret your response)
1	Organisation		
2	Electronic Prescribing (EP) System		
3	EP Version		
4	Hospital Type		
5	eP System spread within organisation - what proportion of inpatients use this system (%)		
	Number of Paediatric Beds		
6	How long has this eP system been in use for children?		
7	Does the system use abbreviations to describe drugs (e.g. AZT or NaCl) rather than approved names?		
8	Does the system allow prescribers to enter drugs as freetext prescriptions (Y/N)?		
9	Can doses be entered by the prescriber using a trailing zero after a decimal point (e.g. 5.0mg or 2.0g)?		
10	If "Yes" what does the system display following entry? If "No" what warning is provided to the prescriber		
11	Does the system require a weight to be entered before any prescribing can take place? Y/N		
12	If "Yes" is the weight used to calculate doses automatically? (if yes please clarify if all drugs or selected drugs)		
13	Does the system check if a weight is out of date based on internal rules? Y/N		
14	Does the system allow a drug that is usually prescibed by weight to be prescribed without the presence of an up-to-date weight (defined by internal rules if present).		
15	Does the system calculate BSA if so please describe how (using weight or weight and height)?		
16	For drugs that are prescribed by BSA does the system allow the drug to be prescribed without the presence of an up to date BSA value (based on internal rules if present).		
17	Does the system round doses Y/N to measurable amounts. - if so please describe for all relevant formulation types (liq, solid, inj) in the notes column		
18	Does the system abbreviate units by using "u" or "iu"		
19	Does the system allow/support 18 hourly or 36 hourly dosing		
20	Does the system abbreviate micrograms and nanograms? Please explain if different in different views		

Appendix 17 – Full Indicator Simulation Results

Full results of indicator simulation exercise
Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
1a	Domperidone prescribed at > 1.2mg/kg/day *(prolongation of QT interval, sudden cardiac death)*	Gastrointestinal	Dosing	15	0	0	0	1	1	0	13	15	4/2	3/2	12
1b	Domperidone prescribed at a dose exceeding 20mg per day *(max BNFC dose)*	Gastrointestinal	Dosing	15	0	0	0	1	1	0	13	15	4/3	2/1	12
2	Digoxin dose not reviewed in light of reduced renal function (less than 50ml/min/1.73m^2)	Cardiovascular	Dosing	15	0	0	0	0	0	0	15	15	5/2.25	3/1.25	12
3a	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor *(increased risk of severe hyperkalaemia)*	Cardiovascular	Drug-Drug Interaction	15	0	0	0	0	6	3	6	15	3/2.25	3/2	12
3b	Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an angiotensin-II receptor antagonist *(increased risk of severe hyperkalaemia)*	Cardiovascular	Drug-Drug Interaction	15	0	0	0	0	4	3	8	15	3/3	3/2	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
4	Beta-adrenoceptor blocking drug prescribed to a patient with asthma *(increased risk of bronchospasm and acute deterioration)*	Cardiovascular	Clinical Contraindication	15	0	0	0	0	2	0	13	15	4/1.5	3/2	12
5	Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment (<30ml/min/1.73m^2) *(increased risk of bleeding)*	Cardiovascular	Dosing	15	0	0	0	1	0	0	14	15	5/1.25	3/1.25	12
6	Antiplatelet prescribed to a patient with a concurrent bleeding disorder *(increased risk of bleeding)*	Cardiovascular	Clinical Contraindication	15	0	0	0	0	0	0	15	15	5/1.25	3/2	12
7	Prescribing of intravenous heparin infusion for treatment of thromboembolic event using the wrong dose or infusion rate based on local protocol *(risk of toxicity or therapeutic failure)*	Cardiovascular	Dosing	4	0	11	0	1	1	0	13	15	3/2.5	2/0.5	8
8	Prescribing of intravenous salbutamol infusion using the wrong dose or infusion rate (*risk of toxicity or therapeutic failure)*	Respiratory	Dosing	6	0	9	0	0	1	0	14	15	3/2.5	2/0.25	8

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
9	Two concomitant opiate analgesics that are not in line with the WHO pain ladder *(injudicious use of two opiates risk of toxicity)*	Central Nervous System	Therapeutic Duplication	14	0	0	0	0	9	2	3	14	3/1.25	2.5/1	12
10	Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. *(risk of toxicity)* e.g. Morphine 10mg IV/PO/SC	Central Nervous System	Therapeutic Duplication	11	3	0	2	3	5	1	3	14	3/2.25	2/1.5	12
11	Phenytoin dose not reviewed in light of low albumin *(potential for toxicity)*	Central Nervous System	Dosing	15	0	0	0	0	0	0	15	15	5/1	3.5/1	12
12	Penicillin containing compound prescribed to a penicillin allergic patient (please describe in the notes whether symptoms of reaction can be added and hence whether a reason for prescribing can be made clear)	Antimicrobial	Allergy	14	1	0	1	0	13	1	0	15	2/0	2/1.25	12
13	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	Antimicrobial	Dosing	14	0	0	0	0	0	0	14	14	5/1,25	3.5/2	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
14	Ceftriaxone prescribed at a total daily dose of 50mg/kg instead of 80mg/kg for severe infection/sepsis in a patient > 1 month of age *(risk of under dosage)*	Antimicrobial	Dosing	14	0	0	0	0	0	0	14	14	5/1	3/1.25	12
15	Meropenem prescribed at a dose of 20mg/kg instead of 40mg/kg for meningitis or respiratory exacerbation of CF *(potential under treatment)*	Antimicrobial	Dosing	14	0	0	0	0	0	0	14	14	5/1	3/1.25	12
16	Gentamicin prescribed to a patient with at least mild renal impairment without dose frequency adjustment according to local policy *(increased risk of toxicity)*	Antimicrobial	Dosing	13	0	1	0	0	0	0	14	14	4/2	3/2	12
17	Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient *(risk of excessive dosing and toxicity)*	Antimicrobial	Dosing	13	0	1	0	0	1	0	13	14	4/1.25	3/1.25	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
18	Macrolide antibacterial prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring *(increased risk of bleeding)*	Antimicrobial	Drug-Drug Interaction	14	0	0	0	0	4	4	6	14	4/3	3/2	12
19	Co-prescribing of macrolides with interacting drug (QT prolongation) Do not test with all possible drugs, please test with three appropriate drugs from the QT Drug worksheet and state which drugs in the notes column	Antimicrobial	Drug-Drug Interaction	14	0	0	0	0	4	4	6	14	4/2	3/1.25	12
20a	Co-prescribing of a macrolide with tacrolimus *(increases plasma levels of anti-rejection agent)*	Antimicrobial	Drug-Drug Interaction	14	0	0	0	0	6	3	5	14	3/1.5	3/1.25	12
20b	Co-prescribing of a macrolide with ciclosporin *(increases plasma levels of anti-rejection agent)*	Antimicrobial	Drug-Drug Interaction	14	0	0	0	0	6	3	5	14	3/1.5	3/1.25	12
21	Vancomycin prescribed intravenously over less than 60 minutes *(rapid infusion of vancomycin can cause severe reactions)*	Antimicrobial	Intravenous Rate	12	0	2	0	3	0	0	11	14	2/2.5	2/1	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
22	Amphotericin B prescribed without additionally stating both brand name and the dose in mg/kg (*risk of fatal overdose due to confusion between lipid based and non-lipid)*	Antimicrobial	Drug Name	6	8	0	9	1	0	0	4	14	1/1	1/1	11
23	Failure to adjust dose or frequency of ganciclovir in the presence of altered renal function (less than 70ml/min/1.73m^2) *(risk of toxicity or treatment failure)*	Antimicrobial	Dosing	14	0	0	0	0	0	0	14	14	4/2.25	2/1.25	12
24	Soluble insulin prescribed to a patient on a when required basis (*increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose)*	Endocrine	Clinical Contraindication	10	1	3	1	3	0	0	10	14	2/3	2/1	12
25a	Dose reduction of ciclosporin not made despite low white cell count (less than 3.5 x 10^9/L) *(risk of neutropenia)*	Immunosuppressant	Dosing	14	0	0	0	0	0	0	14	14	4/2	3/2	12
25b	Dose reduction of tacrolimus not made despite low white cell count (less than 3.5 x 10^9/L) *(risk of neutropenia)*	Immunosuppressant	Dosing	14	0	0	0	0	0	0	14	14	4/2	3/2	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
25c	Dose reduction of mycophenolate not made despite low white cell count (less than 3.5 x 10^9/L) *(risk of neutropenia)*	Immunosuppressant	Dosing	14	0	0	0	0	0	0	14	14	4/2	3/2	12
25d	Dose reduction of azathioprine not made despite low white cell count (less than 3.5 x 10^9/L) *(risk of neutropenia)*	Immunosuppressant	Dosing	14	0	0	0	0	0	0	14	14	4/2	3/2	12
25e	Dose reduction of mercaptopurine not made despite low white cell count (less than 3.5 x 10^9/L) *(risk of neutropenia)*	Immunosuppressant	Dosing	14	0	0	0	0	0	0	14	14	4/2	2.5/2	12
26	Failure to prescribe folinic acid rescue therapy following high dose methotrexate chemotherapy *(risk of methotrexate toxicity)*	Immunosuppressant	Omission	9	0	5	0	0	0	0	14	14	4/2.75	2/1	10
27a	Methotrexate prescribed to a patient with a clinically significant drop in white cell count (< 4 x10^9/L) *(risk of bone marrow suppression)*	Immunosuppressant	Clinical Contraindication	14	0	0	0	0	0	0	14	14	4/2	2.5/2	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
27b	Methotrexate prescribed to a patient with a clinically significant drop in platelet count (< 150 x 10^9/L) *(risk of bone marrow suppression)*	Immunosuppressant	Clinical Contraindication	14	0	0	0	0	0	0	14	14	4/2	2.5/2	12
28	Oral methotrexate prescribed to a patient with an inappropriate frequency *(increased risk of toxicity)*	Immunosuppressant	Dosing	8	6	0	6	2	2	2	2	14	1/1	1/0.25	12
29	Methotrexate prescribed to a patient with abnormal liver function tests *(risk of liver toxicity)*	Immunosuppressant	Clinical Contraindication	14	0	0	0	0	0	0	14	14	4/2	3/2	12
30	Methotrexate prescribed concomitantly with trimethoprim *(increased risk of haematological toxicity)*	Immunosuppressant	Drug-drug interaction	14	0	0	0	0	6	3	5	14	3/2	3/2	12
31	Allopurinol prescribed concomitantly with mercaptopurine *(allopurinol enhances effect of mercaptopurine and increases risk of toxicity)*	Immunosuppressant	Drug-drug interaction	14	0	0	0	0	4	3	7	14	3/2	3/2	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
32	Potassium chloride supplements continued for longer than is required (based on age appropriate local reference ranges approx 3.5–5.3 mmol/litre) *(increased risk of hyperkalaemia)*	Nutrition	Duration	14	0	0	0	0	0	0	14	14	4/1	3/0.5	12
33	Potassium chloride infusions exceeding 40 mmol/litre prescribed to be administered via the peripheral route *(peripheral administration risks venous pooling, which can lead to sudden high concentrations of potassium chloride being delivered to the heart provoking an arrhythmia)*	Nutrition	Route	4	1	9	1	1	0	0	12	14	3/2.25	2/0	8
34	Baclofen dose not reduced in response to decreased renal function (eGFR < 90 ml/min/1.73m^2)	Central Nervous System	Dosing	14	0	0	0	0	0	0	14	14	4/1	3/1.25	12
35	Midazolam prescribed for procedural sedation at a dose inappropriate for the route of administration (e.g. oral dose prescribed via buccal route)	Anaesthetic	Dosing	10	4	0	3	3	0	0	8	14	2/3	2/2	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
36	A prescription for a drug for a patient with a known allergy to that drug *(risk of anaphylaxis)* excluding penicillins	General	Allergy	11	4	0	2	1	11	1	0	15	2/1	2/1.25	12
37	Dose of paracetamol prescribed inappropriate for route of administration	Central Nervous System	Dosing	13	1	0	0	2	3	1	8	14	4/3	2/1	12
38	Amiodarone prescribed to a patient on digoxin, system prompts a review of digoxin dose	Cardiovascular	Drug-Drug interaction	14	0	0	0	0	7	1	6	14	4/1.25	3/2	12
39	Aciclovir prescribed at a dose of 250mg/m^2 instead of 500mg/m2 for herpes simplex encephalitis in patients aged between 3 months and 12 years	Antimicrobial	Dosing	14	0	0	0	0	0	0	14	14	5/1.25	3/2	12
40	Nitrofurantoin prescribed to a patient with renal impairment, avoid if eGFR <60ml/minute/1.73m^2 *(risk of peripheral neuropathy and inadequate concentration in urine)*	Musculoskeletal	Clinical Contraindication	14	0	0	0	0	0	0	14	14	4/1	3/1.25	12

Full results of indicator simulation exercise continued

Key: - R = Restricted, G – Guided, P = Permitted (with input), A = Alert (no input), n = number of responses

No	Indicator	System	Error Type	Permitted			CDS level (see key)						Likert Scores (Median/IQR)		
				Y	N	N/A	R	G	P	A	None	n	Error Prescribed	Reach Patient	n
41	Failure to increase of hydrocortisone to “sick day doses” from “maintenance” doses in those adrenally suppressed	Endocrine	Dosing	14	0	0	0	0	0	0	14	14	4/1	3.5/1.25	12

Appendix 18 - Ethics Documentation

Science Faculty Ethics Committee
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16 February 2017

FAVOURABLE ETHICAL OPINION – FOLLOWING RESUBMISSION

Study Title: Paediatric Prescribing Indicator Simulation – A survey of UK Hospitals using Electronic Prescribing for Paediatric Patients

Reference Number: SFEC 2017- 008

Date Resubmitted: 7 February 2017

Thank you for resubmitting your application to the Science Faculty Ethics Committee (SEFC) for ethical review in accordance with current procedures, for making the requested changes following the first SFEC review, and for the clarifications provided. We also accept your challenge to *Condition B*, your explanation is clear and comprehensive; so just to be explicit, you do not have to abide by the conditon.

Therefore, I am pleased to inform you that SFEC was content to grant a favourable ethical opinion of the above research on the basis described in the submitted documents listed at Annex A, and subject to standard general conditions (*See Annex B)*.

Please note that the favourable opinion of SFEC does not grant permission or approval to undertake the research. Management permission or approval must be obtained from any host organisation, including the University of Portsmouth or supervisor, prior to the start of the study.

Wishing you every success in your research

Dr Paul Morris
Chair, Science Faculty Ethics Committee

Annexes

A - Documents reviewed
B - After ethical review - Guidance for researchers

FORM UPR16

Research Ethics Review Checklist

Please include this completed form as an appendix to your thesis (see the Postgraduate Research Student Handbook for more information

Postgraduate Research Student (PGRS) Information			**Student ID:**	748502
PGRS Name:	Andy Fox			
Department:	School of Pharmacy and Biomedical Sciences	**First Supervisor:**	Prof D Brown	
Start Date: (or progression date for Prof Doc students)	**Feb 2014**			
Study Mode and Route:	Part-time ☒ Full-time ☐	MPhil ☐ PhD ☒	MD ☐ Professional Doctorate ☐	

Title of Thesis:	Can Electronic Prescribing Prevent Harmful Paediatric Prescribing Errors
Thesis Word Count: (excluding ancillary data)	59,493

If you are unsure about any of the following, please contact the local representative on your Faculty Ethics Committee for advice. Please note that it is your responsibility to follow the University's Ethics Policy and any relevant University, academic or professional guidelines in the conduct of your study

Although the Ethics Committee may have given your study a favourable opinion, the final responsibility for the ethical conduct of this work lies with the researcher(s).

UKRIO Finished Research Checklist:
(If you would like to know more about the checklist, please see your Faculty or Departmental Ethics Committee rep or see the online version of the full checklist at: http://www.ukrio.org/what-we-do/code-of-practice-for-research/)

a) Have all of your research and findings been reported accurately, honestly and within a reasonable time frame?	YES ☒ NO ☐
b) Have all contributions to knowledge been acknowledged?	YES ☒ NO ☐
c) Have you complied with all agreements relating to intellectual property, publication and authorship?	YES ☒ NO ☐
d) Has your research data been retained in a secure and accessible form and will it remain so for the required duration?	YES ☒ NO ☐
e) Does your research comply with all legal, ethical, and contractual requirements?	YES ☒ NO ☐

Candidate Statement:

I have considered the ethical dimensions of the above named research project, and have successfully obtained the necessary ethical approval(s)

Ethical review number(s) from Faculty Ethics Committee (or from NRES/SCREC):		SFEC 2017 - 008
If you have *not* submitted your work for ethical review, and/or you have answered 'No' to one or more of questions a) to e), please explain below why this is so:		
Signed *(PGRS)*:		**Date:** 7/12/2017

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