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Paediatric medication error

A systematic review of the extent and nature of the problem in the UK and international interventions to address it

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Terms and abbreviations

Definitions

Adverse drug events (ADE): Injury or harm resulting from a medication error.

Error type: The nature of the error e.g. wrong dose, wrong strength, wrong frequency etc.

Medicines' pathway points: The various decision-making steps that occur between a clinician's decision to prescribe a medication and the patient actually receiving it, including prescribing, transcribing, preparing, dispensing, administering and monitoring.

Off-label prescribing: Prescribing outside of the licence terms or guidance, e.g. using a medication for other age groups or conditions than stated in the licence, or giving medications given at a higher or lower dose than recommended.

Turn-around times: The time taken to prescribe, transcribe, dispense, administer or check medicine (e.g. time taken to calculate correct dose)

Unlicensed use: Prescribing of medicines that have not been licensed for use in the UK or 'specials' medicines prepared in a form which is not licensed.

Abbreviations

ADE	Adverse drug events
CDST	Clinical decision support tools
CPOE	Computerised physician/prescription order entry
CYPHO	Children and Young People's Health Outcomes Forum
DH	Department of Health (UK)
EP	Electronic prescribing (synonymous with CPOE, EP is the preferred term in this report)
GP	General practice/general practitioner
GPASS	General Practice Administration System for Scotland
HCT	Historically controlled trial
ICU	Intensive care unit
NHS	National Health Service (UK)
NICU	Neonate intensive care unit
NPSA	National Patient Safety Agency (UK)
nRCT	Non-randomised controlled trial
NRLS	National Reporting and Learning System (UK)
PICU	Paediatric intensive care unit
PME	Paediatric medication error
PN	Parenteral nutrition
PP	Pathway point
PTI	Scottish Practice Team Information
RCT	Randomised controlled trial
RoB	Risk of bias
RR	Risk ratio

Executive summary

Background

This report describes the methods and findings of a systematic review on paediatric medication error (PME). Paediatric medication errors are failures in the treatment process that cause, or have the potential to cause unnecessary pain or harm to child patients and, in extreme cases, can result in death (Aronson 2009; Department of Health 2006). Medications may be given incorrectly (or omitted) either unintentionally or in ignorance, i.e. a mistake or slip in the medication treatment process. Medication errors are a common occurrence in the healthcare setting (Levine et al. 2001) and are the most common type of errors in paediatric medicine (Ghaleb et al. 2010). This review examines evidence on three key issues: the extent and nature of the problem in the UK; whether interventions, such as electronic prescribing or decision support tools, can reduce PME incidents; and what the key features of successful interventions are, to establish how effective interventions can be developed and implemented successfully. It was commissioned by the Department of Health (DH) in England to support the work of the Children and Young People's Health Outcomes (CYPHO) Forum in tackling the problem of PME.

Methods

The systematic review method was used to assemble a comprehensive and unbiased summary of available research evidence on PME. The work involved employing rigorous methods for identifying and analysing available research evidence to answer the following research questions:

a) What is the nature and extent of paediatric medication error (PME) in the UK?
b) Which international interventions are effective for reducing the incidence of PME?
c) What are the key features of effective interventions and how can they be successfully developed and implemented?

Key findings

a) What is the nature and extent of paediatric medication error (PME) in the UK?

The evidence base

- 11 studies reporting national-level evidence from England, Wales and Scotland were identified.
- Five studies examined evidence from **error reporting systems** largely in relation to **acute care**; six studies identified errors from **prescribing data** largely in relation to **primary care.**

Strong evidence

- In **primary care** settings, off-label prescribing is a common practice, resulting in **dose errors** in relation to a **wide range of drugs**, including antibiotics and paracetamol.
- The **type of drug** and the **age of the patient** affects whether **underdoses** or **overdoses** are more likely to be prescribed.

Promising evidence

- In paediatric and neonatal **acute care** settings, **dose errors** are the **most common type** of medication error, accounting for approximately **one-fifth of all errors**.
- After dose errors, the next most common types of error in acute care are omitted medicine/ingredient, wrong frequency, wrong quantity and wrong drug.

Tentative evidence

- Most medication errors relating to **anaesthesia** are administration errors, of which 'double doses' account for almost half; wrong drug and wrong route administration errors are also common. 10% of incidents are prescription errors but it is unclear what types of prescription errors are involved.
- Almost half of errors relating to **vaccine administration** are due to administration of the wrong vaccine, over one-quarter are documentation errors and one-eighth relate to delayed vaccination.
- In relation to the **preparation of paediatric chemotherapy**, the three most common types of potential error are mislabelled products, wrong expiry date and transcription errors.
- In relation to **parenteral nutrition preparation**, transcription error, wrong drug error and labelling error were the most common types.

Evidence gaps

- Reporting of errors in the UK is currently (a) voluntary and (b) inconsistently recorded, so an accurate and comprehensive picture of rate or types of PME in UK is not currently available.
- There is a lack of evidence directly comparing which pathway points are most commonly associated with PMEs (e.g. prescribing, administration), meaning that it remains unclear as to which types of interventions would be most appropriate to target the problem.
- Although the use of 'specials' (i.e. the preparation of medicines in a form which is not licensed) is known to be an issue for paediatrics, due to a lack of available child-friendly dosage forms, we found no evidence on their use.

b) Which interventions are effective for reducing the incidence of PME?

The evidence base

- **37 trials** were identified which evaluated the impact of interventions on PME outcomes.
- The largest body of evidence relates to electronic prescribing (n=20 trials).
- Reasonable bodies of evidence were identified in relation to education interventions (n=6 trials) and clinical decision support tools (CDST) (n=5 trials).
- **Single trials** were identified for each of a further **six intervention types:** pharmacist support, standardised paediatric formulation, structured prescription order forms, integrated care pathways, mass concentration labelling, patient history-taking software.
- Most studies examined impact on PME; other outcomes included adverse drug events (ADE), mortality, turn-around times and medication knowledge.

Strong findings

- Of fifteen studies examining the impact of **electronic prescribing** on PME, nine found statistically significant reductions and a further four found non-significant trends towards **reduced PME**; two studies found small non-significant increases in PME.
- Overall evidence suggests that electronic prescribing **reduces mortality rates and adverse drug events (ADE)**, though some studies illustrated that it can be responsible for increases in these outcomes.

Promising findings

- Electronic prescribing may reduce turn-around times.
- Clinical decision support tools (CDST) may reduce PME and turn-around times.
- Education interventions may reduce PME and increase medication knowledge.

Tentative findings

- Statistically significant reductions in PME were found in each of the single studies on paediatric formulations, integrated care pathways, structured prescription order forms and mass concentration labelling.
- A non-significant reduction in PME was found in the study on a computer programme for parents to support patient history taking.

Evidence gaps

- The single trial of a **pharmacist support** intervention was found to have **significant risk of bias** – therefore no conclusions can be drawn regarding this type of intervention.
- **No controlled trials** were identified regarding other potentially key interventions such as **smart pumps**.

c) What are the key features of effective interventions and how can they be successfully developed and implemented?

The evidence base

- We examined the content, development and implementation of intervention types for which strong and/or promising evidence of effectiveness was identified.
- A total of 31 interventions were examined in-depth: electronic prescribing (n=20), CDSTs (n=5) and education interventions (n=6).

Strong findings

- **Electronic prescribing** interventions achieving positive outcomes were typically **customised for use with children** and incorporated **extensive decision support**; in the three EP studies with negative findings (e.g. increased mortality) these features were largely absent.
- Evidence suggests that development and implementation of successful electronic prescribing involves: **customisation** for use with child patients, **engaging with a range of stakeholders** during development, fostering a high level of **familiarity with the system** prior to use, ensuring **adequate IT systems** and **compatibility with existing hospital systems** and infrastructure, **careful planning** and ongoing **iterative development** post-implementation.

Promising findings

- **CDST** interventions were less comparable than electronic prescribing interventions; they varied according to whether they were aimed at healthcare professionals or parents/carers – and whether they were designed to support administration or prescription decisions.
- Key features of CDSTs were colour coding systems, hand-held information tools or on-line information tools.
- CDSTs were viewed by users as 'a good idea' and were felt to increase confidence in decision making; authors suggested that the efficacy of CDSTs rests on achieving a balance between simplicity of the tool and comprehensiveness of the information
- Two key types of **education interventions** were identified - paediatric prescribing education for clinicians and pictographic liquid medication administration education for parents/carers
- **Web-based clinician education** and **pictographic instructions for parents** were found to be successful approaches to education; authors indicated that **accessibility**, **low cost** and **ease of delivery** were important features for success.

Evidence gaps

- Few studies incorporated formal process evaluations, so the findings about development and implementation are largely based on informal evidence reported by the authors of the studies.
- The smaller evidence base and the lack of comparability among the CDST and education interventions makes it difficult to determine how to develop and implement these interventions successfully.

Overall conclusions

- Dose errors appear to be a common problem in both primary care (strong evidence) and acute care (promising evidence). However, an accurate and comprehensive picture of the rates and types of PME in the UK is not currently available, largely because error reporting is often voluntary and there is significant inconsistency in the recording and categorising of errors.
- International evidence on **interventions** to tackle PME shows **strong evidence of effectiveness** for **electronic prescribing**; evidence regarding the efficacy of **CDSTs** and **education** interventions is **promising**.
- Evidence suggests that the way **electronic prescribing systems** are **developed and implemented** is **crucial to their success**; successful electronic prescribing systems require careful and considered development and implementation, should feature **comprehensive decision support** and should be **customised for use with children**.

Part I: Background and findings of the review

1. Introduction

Medication errors are a significant problem in the UK and in other countries (Wong et al. 2009) and children are particularly vulnerable (Avery et al. 2012, Kaushal et al. 2001, Walsh et al. 2005). This report describes the methods and findings of a systematic review which examines evidence on the nature and scale of the problem in the UK and international research evaluating the efficacy of a range of preventative interventions. The review was commissioned by the UK Department of Health Policy Research Programme to support the work of the Children and Young People's Health Outcomes Forum (CYPHO) in taking action to address the problem.

1.1 Medication errors in children and young people

Medication errors are failures in the treatment process that cause, or have the potential to cause unnecessary pain or harm to patients and, in extreme cases, can result in death (Aronson 2009, Department of Health 2006). Medication errors are a common occurrence in the healthcare setting (Levine et al. 2001) and are the most common type of errors in paediatric medicine (Ghaleb et al. 2010). Their occurrence creates problems not only within the complex inpatient medical care system, but also in the wider community setting (Levine et al. 2001, Poole and Carleton 2008).

Children and infants are considered to be those most at risk of serious and sometimes fatal adverse drug reactions (National Patient Safety Agency 2007, Poole and Carleton 2008). Drawing on almost 60,000 medication incidents reported via the National Reporting and Learning System (NRLS) in the UK, the National Patient Safety Agency (NPSA) found that children aged four years and under were involved in 10.1 per cent (2,081) of medication incident reports where age was recorded, yet this age group only accounted for 5.6 per cent of all bed days within NHS hospitals (National Patient Safety Agency 2007). In primary care, the PRACtICe Study, which examined 6,048 unique prescription items for 1,777 patients, identified children to be one of the age groups most at risk of errors; prescriptions for those aged less than 15 years were almost twice as likely to contain an error compared to those aged 15-64 years (odds ratio 1.87, 95%CI 1.19-2.94, P=0.006) (Avery et al. 2012).

1.2 Why are children and young people at risk?

Children's vulnerability is in part due to the substantial changes in body proportions and composition that accompany growth and development. The different and varying pharmacokinetic, pharmacodynamic and toxicological parameters between patients at various ages and developmental stages (Ghaleb et al. 2010; Levine et al. 2001, Standing et al. 2005) mean that doses of each medicine need to be calculated for each child on an individual basis, rather than being based on a standard dose as for adults (it should be noted that standard doses for adults are not without complications, as adults vary hugely in size too). In turn, the need for case-by-case calculation opens the door to errors either in terms of not knowing what the correct dose for that child should be (a knowledge-based error), or in terms of miscalculating a dose (an action-based error) (Aronson 2009). One common type of error is factor of 10 errors, also known as decimal place errors or 10-fold or greater overdose, caused by calculation errors or misreading a decimal point. This is a particularly grave error and is made more complex as medicines often come in multiple concentrations and patient weights can vary. For example, in Neonatal Intensive Care Units, patient weight can vary from 0.5 kg up to 5 kg, meaning a 10-fold differential in required doses in the same patient care unit (Ghaleb et al. 2010, Poole and Carleton, 2008).

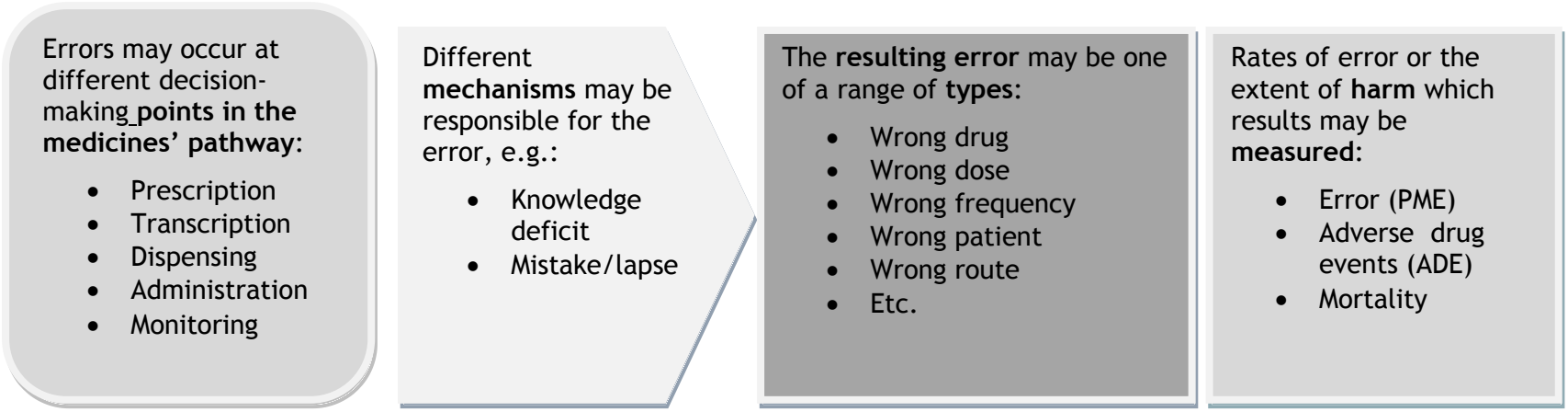
The issue of dosing errors is compounded by the common use of unlicensed and off-label medicines in children (Conroy et al. 2000). Unlicensed medicines are those that do not have marketing authorisation (i.e. a license for use or sale), whereas off-label medicine use is prescribing outside the product licence terms, e.g. using it for different ages, indications or routes from that which has been approved by the regulatory authority (Waller 2007). The use of off-label medicines is particularly common in paediatric medicine because trials in children have not usually been performed during the drug development process (Mason et al. 2012) and therefore many medicines are only licensed for adults. A survey of unlicensed and off-label drug use in paediatric wards in European countries, conducted in 2000, found that almost half of all drug prescriptions (46%) were either unlicensed or off-label (Conroy et al. 2000).

The need to treat serious diseases and provide the most up-to-date medicines for child patients means that unlicensed and off-label prescribing is inevitable in this age group (Auby 2008; Schachter and Ramoni 2007; Waller 2007). However, the need to use medicines formulated for use in adults in the paediatric population means that there is there a lack of research evidence or published information on the safety of using these medicines for children (Levine et al. 2001) and the extrapolation of adult data to be applied in the paediatric population may increase the risk of harm to children (Caldwell et al. 2004, p. 803; Conroy et al. 2000; Garson 1987, p. 84; Johnson 2003, p. 42). This widespread use of medicines formulated for adult use also means a lack of available child-friendly dosage forms (liquids rather than tablets) and concentrations (Ghaleb et al. 2010; Levine et al. 2001) which in turn leads to the use of 'specials' or the preparation of medicines in a form which is not licensed.

As the above discussion indicates, there are a number of dimensions in which medication errors can be understood. First, errors can occur at various points in the medicines' pathway: at the stage of prescribing a medicine, in the transcription of an order (i.e. misreading or misinterpreting a prescription), in the pharmacy at the point of dispensing, during the delivery or administration of drugs, or in monitoring and checking the medication regime. The different pathway points also imply that a range of different practitioners are involved in the decision-making process. Second, at any given point in the medicines' pathway, different *error mechanisms* may be responsible for the resulting error; as described above, these may be deficits in knowledge (knowledge-based errors) or mistakes or lapses in the execution of tasks (action-based errors). Third, the resulting error itself may be one of a variety of *types*, including wrong drug, wrong dose, wrong frequency, wrong patient, wrong route. These three dimensions are illustrated in Figure 1.1. A full understanding of the nature of PME in relation to these three dimensions is essential in order to tackle the problem effectively. Knowing which pathway points and which mechanisms are most commonly associated with PME and which types of error occur most frequently enables targeting of finite resources to the greatest problem areas, such that the greatest benefit can be attained.

Given the plethora of potential problems, there is a clear need to gather robust evidence on the scale and nature of paediatric medication error and on innovative approaches to reduce these types of error among children and young people.

Figure 1.1: The dimensions of medication errors



1.3 Medication errors in children and young people: the policy context

There are moves within health service provision to improve the safety of medicines for children, with policies being introduced to encourage research into children's medicines. In 2002, the United States passed a bill known as the Best Pharmaceuticals for Children Act (US Congress 2002, US Congress 2007). This was followed in 2007 by the introduction of paediatric medication regulations in the European Union (European Union 2006, European Union 2006a).

Patient safety has long been a UK government priority; the National Patient Safety Agency (NPSA) was established in 2001 with a mandate to identify patient safety issues and find appropriate solutions. More recently, the UK Coalition Government published plans for reforming the NHS, *Equity and excellence: liberating the NHS* (Department of Health 2010). This document stresses the importance of improving safety within health service provision and included an outline of the three domains of the NHS Outcomes Framework, one of which focuses specifically on the safety of the treatment and care provided to patients. Later in 2010, the Government published a white paper, *Healthy lives, healthy people* (Department of Health 2010a), which set out the strategy for public health in England. This outlined approaches to 'giving children a healthy start in life and laying the groundwork for good health and wellbeing in later life'.

In 2012, patient safety became one of the Department of Health's priorities, as outlined in the Government's mandate to the NHS (Department of Health 2012), which focuses on the period from April 2013 to the end of March 2015. In a section entitled *Treating and caring for people in a safe environment and protecting them from avoidable harm* (p. 20), it states that there is a need to create systems to prevent error and harm and that there should be a culture of learning from patient safety incidents.

A new forum entitled the Children and Young People's Health Outcomes Forum (CYPHO) was established in January 2012, composed of child health experts with a shared commitment to improve children's and young people's health outcomes. On 19 February 2013, the Government published *Better health outcomes for children and young people: Our pledge* (Department of Health 2013). The pledge is to make five significant improvements for children and young people: reduce child deaths; prevent ill health and improve long-term health opportunities; improve mental health; support and protect the most vulnerable; and provide better care. Chaired by the Chief Medical Officer (CMO), the forum is to collaborate to achieve outcome improvements across the entire child healthcare system. The newly established NHS England aims to improve quality in patient care and outcomes. The NHS Outcomes Framework (Department of Health 2012a) includes Domain 5, patient safety. One of its priorities is the safe provision of care to children.

1.4 Existing research evidence

There has been extensive research effort in the field of paediatric medication error. Indeed, many of the potential risk factors have already been explored, or are being examined via systematic review. The extent of off-label and unlicensed medicine in the paediatric population has been explored (Padolfini and Bonati 2005) as has its association with adverse drug reactions (Mason et al. 2012). Recent systematic reviews have also examined the extent of medication error (Miller et al. 2007), dosing error (Wong et al. 2004) and the extent of medication error specific to paediatric emergencies (Kaufmann et al. 2012). Systematic reviews have also explored the efficacy of interventions to minimise medication error (Soe et al. 2013, van Rosse et al. 2009) and dosing error (Conroy et al. 2007).

Each of these reviews, however, focuses on a single aspect of the issue. By seeking and appraising empirical research on paediatric medication error across the *entire spectrum* of error types across the medicines' pathway, this review aims to provide a much broader

and more comprehensive picture of the problem and the potential solutions; indeed, many of the existing systematic reviews recommend such a course of action. Miller et al. (2007) conclude that understanding of the epidemiology of paediatric medication errors 'remains poor', and unequivocally state the need for greater understanding of all the aspects of medication errors. Likewise, Kauffman et al. (2012) recommend further 'intensive, coordinated research on this subject'.

2. Review questions and methods

Because systematic reviews use explicit and rigorous methods to synthesise evidence, their methods are necessarily described in some detail. This chapter provides a brief overview of the methods used to conduct the review in order to facilitate readability for those more concerned with the findings. A detailed and comprehensive account of the methods is provided in Part II of this report.

2.1 User involvement

We worked closely with the review commissioners throughout in order to ensure that the review is closely aligned with their needs and emerging programme. The review team itself includes members with pharmaceutical and/or medical expertise. Following publication of this report, other input may be sought by consulting relevant children and young people stakeholder groups on the findings, such as the Royal College of Paediatrics and Child Health (RCPCH) Youth Advisory Panel[1] and the Medicines for Children Research Network (MCRN) Young People's Panel.[2]

2.2 Review questions

This review was conducted in two stages. First, a systematic map describing the nature and breadth of research activity relating to paediatric medication error was generated. The initial question that this first stage aimed to answer is:

> What empirical evidence is available regarding the issue of medication error in children? (**Systematic descriptive map)**

The findings of the systematic descriptive map were shared with the review commissioners to support identification of priority questions for in-depth review. The second part of the work involved in-depth appraisal and synthesis of relevant subsets of research to answer the following questions:

> What is the nature and extent of PME in the UK? (**Extent synthesis)**
>
> Which interventions are effective for reducing the incidence of PME? **(Effectiveness synthesis)**
>
> What are the key features of effective interventions and how can they be successfully developed and implemented? **(Intervention features synthesis)**

2.3 Identifying studies

2.3.1 Searching for studies

A comprehensive and systematic search strategy was developed and a broad range of electronic databases in the fields of medicine, biomedicine and nursing, as well as in the social sciences and economics, were searched. Specialist research databases, topic-specific websites and Google Scholar were also searched. Key authors and others working in the field were contacted.

Electronic databases were searched using detailed strings of thesaurus and free-text terms for the three main concepts addressed in this review:

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[1] http://www.rcpch.ac.uk/what-we-do/children-and-young-peoples-participation/youth-advisory-panel/youth-advisory-panel

[2] http://www.mcrn.org.uk

- **Children** (example terms - neonates, infants, babies, toddlers, adolescents)
- **Medicines** (example terms – medicines, drugs, doses, prescriptions, pharmacy)
- **Error** (example terms - error, adverse events, risks, harms, safety)

Search strings for each of these concepts were combined such that the strategy identified research that focuses on children AND medicines AND error. An example of a search strategy is available in Appendix 1, which contains the details of one database search to illustrate the detailed and systematic approach used. A full list of the databases searched is available in Appendix 2.

2.3.2 Screening studies for relevance

Each paper identified in the searches was assessed for relevance. We sought evidence on PME relevant to current practices in the UK and reflecting recent technological and cultural changes within healthcare delivery. Thus, to be included in the systematic descriptive map, studies had to be:

- focused on medication error
- focused on children aged 0-12 years (or aged 0-18 years if specific to psycho-pharmaceuticals)
- empirical research
- published in or since 2003
- conducted in high-income countries or upper-middle-income countries
- published in the English language.

Additional criteria were applied to identify relevant studies for in-depth review. To be included in the **extent synthesis** on the nature and extent of error, studies had to:

- examine rates and types of error in UK settings
- be national-level evidence – i.e. report evidence on error rates/types for the whole of England, Wales, Scotland or Northern Ireland or for the UK as a whole.

For inclusion in the **effectiveness synthesis** on the effectiveness of interventions, studies had to:

- measure the impact of an intervention on outcomes relevant to PME (PME, ADE, mortality, turn-around times or medication knowledge)
- employ a rigorous research design involving the use of an appropriate control or comparison group i.e. randomised or non-randomised controlled trials.[3]

For inclusion in the **intervention features synthesis** on the content, development and implementation of interventions, studies had to:

- evaluate an intervention with strong and/or promising evidence of effectiveness as identified in the effectiveness synthesis.

The results of this screening process are illustrated in Figure 7.1 in Chapter 7.

2.4 Describing studies

To facilitate the identification of studies to review in depth, a standardised coding system was developed to capture the characteristics of all research papers included in the systematic descriptive map. Codes were developed to describe **key features** such as:

- the type of evidence examined (e.g. extent of errors, efficacy of interventions)

[3] Where no randomised controlled trials (RCTs) or non-randomised controlled trials (nRCTs) were identified in relation to a particular intervention type the latter inclusion criterion was relaxed to include studies employing an historical control (HCT) design (i.e. a less-robust study that compares a group of participants receiving an intervention with a similar group from the past who did not).

- the point(s) on the medicines' pathway that the research is concerned with (e.g. prescription, administration, dispensing, formulation, monitoring/checking)
- the types of error(s) that the research focuses on (e.g. wrong drug, wrong dose, wrong strength, wrong frequency, wrong time, wrong route)
- the outcomes reported (e.g. errors, adverse events, mortality)
- any specific issues related to PME risk (e.g. unlicensed medicines, off licence prescribing, manipulation of form, calculation of dose, patient/family adherence).

Other contextual features of the research were also captured to reveal the full nature of the evidence base and any gaps. Such features included the **research design** (e.g. survey, intervention evaluation, case report, cost analysis), the **country** in which the research was conducted, the **setting** (e.g. acute hospital emergency department, intensive care unit, GP practice, home) the **age** range of children, and whether there was a focus on particular **conditions** or **medicines**. The full coding framework is presented in Appendix 3.

2.5 Data extraction and quality appraisal

Data were extracted from studies meeting eligibility criteria for inclusion in the syntheses. Frameworks to extract relevant information were specifically designed for this review and a separate framework was tailored for each synthesis (extent, effectiveness and intervention features). Chapter 7 in Part II of this report provides further details on these coding frameworks. In addition, bespoke quality appraisal tools were developed to appraise the risk of bias of evidence for each of the syntheses. For the extent and effectiveness syntheses, studies were assigned a risk of bias (RoB) rating based on both the robustness of the research design employed and whether the study was executed soundly (e.g. sampling methods and measurement of variables where appropriate). Further details of these methods are provided in Chapter 7.

2.6 Quality assurance

Studies were screened independently by two reviewers at both the title/abstract and full-text screening stages in order to identify potential differences in interpretation of the criteria and refine guidance for reviewers. Screening was conducted by single reviewers once an agreement rate of 90% was achieved.

For each included study, data extraction and quality appraisal was undertaken by two reviewers, who first worked independently and then compared their work to reach a consensus.

2.7 Synthesis methods

All syntheses are comprised of a narrative summary of evidence alongside representation of key evidence in a tabular format. For the extent synthesis, findings were grouped according to error types (e.g. dose errors) and pathway points (e.g. prescription errors, administration errors). For the effectiveness and intervention features syntheses, findings were grouped according to intervention type (e.g. electronic prescribing). In addition to the narrative summary for the effectiveness synthesis, effect-size estimates were calculated (where studies reported sufficient information) to indicate a) whether the intervention reduced errors or not; and b) the scale of any impact (Cooper et al. 2009). The overall strength of conclusions for the extent and effectiveness syntheses was based on an assessment of the risk of bias for each study and the sufficiency and consistency of the overall evidence base (See Chapter 7 for details).

Evidence was rated as:

- **strong** where evidence met the criterion for consistency and comprised four or more studies with low or moderate risk of bias

- **promising** where evidence met the criterion for consistency and was available from less than four but more than one study with low or moderate risk of bias
- **tentative** where evidence was available from only a single study with low or moderate risk of bias
- **inconclusive** where evidence was only available from studies with a high risk of bias.

3. Extent synthesis: what is the nature and extent of PME in the UK?

This chapter draws on evidence from 11 studies that examine national data sets to assess the nature and extent of PME in the UK. The characteristics of the included studies are described in Section 3.1; the findings on the nature and extent of PME in the UK are presented in Section 3.2.

3.1 Description of included studies

- National-level data were available from **11 UK studies.**
- Five studies examined evidence from **error reporting systems**; six studies identified errors from **prescribing data.**
- Five studies examined errors occurring primarily in **acute care settings**, four examined errors occurring in **primary care settings**, and in two studies, the care setting was not specified.
- The **majority** of studies examined PME in relation to a **single drug**; just three examined evidence across a **broad range of drugs**.
- In terms of the **medicines pathway**, the majority of studies included evidence on **prescribing errors**; six studies focused exclusively on prescribing errors, one focused on administration errors, one on preparation errors, and three did not report the pathway point.
- In terms of **error types**, **dose errors** were those most commonly examined (n=10); fewer studies (n=5) examined other error types, with little comparability across studies.

Comprehensive systematic identification of research for the overarching review resulted in the detection of eleven studies examining UK national datasets about the extent of medication errors in children (Bateman and Donyai 2010, Ekins-Daukes et al. 2003, 2004, Elkout et al. 2009, Grover et al. 2008, Kazouini et al. 2011, MacLennan and Smith 2011, National Patient Safety Agency 2008, 2009, Riordan et al. 2009, Rosario 2013). The following sections describe the characteristics of these studies; an overview of their key features is provided in Table 3.2. A more detailed table of their characteristics and findings can be found in Appendix 4, along with structured summaries of each study.

3.1.1 Data sources

Voluntary error reporting schemes (n=5)

Five studies analysed data from voluntary error reporting schemes**.** Four drew evidence from the **National Reporting and Learning System** for England and Wales (MacLennan and Smith 2011, National Patient Safety Agency 2008, 2009, Rosario 2013); the fifth took data from the UK **National Aseptic Error Reporting Scheme** (Bateman and Donyai 2010).

Prescription data (n=6)

Six studies identified errors from prescribing data. One collected **survey data** on prescribing practices from **neonatal pharmacists** in neonatal units in the UK (Grover et al. 2008). The other five studies used a method of prescription review; two drew data from the **General Practice Administration System for Scotland (GPASS)** (Ekins-Daukes et al. 2003, 2004), two examined GP prescribing data via the **Scottish Practice Team Information (PTI) database** (Elkout et al. 2009, Kazouini et al. 2011) and one reviewed prescriptions for tenofovir disoproxil fumarate (TDF) through the UK and Ireland based **Collaborative HIV Paediatric Study (CHIPS)** (Riordan et al. 2009).

3.1.2 Study overlap

Although many of the studies draw from the same reporting schemes or databases, all either assess evidence on a different time period, or they assess a different drug type, such that there is little or no overlap between the studies. Table 3.1 provides an overview. The greatest overlap appears to occur between the dataset examined in Ekins-Daukes et al. (2003) and that examined in Ekins-Daukes et al. (2004), as both studies used prescribing data from GPASS for the same period. Whilst the 2004 study which covers all drug types, will undoubtedly include the data on antibiotics that the 2003 study specifically focuses on, both the overview across drug types and the detail on antibiotics were felt to be valuable to an understanding of rates and types of PME in the UK.

Table 3.1 Overlap between studies drawing from the same data sources

Data set	Studies using database	Time period	Drug types
National Reporting and Learning System (NRLS)	MacLennan and Smith (2011)	Jan 2006 - Dec 2008	Anaesthesia
	National Patient Safety Agency (2008)	Jan 2007 - Dec 2007	Vaccination
	National Patient Safety Agency (2009)	Oct 2007 - Sept 2008	All
	Rosario (2013)	Oct 2009 - Sept 2012	All
General Practice Administration System for Scotland (GPASS)	Ekins-Daukes et al. (2003)	Nov 1999 - Oct 2000	Antibiotics
	Ekins-Daukes et al. (2004)	Nov 1999 - Oct 2000	All
Scottish Practice Team Information (PTI) database	Elkout et al. (2009)	Sep 2001 – Aug 2006	Inhaled steroids
	Kazouini et al. (2011)	Jan 2006 – Dec 2006	Paracetamol

3.1.3 Drug types examined

Three studies examined errors across a range of drugs or drug classes (Ekins-Daukes et al. 2004, National Patient Safety Agency 2009, Rosario 2013). Two reports examined medication incidents in relation to **any/all medication** types (National Patient Safety Agency 2009, Rosario 2013) and one examined prescribing data relating to **215 medicines** representing 94 per cent of all medicines prescribed to 0-16 year olds (Ekins-Daukes et al. 2004).

The remaining eight studies examined error in relation to a single drug or drug class. Evidence pertaining to eight specific drug types was identified including: **antibiotics** (Ekins-Daukes et al. 2003), **anaesthesia** (MacLennan and Smith 2011), **cytotoxic paediatric injections** (Bateman and Donyai 2010), **parenteral nutrition** (Bateman and Donyai 2010, Grover et al. 2008), **inhaled corticosteroids** (Elkout et al. 2009), **paracetamol** (Kazouini et al. 2011), the **antiretroviral** tenofovir disoproxil fumarate (Riordan et al. 2009) and **vaccines** (National Patient Safety Agency 2008).

3.1.4 Populations examined

Care settings

Three studies focused exclusively upon **acute care settings**: UK hospital pharmacies (Bateman and Donyai 2010), hospitals in England and Wales (MacLennan and Smith 2011) and tertiary neonatal units in England, Scotland and Wales (Grover et al. 2008). Two studies drawing on NPSA data for England and Wales covered multiple care settings but

found that the vast majority of data derived from acute care settings (NSPA 2009, Rosario 2013).

Four studies focused exclusively on **primary care settings,** all of which were general practices in Scotland (Ekins-Daukes et al. 2003, 2004, Elkout 2010, Kazouini et al. 2011).

The care setting was **unspecified** in the study on vaccines (National Patient Safety Agency 2008) and the study on the antiretroviral drug tenofovir disoproxil fumarate (Riordan et al. 2009).

Age range of children

One study examined errors among **neonates** between one and ten days old (Grover et al. 2008). All other studies examined a **broad age range of children**; a range which often exceeded the criterion of 0-12 years set for this review (see Chapters 2 and 7 for details). Where age groups were further broken down (e.g. 0-4 years, 5-11 years, 12-16 years) we have focused on data for the age groups within the 0-12 year range. Details of the age range for each study are presented in Table 3.2.

3.1.5 Nature of errors examined: pathway points and error types

The **most common pathway point** examined among the studies was **prescribing**: six studies focused exclusively on prescribing errors. One study examined administration errors exclusively (National Patient Safety Agency 2008), one examined preparation errors (Bateman and Donyai 2010) and one study examined multiple pathway points (MacLennan and Smith 2011). The remaining two studies did not specify or were unclear about which pathway points they examined (National Patient Safety Agency 2009, Rosario 2013).

The **most common type of error** examined across the studies was **dose errors**: 10 of the 11 studies provide evidence on dose errors, of which six focused exclusively on dose errors and four on a range of error types.

In total five studies examined multiple error types. Two that examined NRLS data (National Patient Safety Agency 2009, Rosario 2013) categorised errors as the following: wrong dose/strength of drug, wrong frequency, wrong drug and omitted medicine/ingredient. One study focusing on vaccine administration (National Patient Safety Agency 2008) categorised errors as the following: wrong drug (vaccine), documentation errors, and wrong time (delayed administration). One study (Bateman and Donyai 2010) specified a range of categories that conflated error types and pathway points: transcribing; monitoring/checking; miscalculation; wrong drug; wrong diluent; wrong dose/strength; expiry date; labelling. The study by MacLennan and Smith (2011) principally presented data on pathway points and did not provide comprehensive figures according to error types, although they did specify figures for some error types within administration errors, including duplicated dose and a category combining wrong dose, wrong drug and wrong route errors.

3.1.6 Study size and unit of analysis

Studies examining **error reporting scheme** data reported findings on numbers of **'incidents'**, i.e. errors; those examining **prescription data** largely reported data in relation to numbers of **children provided with a prescription**. It is difficult to compare study sizes because of this difference in the unit of analysis; the prescription review data covers prescriptions both with and without errors, whereas the error reporting scheme data relates only to instances of error. Moreover, many of the prescription review studies examine evidence from a stratified sample of the overall population of, for example, GP practices; the error reporting schemes typically examine incident data from the entire population. However, as Table 3.2 illustrates, there are some distinct differences in the sizes of studies that relate to the type of data, the range of drugs or the specific drug examined.

3.1.7 Risk of bias

None of the included studies were found to have a high risk of bias. Six studies were found to have a low risk of bias (Ekins-Daukes et al. 2003, 2004, Elkout et al. 2009, Grover et al. 2008, Kazouini et al. 2011, Riordan et al. 2009). Five were assessed as having a moderate risk of bias (Bateman and Donyai 2010, MacLennan and Smith 2011, National Patient Safety Agency 2008, 2009, Rosario 2013); in each case, the risk of bias was introduced by the use of passive surveillance study designs (i.e. voluntary reporting). A description of the methods for rating the risk of bias of studies can be found in Chapter 7.

Table 3.2: Comparison of key features of studies examining UK types/rates of error

Study	Setting and data collection					Nature of data		
	Country	Setting	Age group	Data collection	Sample size	Pathway point	Error type	Drug type(s)
Bateman and Donyai (2010)	UK	Hospital pharmacies	Not Specified	Voluntary reporting	313 incidents	Preparation	Multiple	Cytotoxic injections Parenteral nutrition
Ekins-Daukes et al. (2003)	Scotland	Primary care	0-16 years	Prescription review	23,911 children	Prescription	Dose	Antibiotics
Ekins-Daukes et al. (2004)	Scotland	Primary care	0-16 years	Prescription review	167,865 children	Prescription	Dose	Any medication
Elkout et al. (2009)	Scotland	Primary care	0-18 years	Prescription review	7,092 children	Prescription	Dose	Inhaled corticosteroid
Grover et al. (2008)	UK	Acute care	Neonates	Pharmacist survey	48 neonatal units	Prescription	Dose	Parenteral nutrition
Kazouini et al. (2011)	Scotland	Primary care	0-12 years	Prescription review	2,761 children	Prescription	Dose	Paracetamol
MacLennan and Smith (2011)	England, Wales	Acute care	0-16 years	Voluntary reporting	216 incidents	Prescription Preparation Administration	Multiple	Anaesthesia
National Patient Safety Agency (2008)	England, Wales	Not stated	0-17 years	Voluntary reporting	138 incidents	Administration	Multiple	Vaccines
National Patient Safety Agency (2009)	England, Wales	Acute care	0-17 years	Voluntary reporting	61,336 incidents	Not stated	Multiple	Any medication
Riordan et al. (2009)	UK	Not stated	0-15 years	Hospital data	159 children	Prescription	Dose	Antiretroviral
Rosario (2013)	England, Wales	Acute care	0-17 years	Voluntary reporting	45,252 incidents	Not stated	Multiple	Any medication

3.2 Evidence on the extent and types of PME in the UK

This section examines the findings of the 11 studies in relation to the extent and types of PME in the UK. A summary of the findings presented in this section is provided in Table 3.3. The in-depth assessment of evidence which follows examines the findings in relation to dose errors and other error types. As noted in Section 3.1, dose errors were the most commonly examined type of errors in the studies (n=10 studies); evidence on this is presented in Section 3.2.1 below. Section 3.2.2 examines the much smaller proportion of evidence (n=5 studies) which relates to other error types.

Table 3.3 Section 3.2 summary: extent and types of PME in the UK

Error type	Pathway point	Details	Overall strength of evidence
Dose errors (n=10 studies)	Prescription	Underdosing and overdosing common in primary care in relation to a wide range of drugs	Strong
	Unspecified	Dose errors are the most common type of medication error in acute care settings	Promising
	Administration	Almost half of anaesthesia medication incidents are 'double doses'	Tentative
	Preparation	Only a small proportion of potential preparation errors in parenteral nutrition and chemotherapy are dose errors	Tentative
Other error types (n=5 studies)	Unspecified	Common non-dose errors in acute care are omitted medicine/ingredient, wrong frequency, wrong quantity and wrong drug	Promising
	Prescription	Ten per cent of anaesthesia medication errors are prescription errors but it is unclear what types of errors are involved	Tentative
	Administration	Almost half of vaccine administration errors are wrong vaccine Though less common than dose errors, anaesthesia administration errors involving the wrong drug and the wrong route are common	Tentative
	Preparation	Labelling and transcription are the most common potential errors in the preparation of chemotherapy and parenteral nutrition	Tentative

3.2.1 Dose errors

- **Ten studies** report evidence in relation to the extent and nature of dose errors.
- **Strong** evidence indicates that in **primary care** settings, **off-label prescribing** is a **common practice** resulting in dose errors in relation to a wide range of drugs, including antibiotics and paracetamol; the type of drug and the age of the patient affect whether underdoses or overdoses are more likely to be prescribed.
- **Promising** evidence suggests that in **acute care** settings dose errors are the **most common type**, accounting for approximately **one-fifth of all medication errors**.

- **Tentative** evidence suggests that almost half of **anaesthesia administration** incidents are due to **'double doses'** being administered.

Of the ten studies with evidence on dose errors, six focused exclusively on this, specifically in relation to prescription. The remaining four studies examined a range of errors, including dose errors; one study focused on dose errors relating to administration, another focused on preparation errors, whilst the remaining two did not specify the pathway points they examined.

Evidence on prescription dose errors

Six studies assessed prescribing data to determine the extent and nature of **overdoses** (higher than the recommended dose) or **underdoses** (lower than the recommended dose) prescribed to children (Ekins-Daukes et al. 2003, 2004, Elkout et al. 2009, Grover et al. 2008, Kazouini et al. 2011, Riordan et al. 2009). Prescriptions that were identified as contravening current guidance (e.g. British National Formulary for Children (BNFc), Summary of Product Characteristics (SPC)) were classified as **'off-label' prescriptions**. It is unclear whether all such instances relate to error; off-label prescriptions may have been intentional in some cases. However, the study constituting the broadest examination of off-label prescribing (Ekins-Daukes et al. 2004) concluded that underdoses and overdoses were primarily errors and that such errors accounted for the majority of off-label prescribing among Scottish GP practices:

> Despite the widely held belief that off-label prescribing occurs because of insufficient clinical trials data, our results suggest that this only accounts for 15–25% of all off-label prescribing. The main cause of off-label prescribing appears to be a failure to adhere to licensed dose recommendations (Ekins-Daukes et al. 2004, p. 352-353)

Extent of off-label prescribing

All six prescription dose studies indicated that off-label prescribing of medicines for children was a **common practice**; it was possible to draw a strong conclusion regarding off-label prescribing in primary care since four of the six studies focused on this setting (Ekins-Daukes et al. 2003, 2004, Elkout et al. 2009, Kazouini et al. 2011).

Ekins-Daukes et al. (2004) examined rates of off-label prescribing for a broad range of drugs, finding that at least one off-label prescription was issued to over a **quarter of all children** aged 0-16 years (n = 17,715, 26%). When comparing rates of off-label prescriptions for different drug types they found that antibiotics were the drug type most frequently prescribed off-label (26%) followed by antihistamines (12%). Other studies focusing on specific drugs reported high rates of off-label prescribing within specific drug types including: inhaled corticosteroids (16%) (Elkout et al. 2009), paracetamol (18%) (Kazouini et al. 2011), parenteral nutrition (46%) (Grover et al. 2008) and tenofovir disoproxil fumarate (55%) (Riordan et al. 2009).

Extent of prescription underdosing and overdosing

One study (Ekins-Daukes et al. 2004) examined the types of off-label prescriptions across a range of drug types. The authors reported that **lower than the recommended dose** was the most common form of off-label prescribing across all drug types, constituting 39 per cent of off-label prescriptions among children aged 0-4 years, and 52 per cent among children aged 5-11 years. Off-label prescribing due to **higher than the recommended dose** was also common, accounting for approximately one third of all off label prescriptions among both younger and older children (38% and 32% respectively). Other types of off-label prescribing, prescribing drugs licensed for use only with adults to children and prescribing a drug via a non-recommended formulation, constituted much

smaller overall proportions). However, these types of off-label prescribing are presumed to be intentional rather than errors and so they are not discussed further.

The following sections present evidence on the nature of over- and underdosing, in particular in relation to associations with different drug types and different age groups. Table 3.4 summarises this evidence.

Table 3.4: Drugs and age groups associated with prescription underdosing and overdosing in children

Prescription dose error type	Associated drug types (age groups)	Evidence base
Underdose	Antibiotics (all age groups 0-12)	Ekins-Daukes et al. 2003, 2004
	Antihistamines (all age groups 0-12)	Ekins-Daukes et al. 2004
	Parenteral nutrition (neonates)	Grover et al. 2008
	Paracetamol (6-12 years)	Ekins-Daukes et al. 2004 Kazouini et al. 2011
	Tenofovir disoproxil fumarate (TDF) antiretroviral (children <10)	Riordan et al. 2009
Overdose	Inhaled corticosteroids	Ekins-Daukes et al. 2004 Elkout et al. 2009
	Topical corticosteroids (all age groups)	Ekins-Daukes et al. 2004
	Laxatives (all age groups)	Ekins-Daukes et al. 2004
	Paracetamol (0-3 months)	Ekins-Daukes et al. 2004 Kazouini et al. 2011
	Tenofovir disoproxil fumarate (TDF) antiretroviral (children >10)	Riordan et al. 2009

Drugs associated with prescription underdoses

Underdosing of **antibiotics** appears to be common. Ekins-Daukes et al. (2003) reported that almost a fifth of children prescribed antibiotics (19%, n= 4,582) were prescribed an underdose; overdoses of antibiotics were prescribed much less frequently (<2% across all age groups). The risk of being prescribed an underdose of antibiotics was found to increase with age: the proportion of children prescribed an underdose almost doubled between the 0-4 year age group and the 5-11 year age group, from 12 per cent in the former to 19 per cent in the latter group. Although outside the age range for this class of drug specified in the inclusion criteria, it is notable that the trend continued for children aged 12-16 years, almost trebling to 30 per cent (Ekins-Daukes et al. 2003). They conclude that off-label prescribing of antibiotics at less than the recommended dose occurs primarily as the result of a failure to increase antibiotic dosage with age in line with SPC recommendations; they recommend a uniform approach to age banding for antibiotic dose increments to facilitate compliance with recommendations.

Grover et al. (2008) examined **parenteral nutrition** (PN) prescription practices in 48 neonatal units, comparing them to European Society for Clinical Nutrition and Metabolism

(ESPEN) recommendations. The study found that current practice leads to significant underdosing and nutrient deficits in very low birth weight infants in early postnatal life: in comparison to recommended intake of calories and amino acids, the current median prescription would result in a cumulative underdose over the first 10 days of 420 kcal/kg and 11.9 g/kg, respectively. In particular, the study found that units were slow to start PN and followed a slow path to achieving full PN, which resulted in overall nutritional deficits; only half of the units (54%) initiated PN on day 1 of life as recommended by ESPEN. The authors concluded that there was a 'huge gap between current understanding and current practice' (Grover et al. 2008, p.143).

Drugs associated with the prescription of overdoses

Ekins-Daukes et al. (2004) identified **inhaled corticosteroids (ICS)**, **topical corticosteroids** and **laxatives** to be the drugs most commonly associated with overdosing for children (0-16 years). The authors concluded that such overdoses were probably the result of different recommendations in different guidelines, and suggested that agreement between different sets of guidelines was essential to avoid confusion. Elkout et al. (2010) also reported evidence on ICS, finding that the majority of off-label ICS prescriptions were due to the prescription of an overdose (65%, n=638 children).

Drugs associated with underdosing and overdosing depending on age group

Kazouini and colleagues (2011) found that in relation to **paracetamol**, the type of deviation, underdosing or overdosing, was significantly associated with age (p. <0.0001). Paracetamol prescriptions recommending an overdose were most likely among the youngest age group (1-3 months); this amounted to over one-fifth of children of this age (22%). In contrast, paracetamol prescriptions recommending an underdose were most likely in the oldest age group (6-12 years); this amounted to nearly one-fifth of these children (19%). Ekins-Daukes et al. (2004) found that among all off-label prescriptions of paracetamol for children under five, 84 per cent were for overdoses; the figure rose to 93 per cent among children under three months. The problem is much less significant for children aged five to 11 years: the study reports that paracetamol is not even among the ten most commonly prescribed off-label drugs for this age group. The authors concluded that it was likely that higher than recommended doses were prescribed in the very young because of the lack of a suitable formulation strength for children under 3 months.

Similar findings were found on the antiretroviral drug **tenofovir disoproxil fumarate** (TDF) in the study by Riordan et al. (2009). The authors found that with only adult dose TDF tablets being available, considerable amounts of both prescription underdosing and overdosing occurred: 37% (n=14) children not taking the maximum once-daily adult dose of 300 mg were first dosed at less than 80% of the suggested dose, and 18% (n=23) received in excess of 120% of the suggested dose. The study identified a gradual decline in dose by weight as age increased, with a slight jump from lower to higher dose by weight at approximately 10 years of age, when many children increased from a half-tablet to a full tablet per day. The authors concluded that prescriptions deviating from the recommended TDF dose were probably caused by the fact that the only formulation is an adult tablet. This information suggests that administration errors may well also be a problem for this drug, since for many children, the tablet will need to be cut in half.

Evidence on administration dose errors

Just one study provides evidence on administration dose errors. MacLennan and Smith (2011) examined data on 216 medication errors relating to **anaesthesia**. The study found that over three-quarters of errors were identified as administration incidents (n=176, 77%), of which almost half were due to an unintentional additional dose of medication being administered (n=77, 44% of administration errors). Double dosing often occurred as a result of medications and fluids prescriptions being recorded in more than one place (e.g. prescription chart and an anaesthetic chart). The authors also reported that approximately one quarter of administration incidents related to either wrong drug, wrong

dose or wrong route errors (n=40, 23%), but did not specify what proportion of this group of errors related to wrong dose errors.

Evidence on preparation dose errors

One study examined errors associated with the preparation of aseptic injectables **parenteral nutrition** and **chemotherapy** for both adults and children (Bateman and Donyai 2010). The authors noted that only half of one per cent of all errors (in relation to both paediatric and adult medicines) actually reached the patient (0.48%, n=24). In relation to paediatric drugs specifically, the authors reported that dose errors accounted for just a small proportion of potential errors in relation to parenteral nutrition preparations (7%, n=12) and chemotherapy preparations (8%, n=10). The authors did not specify whether any of these potential paediatric dose errors actually reached the patient.

Dose errors with unclear or unspecified pathway points

Two large studies examining the prevalence of different error types among children and neonates in acute care settings identified dose errors to be the most common type, accounting for approximately one fifth of all errors (National Patient Safety Agency 2009, Rosario 2013). The studies, which both drew data from the NRLS reporting system but for different time periods, indicated that there was little change over time, with dose errors remaining the most common type between 2007 and 2012. Both studies identified that neonates were slightly less likely to be affected by dose errors than paediatric patients; in the earlier study, errors recorded as incorrect dose/strength constituted 23 per cent of medication incidents in children and 18 per cent of medication incidents in neonates (National Patient Safety Agency 2008); in the later study, the proportions were 20 per cent and 16 per cent respectively (Rosario 2013).

3.2.2 Errors other than dose errors

- Five studies examine errors other than dose errors; the smaller number of studies and a lack of consistency across them in terms of the other error types reported preclude the identification of strong findings.
- Promising evidence suggests that after dose errors, the next most common types of error in acute care are omitted medicine/ingredient, wrong frequency, wrong quantity and wrong drug.
- Tentative evidence suggests that:
  - following dose errors, the next most common administration errors in relation to **anaesthesia** were wrong drug and wrong route errors. 10% of anaesthesia-related errors were prescription errors, but it was unclear what types of prescription errors were involved.
  - almost half of errors relating to **vaccine** administration were due to administration of the wrong vaccine.
  - in relation to the preparation of **paediatric chemotherapy** and **parenteral nutrition**, mislabelled products and transcription errors were some of the most common potential errors.

Just five studies examined errors other than dose errors (Bateman and Donyai 2010, MacLennan and Smith 2011, National Patient Safety Agency 2008, 2009, Rosario 2013). Moreover, as described in Section 3.1.5, there was a lack of consistency across the studies in terms of the other error types reported. Thus comparison or aggregation of the evidence relating to errors other than dose errors is difficult and precludes the possibility of identifying strong findings (i.e. those supported by a large number of studies).

Non-dose prescription errors

Just one study, MacLennan and Smith (2011), provided evidence about other error types specifically related to prescribing anaesthesia. The authors reported that of 216 **anaesthesia** medication incidents, just 22 (10%) were prescription errors. However, the authors did not specify the types of prescribing errors committed. It is likely that dose errors accounted for at least some portion of the 22 prescription errors, but as the error type is unspecified, this evidence is reported as non-dose error evidence.

Non-dose administration errors

Evidence on non-dose administration errors is available from two studies. One study examining administration errors relating to **vaccinations** found that administration of the **wrong vaccine** accounted for almost half of errors (42.8% n=59). The next most common error types were **documentation error** (27.5% n=38) and **delayed vaccination** (12.3% n=17) (National Patient Safety Agency 2008). Dose errors were not reported in this study. The authors concluded that as vaccination incidents most commonly involve an incorrect vaccination being given to the patient, these could be prevented through improving systems for checking patient records to ensure the patient has not already been given the intended vaccination and recording administered vaccinations more consistently in patient records.

As noted above in relation to dose errors, MacLennan and Smith (2011) found that the vast majority of **anaesthesia** medication incidents related to administration errors. Whilst approximately half of these administration errors related to dose errors, the authors also noted that **wrong drug** and **wrong route** errors also occurred frequently, though they did not quantify the extent of these.

Non-dose preparation errors

The study by Bateman and Donyai (2010) found that by far the largest proportion of preparation errors in relation to paediatric **chemotherapy** (n=129) related to mislabelled products (44%, n=57). Errors in relation to expiry date (10.1%) and transcription (8.5%) were the next most common types. All three types accounted for larger proportions than dose errors (see above). Errors relating to calculation, wrong drug, wrong diluent and final volume each accounted for less than the proportion of dose errors (approximately 3% of the total or less). Similarly, of 184 errors relating to **paediatric PN**, most were categorised as 'other' (n=41, 22.3%), followed by transcription error (n=35, 19%), wrong drug error (n=23, 12.5%) and labelling error (n=21, 11.4%). Calculation errors and wrong final volume were also responsible for significant proportions of errors, each accounting for approximately 10% of PN preparation errors. All of the aforementioned error types accounted for greater proportions than PN dose errors. Few errors were reported in relation to wrong diluent, wrong container and incorrect expiry date, with each accounting for less than 5% of errors.

Non-dose errors with unclear or unspecified pathway points

As noted above, the two studies examining NRLS data to identify multiple error types across unspecified pathway points (National Patient Safety Agency 2009, Rosario 2013) established that dose errors were the most common type reported in acute care settings. However, both studies also reported that other types accounted for significant portions of overall errors. There was little change in the proportions of these other error types over the two time periods examined in the studies (2007-2008, National Patient Safety Agency 2009; 2009-2012, Rosario 2013). In both studies, omitted medicine or ingredient was the most common type of error after dose errors among both neonates (18% in both studies) and children (10% and 12%); the next most common types of incident for both age groups in both studies were wrong frequency (8-12%), wrong quantity (4-8%) and wrong drug (4-7%). It should be noted that in both studies, the error type of almost a quarter of errors (24%) was unspecified.

3.2.3 Strengths and weaknesses of the evidence base on the extent and types of PME in the UK

Five of the 11 data sets included here derived their data from voluntary error reporting schemes: four from the NRLS and one from the National Aseptic Error Reporting Scheme. A voluntary method of reporting errors may skew or bias the evidence such that it is not representative. It may be that certain types of error are under-reported or indeed unreported; for example, minor errors may go unreported such that the results overestimate the proportion of major or more serious errors, or vice versa. MacLennan and Smith (2011) note that under-reporting is common due to a perceived lack of ownership of reporting systems, lack of feedback, lack of time and fear of blame (despite NRLS reports being anonymous). The accumulation of international research indicating significant under-reporting of patient safety incidents is also remarked upon in the National Patient Safety Agency (2009) report, and in particular, significant under-reporting to the NRLS from primary care settings. So, despite being a valuable means of identifying errors, voluntary error reporting systems cannot be regarded as giving an accurate picture of the rate or type of incidents occurring within healthcare settings.

Synthesis of the evidence on errors other than dose errors was made difficult by a lack of comparability of error types examined across the studies. A lack of agreed definitions for error types was also noted as a weakness within individual studies. MacLennan and Smith (2011) noted that, in many reports, sufficient detail was lacking for a full understanding of what had happened. In another study, almost one-third of vaccination incidents were found to have been misclassified (National Patient Safety Agency 2008). Though many studies examined dose errors, one study noted that even this error type was plagued by a lack of agreed definition observing that there was 'often overlap and miscoding within the categories "wrong dose or strength", "wrong frequency" and "wrong quantity"' (National Patient Safety Agency 2009). Bateman and Donyai (2010) noted the overuse of the 'other' category, which was also seen as common in other studies (National Patient Safety Agency 2009, Rosario 2013). Unless the lack of consistency in terms of the way PME is defined and recorded is tackled at a national level, it seems unlikely that an accurate and comprehensive picture of the issue will ever be possible.

Lack of reporting and narrow coverage in relation to the medicines' pathway was another weakness of the evidence. Unfortunately, most of the included studies focused only upon a single point in the pathway (e.g. prescribing or administering medicine) and others covering multiple pathway points did not categorise errors in this way. We were therefore unable to examine at which points in the pathway medication errors are most prevalent.

However, despite the lack of a fully comprehensive and accurate picture, the findings do reveal that PME, particularly in relation to dose errors occurring in both primary and acute care settings, is a problem in the UK. It is suggested that the failure to adhere to licensed dose recommendations may be due to the complexity of age- and weight-based calculations (National Patient Safety Agency 2009), confusion resulting from variations in formulations and guidelines (Ekins-Daukes et al. 2004) and the lack of appropriate formulations for children (Ekins-Daukes et al. 2004, National Patient Safety Agency 2009, Riordan et al. 2010). The following chapter examines the efficacy of interventions for addressing some of these complexities.

4. Effectiveness synthesis: which interventions are effective for reducing the incidence of PME?

This chapter brings together the findings of 37 trials that tested whether interventions were effective for reducing the incidence of PME and other related outcomes.

The first section (4.1) provides an overview of the 37 studies in terms of the types of interventions they tested, the outcomes they measured and their quality. The second section (4.2) opens with a brief summary of the evidence on effectiveness across all intervention types. This is followed by sections with detailed information on the efficacy of each intervention type for which multiple studies were identified, including electronic prescribing (4.2.1), clinical decision support tools (4.2.2) and education interventions (4.2.3). The last section (4.2.4) examines six interventions, for each of which only a single study was identified.

4.1 Description of included studies

- 37 studies evaluating the impact of nine intervention types were included.
- Most studies examined impact on PME; fewer studies examined adverse events, mortality, turn-around times or medication knowledge.
- A range of different trial designs were used; most studies (n=25) were found to have a low risk of bias.

4.1.1 Interventions

Multiple studies were identified for each of three intervention types: Electronic Prescribing (EP) (n=20), clinical decision support tools (CDSTs) (n=5), and education interventions (n=6). Only a single study was identified in relation to each of the remaining six intervention types: paediatric formulations, integrated care pathways (ICP), ward-based pharmacist support, pre-printed structured prescription forms, technology to support parent involvement in patient history taking and a medication labelling intervention. Most interventions were delivered to healthcare professionals, whilst some were designed for and delivered to carers. Many interventions targeted errors occurring at a single pathway point, typically the prescription or administration stage, although some were designed to target other types of error or multiple errors across the pathway. Table 4.1 lists and summarises the extent and nature of evidence relating to each intervention type

Table 4.1: Overview of different intervention types examined in included studies

Intervention	Description	Delivered to	Pathway point
Electronic Prescribing (EP) (n=20)	Electronic prescribing software, typically with on-line decision support (n=18) and safeguarding features (n=16).	Healthcare professionals	Prescription
Clinical Decision Support Tools (CDST) (n=5)	Hand-held devices (n=2), colour-coded tools (n=2), or computer-based decision support (n=1).	Carers Healthcare professionals	Multiple points
Educational interventions	Training for carers on use of pictographic tools for dosing (n=3), or prescribing education	Carers Healthcare	Administration Prescription

Intervention	Description	Delivered to	Pathway point
(n=6)	for clinicians (n=3).	professionals	
Pharmacist support (n=1)	Pharmacists based on clinical units to provide advice to physicians.	Healthcare professionals	Multiple points
Standardised paediatric formulation (n=1)	Comparison of vials with a standardised paediatric concentration to adult vials.	Healthcare professionals	Administration
Structured prescription order forms (n=1)	Structured prescription form requiring specification of dose, weight-adjusted dose, total daily dose, route and frequency.	Healthcare professionals	Prescription
Integrated care pathways (n=1)	Nursing, medical, clinical observation and prescribing charts combined in single document.	Healthcare professionals	Multiple points
Mass concentration labelling (n=1)	Compared performance with drugs labelled 1mg in 1 mL or 1 mL of 1:1000 in a scenario of a child with acute anaphylaxis.	Healthcare professionals	Administration
Patient history taking software (n=1)	Information technology intervention enabling parents to input information via computer to improve the quality of information available to physicians before they prescribe.	Carers	Prescription

4.1.2 Outcomes

Five outcome types relating to PME were measured across the studies; these are illustrated in Table 4.2. Further detail on developing definitions and categorising study outcomes is available in Chapter 7.

Table 4.2: Outcomes measured in the effectiveness studies

Term	Definition used for this review
Adverse Drug Event (ADE)	Actual harm resulting from medication error
Medication knowledge	Relevant medical knowledge (e.g. about appropriate dosing regimens, preparation and storage of medicines)
Mortality	Death rates - not necessarily explicitly connected with errors
Paediatric medication error (PME)	Errors administered but where any harmful impacts of errors were not reported OR errors were detected before drug administration
Turn-around times	The time taken to prescribe, transcribe, dispense, administer or check medicine (e.g. time taken to calculate correct dose)

4.1.3 Context and setting

Just over half of the studies (n=19) were conducted in the USA; seven studies were UK-based. Other studies were from Canada (n=4), Israel (n=2), Belgium (n=1), Greece (n=1), Iran (n=1), The Netherlands (n=1) and Taiwan (n=1).

The vast majority of studies examined interventions designed to address errors occurring in acute care hospitals (n=33); the remainder (n=4) were designed to tackle errors occurring in the home. Among the 33 hospital-based studies, implementation of some interventions occurred in specific acute settings, including intensive care (NICU or PICU) (n=12) and emergency departments (n=7). Other interventions were implemented in multiple paediatric wards either in a general hospital setting (n=7) or in children's hospitals (n=6). In one hospital study, the implementation setting was unclear.

4.1.4 Research design and quality

Approximately two-thirds of the included studies (n=25) were rated as having a moderate or low risk of bias. A range of different trial designs were used, including:

- 12 RCTs, of which 10 were sound
- 6 nRCTs, of which 4 were sound
- 19 HCTs, of which 11 were sound (electronic prescribing synthesis only).

Two studies employed a 'passive' system of surveillance (i.e. error reporting systems) to identify errors (King et al. 2003, Upperman et al. 2005); the remainder (n=35) employed more robust 'active' surveillance systems, either observation of practice or patient outcomes, or prescription or chart review. The studies were typically large, although sample sizes varied; 13 studies had sample sizes greater than 1,000. The largest study was Vardi et al. (2007), which examined over 60,000 prescription orders; the next largest was King et al. (2003), which examined records for 17,485 patients. One study (Upperman et al. 2005) did not report the sample size. Sample sizes for each study are reported in Appendices 4 to 7.

4.2 Evidence on the efficacy of interventions

A summary of the evidence for all interventions and outcomes is provided in Table 4.3. The in-depth assessment of evidence for each intervention type which follows includes detailed information on the findings of each individual study and overall conclusions. For individual studies, we report the direction of evidence (i.e. whether errors or ADEs were reduced or not) and, where available, the size of effect (i.e. by how much they were reduced). We do indicate, where reported, whether the findings of individual studies reached statistical significance or not; however, the direction of effect was our chief consideration in interpreting the findings, since those not reaching statistical significance may have been insufficiently powered to detect a small but operationally significant effect. Assessment of the overall strength of evidence is based on the extent, quality and consistency of the evidence for each intervention type, as described in Chapter 7.

Table 4.3: Interventions to reduce PME: Overview of evidence from included studies

Intervention	Outcomes measured	Overall direction of evidence	Overall strength of evidence
Electronic prescribing (EP)	PME	Positive impact	Strong
	ADE	Positive impact	Strong
	Mortality	Positive impact	Strong
	Turn-around times	Positive impact	Promising
Education	PME	Positive impact	Promising
	Knowledge	Positive impact	Promising
Clinical decision support tools (CDSTs)	PME	Positive impact	Promising
	Turn-around times	Positive impact	Promising
Structured order forms	PME	Positive impact	Tentative
Integrated care pathways	PME	Positive impact	Tentative
Mass concentration labelling	PME	Positive impact	Tentative
	Turn-around times	Positive impact	Tentative
Standardised paediatric formulation	PME	Positive impact	Tentative
Patient history taking software	PME	Positive impact	Tentative
Pharmacist support	PME	Positive impact	Inconclusive

4.2.1 Effectiveness of EP interventions

- **20 trials** of EP interventions were identified.
- We found strong evidence that EP reduces PME, mortality and ADE.
- We found promising evidence of reductions in turn-around times.

Description of EP studies

Interventions examined

The 20 trials all evaluated an intervention that involved entering and processing prescription orders via computer, as opposed to handwritten, paper-based orders. The interventions varied, however, in terms of the software packages used and in terms of additional features: typically interventions featured some level of decision support, such as structured order sets, and some safety features, such as error alerts. Although we use the term 'electronic prescribing' to refer to these systems, it should be noted that many of the studies refer to this technology as computerised physician order entry (CPOE). Table 4.4 provides an overview; a comprehensive account of the nature of individual EP interventions can be found in Chapter 5.

Table 4.4: Overview of EP systems evaluated

Study	Country	Software	Decision support	Safety features	Training provided?
Barnes (2009)	USA	EPIC system, DocConnect	Yes	Yes	Not stated
Cordero et al. (2004)	USA	Invision 24, Siemens	Yes	Yes	Yes
Del Beccaro et al. (2006)	USA	Cerner	Yes	Yes	Yes
Han et al. (2005)	USA	Cerner	Yes	Yes	Yes
Holdsworth et al. (2007)	USA	Eclipsys	Yes	Yes	'User acclimation'
Jani et al. (2010)	UK	JAC Computer Services	Yes	Yes	Not stated
Kadmon et al. (2009)	Israel	Metavision, iMDsoft	Yes	Yes	Not stated
Kazemi et al. (2011)	Iran	Sayan-HIS	Yes	Yes	Yes
Keene et al. (2007)	USA	PHAMIS LastWord	No	Yes	Yes
King et al. (2003)	Canada	Eclipsys	No	No	Not stated
Lehmann et al. (2004)	USA	Not stated – 'in-house'	Yes	Yes	Yes
Lehmann et al. (2006)	USA	Cold fusion	Yes	Yes	Yes
Maat et al. (2013)	The Netherlands	Not stated – 'in-house'	Yes	No	No
Potts et al. (2004)	USA	WizOrder	Yes	Yes	Yes
Sowan et al. (2010)	USA	Not stated – 'in-house'	Yes	No	Not stated
Sullins et al. (2012)	USA	Not stated	Not stated	No	Not stated
Upperman et al. (2005)	USA	Not stated	Yes	Yes	Yes
Vardi et al. (2007)	Israel	Visual Basic	Yes	Yes	Not stated
Walsh et al. (2008)	USA	Eclipsys	Yes	Yes	Yes
Warrick et al. (2011)	UK	Intellivue	Yes	No	No

Context and setting

Whilst eight of the EP studies were published in the last five years, some of the very earliest evaluations of the use of EP with children were included. Han et al. (2005) noted an aim to be amongst 'the first children's hospitals in the United States to attain 100% CPOE status' (Han et al. 2005, p. 1506).

Eleven of the EP systems were evaluated exclusively in intensive care units, either PICUs or NICUs (Barnes 2009, Cordero et al. 2004, Del Beccaro et al. 2006, Kadmon et al. 2009, Keene et al. 2007, Lehmann et al. 2004, Maat et al. 2013, Potts et al. 2004, Sowan et al. 2010, Vardi et al. 2007, Warrick et al. 2011); the remainder were evaluated across a variety of wards in children's hospitals or in general paediatric or neonatal wards. Four studies evaluated the efficacy of EP exclusively with neonatal patients (Cordero et al. 2004, Kazemi et al. 2011, Lehmann et al. 2004, Maat et al. 2013), and a further two examined the use of EP with both neonatal and paediatric patients (Keene et al. 2007, Walsh et al. 2008). Five focused on specific types of drugs or procedures, including parenteral nutrition (Lehmann et al. 2004), continuous intravenous infusions (Lehmann et al. 2006, Sowan et al. 2010) glucose control in neonates (Maat et al. 2013) and resuscitation medications (Vardi et al. 2007).

Study design and quality

EP was the only intervention type for which we relaxed the criterion about study design to include HCTs, since no RCTs or nRCTs on EP were initially identified. During the analysis phase, however, one EP study (King et al. 2003) which described itself as an HCT was actually identified by reviewers to be a nRCT, but since we had initiated analysis of these studies, we continued with the inclusion of HCTs on EP.

As described in Chapter 7, sound studies employing an HCT design were assessed as having a moderate risk of bias. The evidence base for EP therefore comprises:

- 1 sound nRCT with a low risk of bias (King et al. 2003)
- 11 sound HCT studies with a moderate risk of bias (Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Holdsworth et al. 2007, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2006, Maat et al. 2013, Potts et al. 2004, Sowan et al. 2010, Walsh et al. 2008)
- 8 unsound HTC studies with a high risk of bias (Barnes 2009, Jani et al. 2010, Kadmon et al. 2009, Lehmann et al. 2004, Sullins et al. 2012, Upperman et al. 2005, Vardi et al. 2007, Warrick et al. 2011).

Findings of the EP studies

The findings in this section are grouped by outcome: PME, ADE, mortality and turn-around times. Overall, the studies indicate that EP is beneficial for all four outcomes examined, although evidence regarding PME, ADE and mortality is strongest.

Impact of EP on PME (n=15 studies)

Positive findings (n=13 studies)

Nine studies found EP to have a statistically significant impact on reducing PME (Cordero et al. 2004, Holdsworth et al. 2007, Jani et al. 2010, Kadmon et al. 2009, Kazemi et al. 2011, Lehmann et al. 2004, 2006, Potts et al. 2004, Vardi et al. 2007). A further four studies showed non-significant trends towards reduced PMEs (Barnes 2009, Sullins et al. 2012, Walsh et al. 2008, Warrick et al. 2011). Detail of the statistical findings for each study is presented in Appendix 5.

Negative findings (n=2 studies)

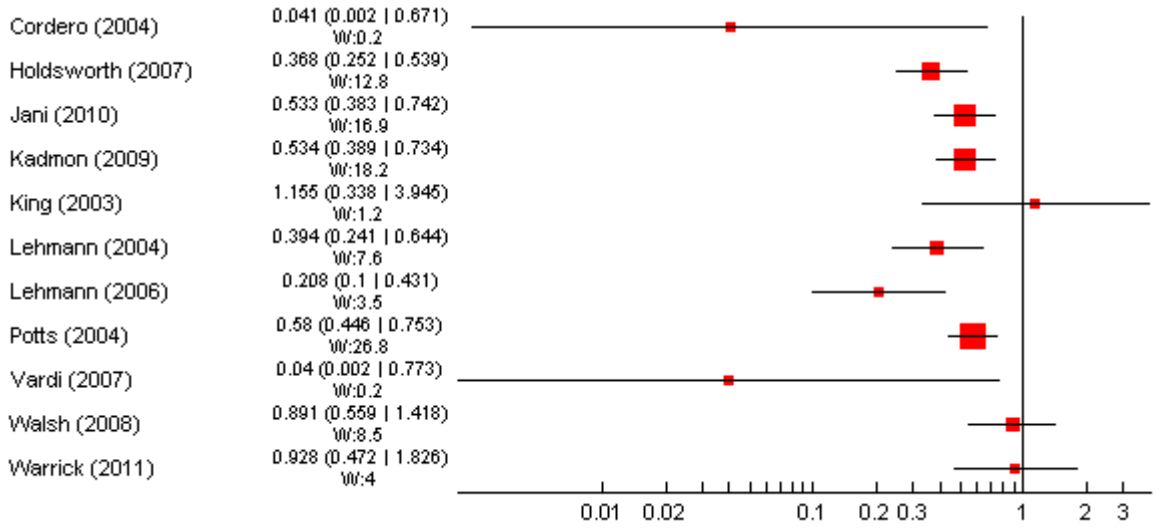
Two studies (neither of which had a high risk of bias) showed a slight non-significant trend towards *increased* PMEs (King et al. 2003, Sowan et al. 2010). Sowan et al. (2010) suggest that their negative finding may be due to a number of factors, including that: a) the EP approach was used inconsistently; b) the simulated test environment may have differed

from real-life conditions; c) users may revert to prior practices based on familiarity, thus negating the potential benefits offered by the new system (64% of nurses using EP used calculators as well); and d) nurses' limited experience with the relatively new pumps may have been the reason for errors (there were high rates of errors in both groups). The nRCT study by King et al. (2003) also found a slight non-significant post-EP increase in errors when examining prescription errors specifically (as opposed to all types of error) (RR 1.155, 95% CI 0.338–3.945). The authors of this study did not attempt to explain this finding, focusing on the significant reduction in overall error rates. Prescribing errors in this study are those most comparable to the measures used in other studies; however, it is notable that the number of prescribing errors as a proportion of total errors was very small, just 3%. The negative findings of this study may result from the nature of the EP package evaluated, as explained in Chapter 5.

Effect size estimates

Effect sizes were calculable for 11 of the 15 studies, and relate specifically to prescription errors. Directions of effect and individual study effect sizes with 95% confidence intervals can be seen in Figure 4.1. Given some distinct differences between the studies, such as the unit of analysis (i.e. orders, patients or drugs delivered), as well as the substantial level of statistical and clinical heterogeneity between the studies (I-squared = 57.2%), it was not appropriate to conduct a statistical meta-analysis to determine a pooled effect size estimate. However, the figure illustrates graphically how the vast majority of studies resulted in reductions in errors.

Figure 4.1: Forest plot showing effect size estimates (risk ratios) of prescription medication error and their confidence intervals for the 11 EP intervention studies with a calculable effect size for this outcome



Two studies that examined PME outcomes both immediately following implementation and at later time periods found greater effects at the later time periods (Lehmann et al. 2004; Warrick et al. 2011). (N.B. Figure 4.1 shows the outcomes for these studies measured immediately following implementation.) These findings support the findings regarding the development and implementation of EP interventions presented in Chapter 5, namely that familiarity with EP interventions is key to their successful application.

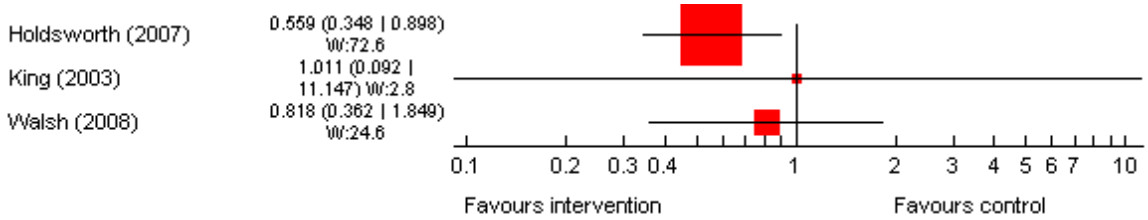
Impact of EP on ADE (n=6 studies)

Six studies measured the impact of EP on ADE. One study had a low risk of bias (King et al. 2003), three a moderate risk of bias (Holdsworth et al. 2007, Maat et al. 2013, and Walsh

et al. 2008) and two a high risk of bias (Jani et al. 2010, Upperman et al. 2005). Of the six studies, five showed reductions in ADEs; the sixth study demonstrated a non-significant increase in ADEs (King et al. 2003).

Effect size estimates were calculable for three studies with low risk of bias illustrated in Figure 4.2, one of which demonstrated a significant reduction in ADE post-EP implementation (Holdsworth et al. 2007), one a non-significant reduction (Walsh et al. 2008) and the third demonstrated a very small non-significant *increase* in ADEs after the implementation of EP (King et al. 2003). Because the unit of analysis was different for each of these studies – Holdsworth et al. (2007) examined ADEs per drug delivered, King et al. (2003) examined ADEs per patient and Walsh et al. (2008) examined rates per 1,000 days – the findings were not sufficiently comparable to conduct a statistical meta-analysis.

Figure 4.2: Forest plot showing effect sizes (risk ratios) of adverse drug events caused by PMEs and their confidence intervals for three EP intervention studies



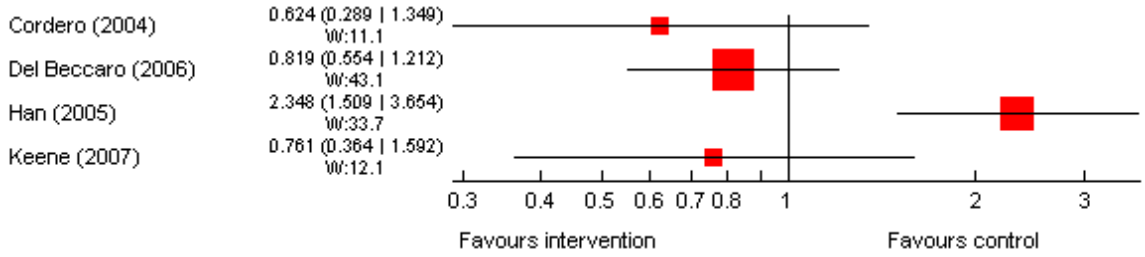
Of the remaining three studies examining ADE, one found a statistically significant reduction in ADEs and two found non-significant trends. Jani et al. (2010) found a significant reduction in minor and moderate ADE after the introduction of EP and a non-significant reduction in severe ADE (minor ADE reduced from 0.89% to 0.44% p<0.009, moderate ADE from 1.17% to 0.69% p<0.019, severe ADE from 0.18% to 0.06% p<0.11). Upperman et al. (2005) found a non-significant decrease in total ADEs post-EP implementation (reduction from 0.3 ± 0.04 per 1,000 doses pre-EP to 0.37 ± 0.05 per 1,000 doses post-EP p = 0.3) and a statistically significant decrease in harmful ADEs (pre-EP 0.05 ± 0.017 per 1,000 doses, post-EP 0.03 ± 0.003 per 1,000 doses p = 0.05). Upperman et al. (2005) also reported that their calculations demonstrated that EP would prevent one ADE every 64 (95% CI 25-100) patient days. The final study, Maat et al. (2013) found a very small non-significant decrease for both hypoglycaemias (reduction from 4.0 episodes per 100 patient days pre-EP [95% CI, 3.2-4.8] to 3.1 post-EP [95% CI, 2.7-3.5], p = 0.88) and hyperglycaemias (reduction from 6.0 episodes per 100 patient days pre-EP [95% CI, 4.3-7.7] to 5.0 post-EP [95% CI, 3.7-6.3] p = 0.75).

Impact of EP on mortality rates (n=4 studies)

Four studies, none of which had a high risk of bias, examined the impact of EP on mortality rates. These were all included in the meta-analysis conducted in the review by van Rosse (2009). Three of the four studies (Cordero et al. 2004, Del Beccaro et al. 2006, and Keene et al. 2007) identified non-significant reductions in mortality rates. The study by Han et al. (2005), however, identified a statistically significant *increase* in mortality in their study. The authors concluded that the finding may have been due to other factors, including the implementation of the EP system in the hospital and its suitability for PICU patients. Nevertheless they cautioned that 'when implementing EP systems, institutions should continue to evaluate mortality effects, in addition to medication error rates, for children who are dependent on time-sensitive therapies' (p. 1512). The deficiencies of the EP system evaluated by Han and colleagues are explored in more detail in Chapter 5.

We calculated effect size estimates for each of the four studies. Individual study effect sizes and 95% confidence intervals are presented in Figure 4.3. However, due to considerable statistical heterogeneity between the studies (I-squared = 81.8%), it was inappropriate to conduct meta-analysis to calculate a pooled statistic representing the weighted mean average across all studies. (The calculation of a pooled statistic for these four studies in the van Rosse systematic review appears to be in error as the I-squared statistic is reported as 0%.)

Figure 4.3: Forest plot showing effect sizes (risk ratios) for the four EP intervention studies measuring mortality



Impact of EP on turn-around times (n=4 studies)

Three studies with moderate risk of bias (Cordero et al. 2004, Maat et al. 2013, Sowan et al. 2010) and one study with high risk of bias (Vardi et al. 2007) examined the impact of EP on checking and delivering medicines; all found significant positive effects of EP on turn-around times. Cordero et al. (2004) reported statistically significant ($p < 0.01$) reductions in medication turn-around times post-EP implementation (pre-EP n=41, mean 10.5±9.8 SD hours, post-EP n=48, mean 2.8±3.3 SD hours). Maat et al. (2013) reported a significant reduction in prescribing times after EP implementation. They found a 16% time reduction (1.3 minutes 95% CI 0.3-2.3) for simple and 60% (8.6 minutes 95% CI 5.1-12.1) for complex calculations. Sowan et al. (2010) report a significant reduction in the time taken to check the accuracy of orders (EP orders 6 minutes 18 seconds ± 2 minutes 26 seconds; handwritten orders 8 minutes 47 seconds ± 3 minutes 6 seconds; $p < 0.0001$). Vardi et al. (2007) reported that time to completion of drug forms dropped from 14 minutes 42 s to 2 minutes 14 s ($p < 0.001$).

Overall conclusions on EP

PME: Despite being unable to calculate a pooled statistic representing the weighted mean average across all studies, there is ample evidence to conclude that EP is effective for reducing PME; there is both a high level of consistency in the direction of the findings (87% positive findings) and a sufficient number of studies with moderate or low risk of bias (n=8). Indeed, were we to focus only on those studies with moderate or low risk of bias, the level of consistency would still reach the 75% accepted threshold for strong findings. The findings thus meet the criteria for strong evidence.

ADE: The findings regarding ADE should also be considered strong: five of the six studies (83%) indicated reductions in ADEs, meaning that these findings meet the criterion for consistency, and four of the six studies were found to be sound meaning that they also meet the criterion for sufficiency. As noted above in relation to its negative impact on PME, the negative findings identified in the study by King et al. (2003) in relation to ADEs may be explained by deficiencies in the particular EP system evaluated. See Chapter 5 for further details.

Mortality: As the evidence base regarding mortality is comprised of four sound studies, of which three (75%) found consistent findings, the criteria for both consistency and sufficiency is met, so the findings regarding mortality can be considered strong.

Turn-around times: The direction of findings on turn-around times is positive across each of the studies (100% consistency); however, as one of the four studies has a high risk of bias, the criterion for sufficiency is not met. These findings should thus be regarded as 'promising' rather than strong. In addition, it should be noted that the four studies examined the impact of EP on turn-around times in relation to specific drugs and/or in relation to specific conditions, such that the findings may not be generalisable to general paediatric use.

Strengths and weaknesses of the evidence base on EP interventions

A key weakness of the evidence base regarding EP was the large proportion of studies with a high risk of bias (40%, n=8) and the paucity of studies with a low risk of bias (n=1). However, this weakness is mitigated by the large number of studies overall and the consistency of findings between those with a high risk of bias and those with a moderate or low risk, such that strong findings were available for three key outcomes (PME, ADE, mortality).

A second weakness was that differences between the studies meant that a pooled statistic was not calculable for any of the four outcomes examined. Greater consistency in the measurement and presentation of evidence regarding PME, ADE and turn-around times, including in relation to the unit of analysis (patients, orders, patient days, drugs delivered), would enable better comparison of effects across studies.

Gaps in the evidence base on EP interventions

A key gap in the evidence base is the lack of recent studies on mortality outcomes. No new studies published since the van Rosse et al. (2007) review were identified. Possibly this may represent a weakness in our search strategy, which focused on errors rather than mortality specifically, rather than a dearth of studies on this issue. Unless papers were explicit that they were investigating mortality rates in relation to medication error, they may not have been picked up by our searches, and indeed two of the studies in the van Rosse et al. (2007) review were not picked up by our searches. Further investigation of the link between EP and paediatric mortality may be warranted. A second potential gap is that there was little evidence regarding the persistence of effects of EP. Evidence examined for the intervention features synthesis (Chapter 5) indicates that greater reductions in PME may be achieved once users have had sufficient time to become familiar with the system and any initial glitches have been ironed out. Although this finding is concordant with evidence presented in this chapter, such evidence is limited; only two studies measured outcomes at multiple time points. Other studies which measured outcomes at a single time point conducted their assessments at different times, ranging from two months to two years after the intervention. Thus the collection of further evidence on the persistence of effect is warranted.

In conclusion, the findings regarding EP indicate that it does reduce rates of PME, ADE and mortality. Additionally, it may also have a beneficial impact on turn-around times, though the evidence for this last outcome is not conclusive. However, more robust study designs such as cluster-randomised controlled trials would greatly strengthen the evidence base.

4.2.2 Effectiveness of educational interventions

- **Six studies** evaluated the effectiveness of education and training in reducing PME.
- We found promising evidence that education interventions reduce PME and increase medication knowledge.

Description of education studies

Interventions examined

Two subgroups of interventions were evident in this dataset: those that targeted medication *administration* for parents and carers and those that targeted medication *prescription* for healthcare professionals (see Table 4.5). Further detail on the interventions and the differences between them is provided in Chapter 5.

Context and setting

One of the studies was conducted in the UK (Gordon et al. 2011); the others were conducted in the US (Frush et al. 2006; Yin et al. 2008; Yin et al. 2011), Canada (Kozer et al. 2006), and Taiwan (Hu et al. 2013).

Study design and quality

Four of the studies were RCTs (Frush et al. 2006, Gordon et al. 2011, Yin et al. 2008, Yin et al. 2011), two were nRCTs (Hu et al. 2013, Kozer et al. 2006); all but one (Kozer et al. 2006) were judged as having a low risk of bias.

Table 4.5: Overview of education systems evaluated

Pathway	Study	Type	Target	Content
Administering	Hu et al. (2013)	Pictographic materials + face-to-face	Parents/carers	Medication dosing education and pictographic educational sheet
	Yin et al. (2008)	Pictographic materials + face-to-face	Parents/carers	Dosing accuracy, knowledge, adherence
	Yin et al. (2011)	Pictographic materials only	Parents/carers	Written dosing instructions plus pictographic instructions
Prescribing	Frush et al. (2006)	Computer (web/online)	Advanced practice nurses, doctors and paramedics	Broselow Paediatric Emergency Tape use
	Gordon et al. (2011)	Computer (e-learning)	Junior doctors	Drug selection, prescription calculations, therapies, sources of error
	Kozer et al. (2006)	Taught	Junior doctors	Appropriate methods of prescription

Findings of the education studies

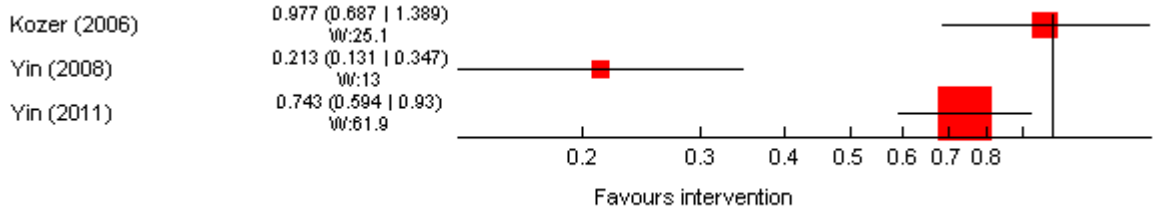
Impact of education interventions on PME (n=4 studies)

Four studies examined the impact of their intervention on PME (Frush et al. 2006, Kozer et al. 2006, Yin et al. 2008, 2011). Three of these (Kozer et al. 2006, Yin et al. 2008, 2011) could be translated into effect sizes, which are graphically displayed in Figure 4.4.

The direction of effects tends to favour the intervention group, although note the non-significant effect reported in the study by Kozer et al. (2006), which was assessed as having a high risk of bias. The other study that measured medication error not shown in

Figure 4.4 (Frush et al. 2006) did not report sufficient information from which to calculate an effect size, although it is noteworthy that the authors reported a significant effect in favour of the intervention.

Figure 4.4: Forest plot showing effect sizes (risk ratios) of medication error and their confidence intervals for the three education interventions studies for which medication error effect sizes could be calculated



Impact of education interventions on medication knowledge (n=3 studies)

Three studies reported an outcome relating to medication knowledge (Gordon et al. 2011, Hu et al. 2013, Yin et al. 2008). All three studies reported statistically significant effects in favour of the intervention. These could not be shown graphically because of the extreme outlier effect size for one of the studies (Hu et al. 2013).

Overall conclusions regarding education interventions

PME: Although the evidence meets the criterion for consistency (100% consistency), since one of the four studies had a high risk of bias, the criterion of sufficiency is not met and the findings must be regarded as promising rather than strong.

Medication knowledge: The criterion for consistency is again met (100% consistency), but since only three studies measured this outcome, the criterion for sufficiency is not. The findings on medication knowledge should also be regarded as promising.

Strengths and weaknesses of the evidence base on education interventions

Overall the evidence suggests that benefits may be gained from educational interventions but the evidence must be regarded as promising rather than strong. In terms of the strength of the evidence base five of six studies had low risk of bias, in terms of outcomes five of the six studies reported an effect that favoured the intervention condition. However, variance in the type of interventions evaluated and in the outcomes examined mean that the evidence regarding educational interventions cannot be regarded as strong.

A further weakness in the evidence base stems from the way in which effectiveness was measured in these studies. Four of the studies (Frush et al. 2006, Gordon et al. 2011, Hu et al. 2013, Yin et al. 2011) used simulated or artificial scenarios to test errors or medication knowledge. Although this is appropriate given the context of the particular interventions, we cannot be certain that improvements under simulated or test-based conditions would reflect actual reductions in error in practice.

Gaps in the evidence base on education interventions

The studies are all focused on either the prescribing or administering stage of the medication pathway. There are therefore substantial gaps in our knowledge about whether education interventions might work to improve errors at different points in the pathway.

The studies tended to focus on either junior/trainee physicians or parents and caregivers. Apart from Frush et al. (2006), which delivered the intervention to emergency providers (nurses, physicians and paramedics), there is no evidence on the effectiveness of

continuing professional development or training for fully qualified or more established health professionals.

Moreover, the variety of characteristics of the interventions included in this review make it difficult to draw conclusions about specific features of interventions that work. For instance, although it appears that face-to-face combined with pictographic modes works well with parents and caregivers, what works best for health professionals? These issues are explored further in Chapter 5.

Finally, further gaps relate to the evaluation of the interventions. First, do education interventions reduce harmful outcomes such as ADEs and mortality? Second, are the effects of the interventions long-lasting? Only one study conducted a follow-up assessment at three months after the intervention; they reported significant but reduced effects (Gordon et al. 2011). And third – as noted under the weaknesses section – do the medication knowledge and simulated error outcomes translate to real-world improvements in PMEs?

In conclusion, education interventions appear to be a promising way to tackle paediatric medication errors. However, little is known about what specific mechanisms work, for whom, and whether the effects are maintained.

4.2.3 Clinical decision support tools (CDSTs)

- **Five studies** evaluated the effectiveness of CDSTs.
- We found promising evidence that CDSTs reduce PME and turn-around times.

Description of CDST studies

Interventions examined

The five studies included in this synthesis were quite distinct and not directly comparable. Whilst three studies (Frush et al. 2004, Hixson et al. 2009, 2010) used some kind of hand-held device such as a colour-coded measuring tool for prescribing or determining doses, and related to analgesic medications, they differed in terms of who they were targeted at (caregivers or physicians) and the point in the medications pathway that was being addressed. The two computer-based interventions (Burgess 2009; Skouroliakou et al. 2005) were targeted at different participants (student nurses versus physicians), related to different medication types and focused on different points in the medications pathway (transcribing and administering versus prescribing and formulating). Table 4.6 shows these key differences. Chapter 5 explores the features of these interventions and the differences between them in more detail.

Table 4.6: Overview of CDST interventions

Study	Computerised intervention?	Targeted at	Medication type	Pathway point
Burgess (2009)	Yes	Student nurses	Various	Transcribing, administering
Frush et al. (2004)	No	Caregivers	Analgesic	Formulating, administering
Hixson et al. (2009)	No	Physicians	Analgesic	Prescribing
Hixson et al. (2010)	No	Caregivers	Analgesic	Administering
Skouroliakou et al. (2005)	Yes	Physicians	Parenteral nutrition	Prescribing, formulating

Context and setting

Two of these studies were conducted in the USA (Burgess 2009, Frush et al. 2004), two in the UK (Hixson et al. 2009, 2010) and one in Greece (Skouroliakou et al. 2005). Four were carried out in acute hospitals (Frush et al. 2004, Hixson et al. 2009, 2010, Skouroliakou et al. 2005) and one in the simulation laboratory at a nursing school (Burgess 2009).

Study design and quality

Three of the five studies were RCTs with a low risk of bias (Burgess 2009, Frush et al. 2004, Hixson et al 2009). Two studies were found to have a high risk of bias: one RCT (Hixson et al. 2010) and one nRCT (Skouroliakou et al. 2005).

Findings of CDST studies

Impact of CDSTs on PME (n=5 studies)

All five studies reported medication error outcomes and all demonstrated significantly lower error rates in the CDST intervention condition compared to a control condition. Two of the studies reported binary outcomes, and we therefore calculated risk ratios (RR) for these studies (Frush et al. 2004; Skouroliakou et al. 2005). A further two studies reported continuous data, so the effect size for these is the standardised mean difference, d (Burgess 2009; Hixson et al. 2009). One study (Hixson et al. 2010) did not report data that could be used to calculate an effect size. The results are presented below by outcome type: prescribing or administering error.

Prescribing error

The intervention reported in Skouroliakou et al. (2005), in which a computer program assisted in prescribing and formulating parenteral feeding, resulted in significantly fewer errors than prescriptions that were manually calculated by physicians and pharmacists (RR = 0.02, 95% CI 0.00-0.29). This effect represents a risk of committing an error that is two-hundredths of that in the control group, which is a very substantial reduction in risk (although note that this study was deemed to have a high risk of bias).

Hixson et al. (2009), a study with low risk of bias, also reported an effect favouring the intervention. By using the Paediatric Analgesia Wheel, caregivers committed fewer prescribing errors than those using the 2006 BNFC and a calculator (d = 2.90, 95% CI 2.10 to 3.69). This effect size estimate is considered to be very large.

Administering error

Burgess (2009) reported that the Color Coding Kids (CCK) computerised system was associated with a significantly lower administering error rate for student nurses, compared to usual practice (d = 0.87, 95% CI 0.37-1.37). This effect size estimate is considered to be large.

Frush et al. (2004) reported a significant decrease in the risk of dose determination (a type of administration error) in the intervention group, which used a colour-coded device, compared to controls (RR = 0.16, 95% CI 0.06 to 0.43); this effect is both large and statistically significant.

Although we could not calculate an effect size from Hixson et al. (2010), there was a clear, statistically significant ($p < 0.001$) difference in the absolute percentage dose error between the intervention and the control group, with a median error of 33.3% in the control condition and 0% when using the Parental Analgesia Slide intervention.

Impact of CDSTs on turn-around times (n=3 studies)

Two of three CDST studies measuring turn-around times reported significant decreases; the third reported a small non-significant trend.

Burgess's (2009) evaluation of the CCK system found a negligible non-significant reduction in turn-around times for the CDST group compared to the control group; mean turn-around time for the CDST group was 17.18 minutes, and for the control group was 17.65 minutes ($p = 0.72$).

In contrast, Hixson et al. (2009) reported that the mean time taken to complete the prescription chart was significantly shorter when using the Paediatric Analgesia Wheel (5.8 minutes) compared with the BNFC (12.4 minutes). Skouroliakou et al. (2005) also reported significant reductions for both physician's time spent on the prescription of the total parenteral nutrition (TPN) formula, and pharmacist's time spent on calculations. Furthermore, the average time taken to prepare the individual TPN solutions in the intervention was significantly shorter (5.2 minutes) compared to the manual preparation procedure (15.4 minutes).

Overall conclusions regarding CDSTs

PME: Although the studies all found a positive impact of CDSTs on PME such that the criterion for consistency is met (100% consistency), since two of the five studies were assessed as having a high risk of bias, the findings must be considered promising rather than strong.

Turn-around times: The findings meet the criterion for consistency (100%) but not sufficiency (i.e. there are fewer than four sound studies). However, since there is corroborative evidence from three studies, two of which had a low risk of bias, the findings should be considered promising. The substantial differences between the interventions in each of the studies should be noted when interpreting the overall findings.

Strengths and weaknesses of the evidence base on CDST interventions

The studies were mixed in terms of their individual risk of bias: three had a low risk and two had a high risk. However, all five studies were consistent in their direction of effect in favour of the intervention – with large or very large effect size estimates in relation to PME – which lends support to the conclusion that there is promising evidence that reductions in error and turn-around times will result from CDST interventions.

A weakness in the evidence base stems from the way in which effectiveness was measured in these studies. Only one of the five evaluations (Skouroliakou et al. 2005) was conducted under actual healthcare provision conditions; the remainder used simulated or artificial scenarios. Although this may be appropriate given the context of the particular interventions, we cannot be certain that improvements under simulated or test-based conditions would reflect actual reductions in error in practice.

The primary limitation of this evidence base, however, lies in its diversity. The studies were very distinct, covering a range of clinical decision support tool and system types (computerised or not), targeting a range of people (caregivers and practitioners), focused on a variety of medication types (mixed, analgesics or parenteral feeding), and intervening at different points in the medications pathway (transcribing, administering, formulating, and/or prescribing). This makes it difficult to draw conclusions about the relative effectiveness of any one particular CDST, and no clear recommendations can be made about which specific intervention options offer more potential than others. These issues are explored further in Chapter 5.

Gaps in the evidence base on CDST interventions

Given the diversity in the evidence base, there are many gaps. Firstly, there was no replication – no two studies explored the same intervention.

Secondly, the studies are all focused on either prescribing or administering errors. There are therefore substantial gaps in our knowledge about whether interventions might work to improve errors at different points in the pathway. We also do not have evidence about error-related harm outcomes, such as adverse drug events and mortality.

Thirdly, we do not know much about whether CDSTs can be used for various medication types. Three of the five studies (Frush et al. 2004, Hixson et al. 2009, 2010) examined CDSTs that were useful for certain analgesics, but even that group is quite differentiated

in terms of the targeted recipients (caregivers or physicians) and the point in the medication pathway that was addressed by the intervention.

Finally, further gaps relate to our understanding of the longevity of the CDST tool after the evaluation ends. In particular, do the CDSTs continue to be used effectively? In the case of handheld devices such as the Slide, do parents and caregivers continue to use these devices in the home setting? Do they continue to do so correctly when they are not monitored or have not received recent instruction on their use? In the case of computerised systems, are health professionals supported (e.g. with continuing professional development) to be able to effectively use the CDST long after the evaluation ends?

In conclusion, CDST interventions appear to be a promising way to tackle paediatric medication errors, whilst also reducing the time taken to prescribe or administer medications. However, more evidence is required to establish the key features of CDSTs, how effective they are in real-life settings and whether the CDST is used effective long after the evaluation finishes.

4.2.4 Other 'miscellaneous' interventions

- Six trials were identified which evaluate interventions that are not comparable with one another.
- Since criteria for sufficiency and consistency cannot be met, further evidence on each of these interventions is required.
- Reductions in PME were demonstrated in all six studies, five of which had low risk of bias, allowing us to draw **tentative conclusions** about paediatric formulations, integrated care pathways (ICP), structured prescription order forms, ParentLink computerised patient history taking and mass concentration labelling.
- Since the study on **ward-based pharmacist support** had a high risk of bias, **no conclusions** can be drawn regarding this intervention.

Description of 'miscellaneous' studies

Interventions examined

This section of the findings presents evidence on a range of miscellaneous interventions for which just a single randomised or non-randomised controlled trial was identified.

Allegaert et al. (2006) examined the introduction of a **paediatric vial to deliver a more appropriate concentration** of antibiotics for neonates, comparing it to standard adult vials. The introduction of the vial increased the average volume of drug required (based on mean birth weight and gestational age) from 0.088 ml of the adult vial to 0.44 ml of the paediatric vial. It was hypothesised that this increase in required volume would improve accuracy of dosing.

Cunningham et al. (2008) examined whether an integrated care pathway (ICP) could improve care delivered to paediatric patients. An ICP combines all nursing, medical, clinical observation and prescribing charts chronologically within a single document.

Kaushal et al. (2008) examined the impact of having **full- and part-time ward-based pharmacists** to support clinical teams through: the provision of information and advice to physicians; the facilitation of communication between the medical care team and the pharmacy; the provision of information on administration and monitoring to nurses; and monitoring of medication transcription, preparation, storage and distribution.

Kozer et al. (2005) evaluated the effectiveness of a **pre-printed structured prescription order sheet** compared to blank order sheets. The pre-printed sheet required staff to specify the dose, weight-adjusted dose, total daily dose, route of administration and frequency for each medication ordered.

Porter et al. (2008) evaluated the impact of a **computer programme, ParentLink, designed to collect patient histories from parents** as they waited in an emergency department to see a physician. The aim was to improve the quality of information available to physicians before ordering medications.

Wheeler et al. (2008) investigated whether **labelling drugs using mass concentration** (1 mg in 1 mL) rather than ratio concentration (1 mL of a 1:1000 solution) would improve physicians' accuracy of drug dosing and reduce the time taken to do the calculation during a simulated emergency scenario.

Context and setting

In terms of the medications pathway, the studies by Cunningham et al. (2008), Kozer et al. (2005) and Porter et al. (2008) addressed prescription, the studies by Allegaert et al. (2006) and Wheeler et al. (2008) addressed administration and the study by Kaushal et al. (2008) examined an intervention addressing multiple points on the pathway. Two studies were conducted in the UK, two in USA, one in Belgium and one in Canada. The majority of the studies were carried out in emergency settings (Cunningham et al. 2008, Kozer et al. 2005, Porter et al. 2008, Wheeler et al. 2008). Kaushal et al. (2008) worked in the PICU and on a general ward, whilst Allegaert et al. (2006) focused on care in a NICU.

Study design and quality

Four of the six studies were RCTs (Cunningham et al. 2008, Kozer et al. 2005, Wheeler et al. 2008, Kaushal et al. 2008), one of which was found to be not sound and therefore at high risk of bias (Kaushal et al. 2008). The remaining two studies were nRCTs; both were sound (Allegaert et al. 2006, Porter et al. 2008).

Findings of miscellaneous studies

Paediatric medication error (PME) (n=6 studies)

All six studies examined the impact of interventions on PME. Evidence on all six interventions indicated reductions in PME, five of which were studies with a low risk of bias.

Paediatric vials for antibiotic administration in neonates were found to reduce dose error when compared to adult vials (Allegaert et al. 2006). The authors found that 72% of drug concentrations were in the target zone with the paediatric vial compared to 58% with the adult vial. The authors of this study did not report whether this finding was statistically significant.

Integrated care pathways were found to significantly reduce prescribing errors by approximately 30% when compared to controls (ICP mean errors per patient = 10.4, control mean errors per patient =14.8, P=0.002) (Cunningham et al. 2008).

Full-time ward-based pharmacist support in a PICU was found to result in significantly fewer serious PMEs compared to a PICU without pharmacist support (30 fewer serious medication errors per 1000 patient days in intervention (IV) group compared to control (CT), p = 0.01) (Kaushal et al. 2008). However, the introduction of a part-time pharmacist on the general wards did not result in statistically significant differences compared to controls (PMEs per 1,000 patient days - surgical unit IV = 9, CT = 10, p = 0.89; medical unit IV = 9, CT = 8, p = 0.78). Moreover, this study was assessed as having a high risk of bias meaning that these findings must be regarded as inconclusive.

The use of pre-printed structured prescription order sheets was associated with a significant reduction in prescription errors compared to blank order sheets (odds ratio: 0.55; 95% confidence interval: 0.34-0.90) (Kozer et al. 2005).

The study by Porter et al. (2008) identified fewer PMEs in the group receiving the **ParentLink patient history taking intervention**; the findings were not statistically significant (rate of error per 100 patients in intervention group = 134 and in control group = 173, p = 0.35).

The use of **mass concentration labelling** was associated with significantly fewer medication errors than ratio concentration labelling (79% of providers in the mass concentration group calculated a dose within 10% of that recommended by the protocol, compared with 14% in the ratio group, p = 0.009, chi-square test) (Wheeler et al. 2008).

Turn-around times (n=1 study)

The study by Wheeler et al. (2008) found a significantly shorter median time taken to administer drugs for the mass concentration group compared to the ratio group (IV = 35.5 seconds - Interquartile range (IQR) 27.0 to 65.0 seconds, CT = 130.0 seconds – IQR 112.0 to 171.0 seconds, p ≤0.001).

Overall conclusions regarding miscellaneous interventions

PME: The majority of the individual studies had a low risk of bias; three were sound RCTs (Cunningham et al. 2008, Kozer et al. 2005, Wheeler et al. 2008) and a further two were sound nRCTs (Allegaert et al. 2006, Porter et al. 2008). However, since evidence on each intervention type comes from just one study, the criteria for sufficiency and consistency cannot be met. Thus, conclusions about the effectiveness of any of these interventions for reducing PME must be considered tentative (see Chapter 7 for the scoring system). One study was assessed as having a high risk of bias (Kaushal et al. 2008); the evidence regarding ward-based pharmacist support thus remains inconclusive.

Turn-around times: Tentative evidence indicates that mass concentration labelling may reduce turn-around times.

Strengths and weaknesses of the evidence base on miscellaneous interventions

Plainly, the major weakness relating to each of these interventions is the lack of corroborative evidence to enable identification of patterns in the evidence base or key characteristics of effective interventions. The studies did, however, employ robust research designs and were, with one exception, found to be sound.

Gaps in the evidence base on miscellaneous interventions

The positive findings from studies with low risk of bias on paediatric vials, integrated care pathways, structured pre-printed order sheets, ParentLink computerised patient history taking and mass concentration labelling indicate that these interventions could deliver potential benefits. Although we cannot draw firm conclusions about any of these interventions due to the lack of available evidence, the 'indicators' from these sound studies signify areas of practice that should be evaluated more thoroughly.

The complete lack of sound studies about ward-based pharmacist support is of greater concern. In our initial map, we identified 42 studies with information about pharmacist-support interventions, suggesting their interest to researchers and clinicians. However, given the current absence of any sound concurrently controlled trials, we did try to identify studies employing less rigorous study designs (i.e. HCTs) within our database but none were found.

Aside from the overall lack of evidence on each intervention type, within this set of studies there is also a dearth of evidence on key outcomes. None of these studies reported evidence regarding the impact of the interventions on ADEs or mortality and just one examined impact on turn-around times. It is particularly frustrating that some studies were explicit that they measured ADE but did not provide data on it separately from that on PME. Future research into interventions aiming to reduce medication error and any resulting harm should examine and report evidence on these key outcomes.

5. Intervention features synthesis: what are the key features of effective interventions and how can they be successfully developed and implemented?

The aim of this chapter is to support practical application of the evidence on effective interventions for reducing PME. It presents detailed information on intervention content and collates evidence on the experiences of users to illustrate what a successful intervention 'looks like', as well as effective approaches for development and implementation. This chapter focuses on interventions for which there was strong and/or promising evidence, namely EP, education and CDSTs. It provides:

- in-depth detail about the content of intervention packages
- evidence on the strengths and weaknesses of individual intervention features
- evidence on developing and implementing successful interventions.

Section 5.1 provides an in-depth analysis of the content, development and implementation of EP interventions, Section 5.2 focuses on CDSTs and Section 5.3 on education interventions. The section on EP is considerably more detailed than those on education interventions and CDSTs for a number of reasons. First, there are far more studies on EP. Second, there is more commonality between the features of each EP intervention than there is between each of the education or CDST interventions; thus a greater level of comparison is possible. Third, the education and CDST interventions are less complex in nature than EP, with fewer components. Fourth, the EP studies typically provided more extensive detail on interventions components and greater reflection on the impact of individual components than did the studies of the other intervention types.

Whilst the data contributing to this chapter are rich and illuminate the findings about the efficacy of interventions there are some significant weaknesses to this data which should be noted. First, the comprehensiveness and accuracy of evidence on the content of interventions is hampered by inconsistency in the level of detail provided by studies. Second, as we took a broader view of 'evidence' than is typical for systematic reviews, in examining authors' views about intervention content, implementation and development, the findings are susceptible to bias. Details of these weaknesses and approaches for mitigating them are described in Chapter 7.

5.1 E-prescribing

Whilst EP was the intervention for which we had the largest body of evidence, it was also the intervention with the greatest level of comparability across the studies. The 20 EP studies were all explicit that they evaluated an intervention for clinicians which involved entering and processing prescription orders via computer as opposed to handwritten paper-based prescriptions. However, there was an array of additional features which varied according to each individual package.

5.1.1 E-prescribing: intervention features

EP packages varied according to whether they:

- were 'off the peg', 'customised' or 'home-grown'
- were generic 'adult based' tools or specific to paediatrics
- included decision support tools (dose calculators, order sets, information access)
- incorporated safety features (alerts, mandatory fields, access security).

Table 5.1 gives an overview of the components featured in each EP package, and Appendix 9 provides additional detail. There appear to be some distinct differences between the sophistication and comprehensiveness of successful EP packages and unsuccessful ones, in

particular the Han et al. (2005) study, which found EP to result in significant increases in mortality, and the King et al. (2003) study which found non-significant negative findings.

'Off the peg', 'customised' and 'home-grown' EP systems

Four studies, evaluated 'off-the-peg' or unmodified commercially available packages (Han et al. 2005, Jani et al. 2010, King et al. 2003, Walsh et al. 2008), of which only one was specifically designed for use with children (Walsh et al. 2008). Eight studies evaluated commercially available packages that had been 'customised' to make them appropriate for use in a paediatric setting (Cordero et al. 2004, Del Beccaro et al. 2006, Holdsworth et al. 2007, Kadmon et al. 2009, Kazemi et al. 2011, Keene et al. 2007, Upperman et al. 2005, Warrick et al. 2011). Six studies evaluated bespoke or 'home grown' packages that were developed from scratch by staff in the hospitals in which they were evaluated (Lehmann et al. 2004, 2006, Maat et al. 2013, Potts et al. 2004, Sowan et al. 2010, Vardi et al. 2007); all except the intervention evaluated by Potts et al. (2004) were designed specifically for use with children. In two papers, details of the package evaluated were so scant that it was not possible to ascertain whether they were customised or developed specifically for use with children (Barnes 2009, Sullins et al. 2012).

Decision support

All but two of the studies described at least one element of decision support within the EP package they evaluated. Decision support was defined as 'front-end' features of the system (Wright et al. 2011) which are actively accessed and manipulated by the user to support decision making such as dose calculation, structured order sets and information access. Studies not describing decision support included Sullins et al. (2012), which provided no details of the EP package and Han et al. (2005) which showed increased mortalities following EP implementation. The study by King et al. (2003), which found non-significant increases in prescription errors, incorporated only minimal decision support in the form of access to laboratory results.

Dose calculation

Twelve EP studies described dose calculators as part of the EP system (Cordero et al. 2004, Holdsworth et al. 2007, Kazemi et al. 2011, Lehmann et al. 2004, 2006, Maat et al. 2013, Potts et al. 2004, Sowan et al. 2010, Upperman et al. 2005, Vardi et al. 2007, Walsh et al. 2008, Warrick et al. 2011). Typically, studies described the use of algorithms to automate dose calculation based on drug selection, age and weight. Dose calculators were also typically customisations of commercially available packages (n=4) or part of in-house developed packages (n=6).

Structured order sets

Twelve of the evaluated EP packages were described as incorporating rule-based order sets (Cordero et al. 2004, Del Beccaro et al. 2006, Holdsworth et al. 2007, Kadmon et al. 2009, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2004, 2006, Maat et al. 2013, Upperman et al. 2005, Walsh et al. 2008, Warrick et al. 2011). Studies described order sets as limiting user choices by enabling them to select options from various order menus and sub-menus appropriate to the drug selected. One study (Del Beccaro et al. 2006) described developing pre-programmed order sets for common scenarios, enabling users to select an entire 'sentence' incorporating all the necessary elements for an order; i.e. the prescriber was not required to select each element in serial fashion such as the dose, dose unit, route, frequency, etc. Holdsworth et al. (2007) described a system which used default doses for the most common indication for any particular drug. Order sets were most commonly described as customisations of EP systems (n=8) or part of in- house developed packages (n=3) requiring some significant investment of staff and time resources to develop.

Information access/interfacing with other departments

All but three of the studies (Han et al. 2005, Sullins et al. 2012, Walsh et al. 2008) described information access as a feature of the EP package they evaluated. Ten studies described access to an online formulary or some form of evidence database. Bidirectional information access between the prescriber and other departments to support decision making was even more common (n=12); studies particularly described interfacing with hospital laboratories (n=9) and pharmacies (n=6). Access to patient histories and/or medical records was another common source of information made available to support decision making (n=8). See Appendix 9 for details of information access types for each study.

System safeguards

System safeguards are defined as 'back-end' features of the system, or notifications which are triggered by the 'front-end' actions of the users (Wright et al. 2011). The most common safeguarding feature described was the use of alerts or warnings about potentially harmful scenarios (n=14). The next most commonly described were the use of mandatory fields (n=7) and access security (n=6). It is notable that two of the three studies with negative findings (King et al. 2003, Sowan et al. 2010) did not describe any system safeguard features. However, the study by Han et al. (2005), the only one showing statistically significant harm, described both alerts and mandatory fields as part of their system.

Alerts

Fourteen of the EP studies described some form of alert system as part of the package (Barnes 2009, Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Holdsworth et al. 2007, Jani et al. 2010, Kadmon et al. 2009, Kazemi et al. 2011, Lehmann et al. 2004, 2006, Potts et al. 2004, Upperman et al. 2005, Vardi et al. 2007, Walsh et al. 2008). Alerts were triggered for a variety of reasons, including: deviations from recommended dose limits (n=10), allergy checking (n=7), interactions with other prescribed drugs (n=5), interactions with findings from laboratory test results (n=3), age/weight ratio exceeding expected parameters (n=3), drug route restrictions (n=2), drug-food interactions (n=2), duplication (n=2) and other (n=5). Two studies were explicit that physicians were able to 'override' or 'ignore' system alerts (Han et al. 2005; Kazemi et al. 2011); other studies implied that it was possible to ignore warnings.

Mandatory fields

The use of mandatory fields, preventing prescribers from continuing with or submitting an order until all necessary fields were completed, was described in eight studies (Cordero et al. 2004, Han et al. 2005, Holdsworth et al. 2007, Jani et al. 2010, Kazemi et al. 2011, Lehmann et al. 2004, Upperman et al. 2005, Warrick et al. 2011).

Access security

Access security was the third most commonly described safeguarding feature of the EP interventions; it was described by 6 of the 20 studies. Del Beccaro et al. (2006) described the use of a 'secure web portal', two studies described the use of electronic signing (Kadmon et al. 2009, Keene et al. 2007) and the remaining three described systems which were password protected (Lehmann et al. 2004, Vardi et al. 2007, Walsh et al. 2008).

Other safeguarding features

Two studies described how rules were in place in their EP systems prohibiting prescription of medicines outside of the expected dose range (Kadmon et al. 2009) or infusion concentration range (Lehmann et al. 2006). Three studies described countersigning as a requirement for an order to be processed (Barnes 2009; Han et al. 2005; Kazemi et al. 2011). A further three described a function for reminders, e.g. to alert staff when drugs or tests were due.

Table 5.1: Features of EP interventions described by the studies (A shaded cell indicates this feature was present)

Study	Paediatric-specific tool	Decision support tools			Safeguarding features		
		Dose calculation	Order sets	Info access	Alerts	Mandatory fields	Access security
'Off the peg' commercially available packages							
Han et al. (2005)					■	■	
Jani et al. (2010)				■	■	■	
King et al. (2003)				■			
Walsh et al. (2008)	■	■	■		■		■
'Customised' commercially available packages							
Cordero et al. (2004)	■	■	■	■	■	■	
Del Beccaro et al. (2006)	■		■	■	■		■
Holdsworth et al. (2007)	■	■	■	■	■	■	
Kadmon et al. (2009)	■		■	■	■		■
Kazemi et al. (2011)	■	■	■	■	■	■	
Keene et al. (2007)	■		■	■			■
Upperman et al. (2005)	■	■	■	■	■	■	
Warrick et al. (2011)	■	■	■	■			
'Home grown' packages							
Lehmann et al. (2004)	■	■	■	■	■	■	■
Lehmann et al. (2006)	■	■	■	■	■		
Maat et al. (2013)	■	■	■	■			
Potts et al. (2004)		■		■	■		
Sowan et al. (2010)	■	■		■			

Study	Paediatric-specific tool	Decision support tools			Safeguarding features		
		Dose calculation	Order sets	Info access	Alerts	Mandatory fields	Access security
Vardi et al. (2007)	■	■		■	■		■
Unidentified package type							
Barnes (2009)				■	■		
Sullins et al. (2012)							

5.1.2 E-prescribing: strengths and weaknesses of intervention components

- A small number of studies (n=4) provide evidence on general acceptability, largely suggesting that users were satisfied with using EP.
- Three-quarters of the studies (n=15) suggest that decision support tools are useful for reducing error.
- Much less evidence is available on safeguarding features, although some studies (n=4) suggest that alerts can be beneficial but overuse may result in 'alert fatigue'.

Acceptability of EP

Three studies used formal research methods to assess the acceptability of EP packages; two of acceptability assessments were assessed as being of high quality (Lehmann et al. 2004, Sowan et al. 2010) and one as being of low quality (Keene et al. 2007).

The acceptability evidence reported by Keene et al. (2007) was assessed as being of low quality due to a lack of detail in reporting of methods for sampling, data collection and analysis. It also provided little detail regarding the findings of this process, reporting only that 'the system was perceived as cumbersome and non-intuitive' (Keene et al. 2007, p. 2).

The other two studies used Likert scales to assess acceptability. Sowan et al. (2010) reported users to be significantly more satisfied with EP than with handwritten orders. Lehmann et al. (2004) reported that users felt that, in comparison to handwritten orders, EP was easier to learn and to use, protected against errors, saved time, was helpful and constituted an improvement. Other data collected indicated that respondents were neutral when considering potential problems of EP, but disagreed that it caused 'data overload' (Lehmann et al. 2004). The authors reported that:

> Users of the system (including those who were involved only peripherally, e.g., nurses) were enthusiastic and supportive and compared it favourably with the previous paper-based system. (Lehman et al. 2004, p. 748)

Two studies also provided informal evidence about general acceptability, inferring that rates of voluntary uptake indicated acceptability (Lehmann et al. 2004, 2006).

> The tremendous prescriber acceptance for the calculator was reflected by the overwhelming percentage (88%) of infusion orders being calculator-generated during the initial voluntary use period. (Lehman et al. 2006, p. 228)

Decision support: strengths and weaknesses

- 15 studies which commented on the value of decision support within EP were united in the view that it contributes to error reductions.

- The Han et al. (2005) study, which showed significantly increased mortality, described no decision support features; none of the three studies with negative findings incorporated order sets in their EP system.
- Two studies which examined EP both with and without decision support found much greater effects after its addition.
- Automated decision-support features were responsible for introducing some new types of errors.

Just five of the 20 EP studies did not comment on decision support tools (Barnes 2009, Cordero et al. 2004, Keene et al. 2007, King et al. 2003, Sullins et al. 2012). Those that did were unanimous in the view that decision support components contributed to the success of EP; although some studies observed that automated decision support tools could also introduce new errors.

Some hypothesised that decision support contributed directly to reductions in errors:

> Similar findings may not be reproducible with commercially available CPOE systems with nominal decision support. It would seem logical that the less comprehensive the dosing decision support the less likely a CPOE system will have the ability to reduce preventable ADEs. (Holdsworth et al. 2007, p. 1064)

Jani et al. (2010) concluded that 'EP can reduce dosing errors, *even in the absence of dose-related advance clinical decision support'* but acknowledged that larger reductions in dose errors may be achieved with more extensive decision support (Jani et al. 2010, p. 339). Two studies examined the efficacy of EP with and without decision support; Kazemi et al. (2011) found beneficial effects only when decision support was incorporated and Kadmon et al. (2009) found much greater reductions in errors after decision support was added.

Some studies provided more specific commentary about the beneficial features of decision support. For example:

> The most important decision support modifications were likely the provision of pertinent patient demographic information during the ordering process, drug knowledge in order-detail screens, dosing recommendations, and notification to the pharmacy of discontinuation orders. (Holdsworth et al. 2007, p. 1064)

'Streamlining repetitive processes and simplifying complex ones' (Lehmann and Kim 2005, p. 511) through automation of tasks was seen as a major benefit of decision support. Order sets, a key automated feature, were seen as the likely EP component responsible for reducing turn-around times in four studies, three of which formally measured the impact of EP on turn-around times (Maat et al. 2013, Sowan et al. 2010, Vardi et al. 2007). The fourth study also found a reduction in turn-around times but based the following conclusion on informal observation:

> order sentences and code-set filters … dramatically reduced the time it takes a clinician to enter orders. (Del Beccaro et al. 2006, p. 294)

Conversely, the Han et al. (2005) study which evaluated a system without structured order sets suggested that EP increased the time required to complete an order:

> The physical process of entering stabilization orders often required an average of ten 'clicks' on the computer mouse per order, which translated to 1 to 2 minutes per single order as compared with a few seconds previously needed to place the same order by written form. (Han et al. 2005, p. 1508)

Error reduction was also hypothesised to result directly from structured order sets in one study for example:

> After the addition of CDSS tools that limited medication doses according to weight, the rate of prescription errors dropped significantly. (Kadmon et al. 2009, p. 938)

Five of the 12 studies that evaluated EP with dose calculators were explicit in their view that this feature enhanced error reduction (Holdsworth et al. 2007, Lehmann et al. 2004, 2006, Maat et al. 2013, Warrick et al. 2011). Other automated features regarded beneficial were automatic discontinuation of orders (Holdsworth et al. 2007) and automatic uploading of patients' date of birth from the hospital management system (Jani et al. 2010).

However, automated features of EP were also noted as introducing new problems:

> Physicians should be aware that the newly implemented computerized systems can themselves lead to new types of medication errors. (Kadmon et al. 2009, p. 939)

Two studies identified the introduction of minor errors, including prescriptions being signed off electronically by a nurse instead of a physician, which occurred when a physician entered an order whilst a nurse was signed on to a computer (Kadmon et al. 2009) and the creation of orders without an identification number (Lehman et al. 2004). Both of these more minor technical glitches were quickly identified and rectified.

Some more serious problems were also observed. The mis-selection from drop-down menus was one such potential problem, as observed in two studies. One study cited an example of incorrect frequency selection, twice a week instead of twice a day (Jani et al. 2010); another cited the mis-selection of an incorrect infusion rate (Warrick et al. 2011).

The study by Han et al. (2005) which observed increased mortalities following implementation of EP, also found some worrying problems as a result of automation:

> For example, it was discovered that with antibiotic administration, subsequent dosing schedules were not timed according to the time of initial dose administration but rather at predetermined default times. Hence, children sometimes received the first 2 doses of an antibiotic in an unacceptably brief time interval. At the back end of antibiotic administration, default 'stop order' mechanisms sometimes terminated standing antibiotic orders without physician notification or knowledge. (Han et al. 2005, p. 1511)

Safeguarding features: strengths and weaknesses

- Just four studies discussed the issue of error alerts, and reflections on other safeguarding features were even more scant.
- Alerts were viewed as beneficial for error reduction but authors warned against overuse, which was seen to result in 'alert fatigue'.
- Four authors expressed the view that improved legibility resulting from EP was a key factor in reducing errors.

The most common reflections on safeguarding features were in relation to system alerts. The authors of four EP studies were of the view that system alerts were beneficial (Barnes 2009; Kazemi et al. 2011; Upperman et al. 2005; Warrick et al. 2011). However, three of these studies explicitly advised against the overuse of alerts to avoid 'alert fatigue' among users causing them to disregard warnings (Barnes 2009; Kazemi et al. 2011; Upperman et al. 2005). In an additional paper concerning the study by Upperman et al. (2005) the authors reported that:

> Good rules fire occasionally, under appropriate circumstances, and when there is the greatest potential for impact on patient treatment. (Upperman et al. 2005a, p. e638)

Suggestions for avoiding alert fatigue included providing explanations with alerts (Barnes 2009, Kazemi et al. 2011) or demonstrating the impact of the rules which fire alerts (Upperman et al. 2005a):

> A warning without any explanation is probably effective when an obvious mathematical calculation occurs. However, for the other causes of errors, the method of calculation and the reason that the warning was appeared should be demonstrated to increase physician's compliance. (Kazemi et al. 2011, p. 34)

Discussion of other safeguarding features was scarce, although a related issue was the improved legibility afforded by EP. Four studies expressly regarded improved legibility and completeness of orders following the implementation of EP to be responsible for the reduction in errors and improved turn-around times seen in their studies (Jani et al. 2010, Kadmon et al. 2009, Sowan et al. 2010, Warrick et al. 2011):

> The reason for the decrease in MPEs after implementation of CPOE is obvious: computerized orders cannot be illegible or incomplete. (Kadmon et al. 2009, p. 938)

5.1.3 E-prescribing: development and implementation

In addition to appraising the content of intervention packages, authors also commented on procedures to enhance the development and implementation of successful packages. Indeed the importance of development and implementation issues was emphasised in particular by the negative findings of the Han et al. (2005) study which were attributed by several authors to implementation issues rather than EP per se. Five major themes emerged from the studies which related to barriers and facilitators of EP development and implementation. The themes and how they relate to each other are illustrated in Figure 5.1.

Theme 1: Customisation is essential

- 14 of the 20 EP studies recommended developing customised EP systems or warned against the use of generic 'off the peg' tools.
- Two of the three studies with negative findings evaluated 'off the peg' interventions.
- Customisation was seen as vital when using EP with child patients and children in critical or intensive care.
- Though seen as an essential process, customisation was felt to be challenging and resource-intensive.

A very common theme across the studies was the need to customise generic EP systems to render them suitable for use with particular patient groups.

Seven authors postulated that the success of EP in reducing error in their study was in part due to having a bespoke patient-appropriate tool (Del Beccaro et al. 2006; Holdsworth et al. 2007; Kadmon et al. 2009; Keene et al. 2007; Maat et al. 2013; Upperman et al. 2005; Warwick et al. 2011). A further seven concluded that additional customisation of the system they evaluated would probably increase efficacy in the setting in which it was employed (Cordero et al. 2004, Han et al. 2005, Jani et al. 2010, Kazemi et al. 2011, Potts et al. 2004, Vardi et al. 2007, Walsh et al. 2008).

Paediatric appropriate tools, for example with decision support regarding age- and weight-based dosing, were discussed in twelve studies. Seven authors claimed that the success of their EP system was related to it being adapted for use with children (Del Beccaro et al. 2006; Holdsworth et al. 2007; Kadmon et al. 2009; Keene et al. 2007; Maat et al. 2013; Upperman et al. 2005; Warwick et al. 2011). A further three authors concluded that although the EP tool they evaluated was partially adapted for use in paediatric settings, additional paediatric-specific decision support was likely to achieve greater reductions in errors (Kazemi et al. 2011, Walsh et al. 2008, Vardi et al. 2007).

Two studies which found negative findings (Han et al. 2005, King et al. 2003) evaluated off-the-peg commercially available packages not customised for use with children. Indeed Han et al. (2005) concluded that:

> Utilization of an adult-based clinical application platform in a children's hospital may be suboptimal (Han et al. 2005, p. 1511).

Three studies suggested that paediatric customised systems were an *essential* feature when using EP for children (Del Beccaro et al. 2006, Holdsworth et al. 2007, Upperman et al. 2005):

> The risk of failing to customize existing systems to assist with prescribing for pediatric patients is likely substantial. (Holdsworth et al. 2007, p.1064)

The recent study by Maat et al. (2013) indicated that the issue remains current:

> CPOE systems need further evolution by the development of CDS [clinical decision support] specific for pediatric and neonatal settings (Maat et al. 2013, p. 90)

Customisation for use among children in critical or intensive care was also viewed as beneficial (Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Keene et al. 2007). Han et al. (2005) acknowledged that:

> It is possible that the association between ICU admission and increased mortality that we observed might have been related to using a general program in an ICU environment (Han et al. 2005, p.1511).

The study by Keene et al. (2007) noted the contrast between their approach and their findings in relation to the Han et al. study:

> Careful preparation, unit-by-unit tailoring, and extensive technical support may have improved the results at MMC. (Keene et al. 2007, p. 271)

However, despite the common view that customisation of EP tools is essential for error reduction, seven studies also acknowledged that developing bespoke systems is challenging and/or requires a significant investment of resources (Cordero et al. 2004, Del Beccaro et al. 2006, Holdsworth et al. 2007, Kazemi et al. 2011, Potts et al. 2004, Upperman et al. 2005, Vardi et al. 2007):

> Designing and implementing effective CPOE (whether 'homegrown' or vendor-based CPOE) with decision support is time consuming and difficult. (Cordero et al. 2004, p.92)

Some warned that the expense may be prohibitive:

> The complexity of decision support development, however, may preclude its development in institutions where substantive resources are not available to dedicate to these functions. (Holdsworth et al. 2007, p. 1064)

One study considered that the complexity of neonatal care would render dose-related decision support impossible in this field (Kazemi et al. 2011). Another regarded it to be unlikely that paediatric-specific 'off the peg' tools would ever become available, due to a lack of financial viability for commercial vendors (Potts et al. 2004).

Despite the widely acknowledged complexity and the significant resource implications associated with implementing these types of interventions, the view of the majority of the studies was that this work was indispensable:

> Although the intense preparation seemed exhaustive, it was critical to the success of the CPOE phase-in at CHP. (Upperman et al. 2005a, p. e637)

The significance of customisation as an essential part of the development of successful EP systems is represented in Figure 5.1, as is its relationship to the other key features of development and implementation discussed below.

Theme 2: Engage with a range of stakeholders

- Nine studies described engaging with stakeholders as part of the intervention development process.
- None of the studies with negative findings described having input from stakeholders.
- Six studies were explicit in their view that the involvement of a wide range of stakeholders enhanced the success of EP interventions.

Nine studies described the involvement of stakeholders in the development of 'home grown' or 'customised' EP systems (Cordero et al. 2004, Del Beccaro et al. 2006, Holdsworth et al. 2007, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2004, 2006, Sullins et al. 2012, Upperman et al. 2005). Typically the studies emphasised the involvement of multidisciplinary teams or a wide range of different stakeholders:

> A collaborative effort among pharmacists, physicians, informatics specialists, nurses, and performance improvement specialists was undertaken to create a pediatric dosing table (PDT) that was used as a source database for the dosing recommendations triggered by the system after drug selection. (Holdsworth et al. 2007, p. 1060)

In addition to descriptions of the process of engagement, six studies provided their views on the benefits of stakeholder input. One study was explicit that it was undertaken to ensure that the system was 'as safe as possible' (Sullins et al. 2012, p. 867); another was clear that its purpose was to enhance relevance and utility (Keene et al. 2007).

The study by Del Beccaro et al. (2006) contrasted their development and implementation approach to that of the unsuccessful intervention evaluated by Han et al. (2005); they considered one of the key differences accounting for the divergent findings between the studies to be 'active involvement of our intensive care staff during the design, build, and implementation stages' (Del Beccaro et al. 2006, p. 294). Another author reflected that having a stakeholder group 'provided a tangible point of action for employees and aided in supporting change' (Upperman et al. 2005a, p. e640).

The two studies by Lehmann and colleagues (2004, 2006) provided extensive reflection on the value of multidisciplinary stakeholder input during the development and implementation phases. In an additional paper building on the 2004 report of a study evaluating a total parenteral nutrition calculator, Lehmann and Kim (2005) credited stakeholder engagement for streamlining problem solving:

> The small size and multiple expertise of the team reduce the need for meetings and discussions and allow rapid decisions and adjustments in programming and implementation of solutions. (p. 512)

In this paper, in which they reflected on the process of developing and implementing a number of error reduction interventions, they stressed the value of 'tribal knowledge', described as 'unwritten information known to experienced personnel that may be required to produce a quality product or service' (p. 516). They argued that without the input of a wide range of stakeholders, 'certain error types or vulnerabilities may go unaddressed', and ultimately concluded that 'collaboration among different disciplines is vital to success' (p. 515).

Upperman et al. (2005) recommended a number of strategies for engaging with stakeholders including: surveying staff to gain their views, open forum meetings, a physicians' advisory group, leadership workshops and readiness assessments.

Stakeholder engagement is illustrated in Figure 5.1 as the primary undertaking for successful development of EP, as authors emphasised the benefits of engaging stakeholders from the point of project initiation and throughout the process.

Theme 3: Foster familiarity with the EP system

- Thirteen EP studies recommended enhancing user familiarity with the EP system to gain the most benefit.
- The effectiveness synthesis on EP also suggests that error reduction increases as users become more familiar with the system.
- Adequate and timely training was the solution most commonly suggested to foster familiarity; other suggestions included on-site support during implementation, a long acclimation phase, gaining experience in other wards/hospitals, and designing EP systems to be similar to existing systems.

Studies suggested that both acceptability and efficacy could be detrimentally affected by a lack of familiarity with EP systems. Thirteen of the EP studies advocated enhancing familiarity with the EP system prior to the 'go live' stage (Barnes 2009, Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Holdsworth et al. 2007, Kadmon et al. 2009, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2004, Sowan et al. 2010, Sullins et al. 2012, Upperman et al. 2005, Walsh et al. 2008). The apparent association between length of time since implementation and error reduction as identified in Chapter 4 indicates the validity of such assertions. Indeed, Han et al. (2005) acknowledge the possibility that a lack of familiarity with the system may have contributed to their negative findings:

> Our observation period after CPOE implementation was brief and may simply reflect the adjustment period that commonly follows any major, sweeping change. It is possible that had we extended our study another quarter, we might have observed a return to better-than-expected outcomes. (Han et al. 2005, p.1511)

Kadmon et al. (2009) explicitly asserted that the 'learning curve and the consequent improvement in staff expertise in CPOE use' was part of the reason for enhanced error reduction in a second phase of data collection (p. 938); Sowan et al. (2010) warned that:

> Even after the introduction of a new system, users may revert to prior practices based on familiarity, thus negating the potential benefits offered by the new system. (Sowan et al. 2010, p. 115)

A variety of methods for accelerating the process of familiarity with EP tools were suggested.

Nine studies provided reflections on the issue of training (Barnes 2009, Cordero et al. 2004, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2004, Sowan et al. 2010, Sullins et al. 2012, Upperman et al. 2005 and Walsh et al. 2008). Five studies expressed the view that adequate training was essential (Barnes 2009, Cordero et al. 2004, Keene et al. 2007, Sullins et al. 2012, Upperman et al. 2005):

> Probably the most important and fundamental activity necessary for a smooth transition to CPOE is staff CPOE training ... Poor training may lead to a lack of system understanding, which can result in frustration, poor acceptance, and a lack of full utilization. (Upperman et al. 2005a, p. e639)

Upperman et al. (2005) found the timing of training to be important for mitigating the problems associated with unfamiliarity:

> Early training proved to be a useful support tactic to quench change anxiety. Users had ample time to practice using the system and to gain comfort before the stressful live period. (Upperman et al. 2005a p. e639)

Although Sullins et al. (2012) identified a decrease in errors when all types of errors were combined, they suggested that the increase in errors of one sub-type (prescribing errors) may have been due to insufficient training (90 minutes total length).

Walsh et al. (2008) noted the possibility that the smaller than expected effect of EP in their study may have been due to an insufficient period of training:

> The time period that was permitted for implementation and learning of the system (3–6 months) did not allow trainees enough time to learn the system adequately. (Walsh et al. 2008 p. e426)

Keene et al. (2007) highlighted the risks of a lack of preparatory training. They compared their study against the Han et al. (2005) study, indicating that the more extensive hospital-wide training in their study may have contributed to the positive findings.

Twelve EP studies described the provision of pre-implementation training (Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2004, 2006, Potts et al. 2004, Sullins et al. 2012, Upperman et al. 2005, Walsh et al. 2008, Warrick et al. 2011). Most studies described providing training to all hospital healthcare personnel, although several suggested that training was provided exclusively to the clinicians who would prescribe via the EP system (Kazemi et al. 2011, Lehmann et al. 2004, Walsh et al. 2008, Warrick et al. 2011). Seven provided details on the length of training periods; most described sessions of between two and four hours (Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Keene et al. 2007, Sullins et al. 2012, Walsh et al. 2008). One described sessions lasting less than ten minutes (Lehmann et al. 2004) and another described providing extended training (16 hours) for nurses designated to support physicians in its use (Cordero et al. 2004). Of the studies that described the timing of training initiation, the vast majority described it as being between one and three months prior to implementation. The typical format for training delivery appeared to be group-based face-to-face training, although four studies described providing both group and individual sessions (Cordero et al. 2004, Del Beccaro et al. 2006, Kazemi et al. 2011, Upperman et al. 2005). As noted above, Keene et al. (2007) felt that the training provided in the Han et al. (2005) study was deficient; moreover, no pre-implementation training was described in the two studies with non-significant negative findings (King et al. 2003, Sowan et al. 2010).

Five studies suggested ways to deliver effective training. Upperman et al. (2005) recommended early initiation 'to quench change anxiety', and for training to be highly accessible, comprehensive and appropriate for the particular end users; they also suggest introducing 'end-users to real but hypothetical problems' via EP training. Lehman et al. (2004) suggested basing the interface of the EP system on existing paper-based prescribing forms to provide a familiar format, thereby reducing the time required for training. Sowan et al. (2010) recommended focusing training on compliance with EP procedures to gain the benefits of using EP. Barnes (2009) suggested that EP users should be proactive in training themselves on the technology and keeping up to date with software changes, though they acknowledged that it was also the responsibility of the organisation to provide training to end users.

Another approach to offset the problem of change anxiety or a lack of familiarity with the new system was to provide on-site support during implementation. Six EP studies reported the provision of on-site support (Cordero et al. 2004, Del Beccaro et al. 2006, Han et al. 2005, Keene et al. 2007, Lehmann et al. 2004, Upperman et al. 2005). Two studies described support from technology specialists (Cordero et al. 2004, Keene et al. 2007) and three described support from specially trained health-care practitioners (Keene et al. 2007, Lehmann et al. 2004, Upperman et al. 2005). Two studies did not specify who was providing the support (Del Beccaro et al. 2006, Han et al. 2005).

Typically the studies described support as being available round the clock (Cordero et al. 2004, Del Beccaro et al. 2006, Keene et al. 2007, Upperman et al. 2005) for a limited time period (Cordero et al. 2004, Han et al. 2005), which two studies specified as two to three weeks (Del Beccaro et al. 2006, Keene et al. 2007).

In the study conducted by Upperman et al. (2005), specially trained healthcare staff or 'superusers' provided ongoing support for regular end users of the EP system. A 'superuser' was defined as 'an individual who is expected to know more about the CPOE system and to assist regular end-users with problems on the floors' (Upperman et al. 2005a p. e639). Other ongoing support systems in this study included a physician advisory committee, the leader of which dealt with everyday concerns regarding the system, and a technology support team who provided assistance on a daily basis.

In the study by Keene et al. (2007), live technical support was originally only provided for a brief period. However, because of the complexity of the EP initiation, where the implementation was felt to be 'difficult' and 'tedious' and the system cumbersome and non-intuitive, the period of on-site assistance in the ICUs was then extended by 1–2 weeks. They attributed the presence of live support from technicians, pharmacists and other personnel with knowledge of the system to the lack of compromise on patient care and to the improved results.

Other solutions for enhancing familiarity included a prolonged acclimation phase (Holdsworth et al. 2007), designing systems to be similar to existing systems to enhance familiarity (Han et al. 2005, Lehmann et al. 2004) and drawing on the experience of EP systems implemented in other hospitals (Del Beccaro et al. 2006) or other wards (i.e. non-paediatric wards) (Keene et al. 2007):

> The most vulnerable patient groups were involved only after extensive hospital-wide experience with the system (Keene et al. 2007, p. 270).

Theme 4: Ensure infrastructure is adequate and appropriate to support EP

- Six studies described the importance of ensuring that appropriate infrastructure is in place to support EP.
- Inadequate IT systems and a lack of streamlining with other hospital procedures were seen as factors that could hamper the success of EP.
- One study concluded that increases in mortality may have resulted from infrastructure problems rather than from the EP system itself.

Six studies commented on the issue of inadequate infrastructure for implementing EP. As illustrated in Figure 5.1, both inadequate IT systems and inappropriate hospital systems were seen as influencing the success of EP. The study by Han et al. (2005) explicitly acknowledged the potential for such failures to have contributed to the increased mortalities found in their study:

> We again consider the possibility that our finding may reflect a clinical applications program implementation and systems integration issue rather than a CPOE issue per se. (Han et al. 2005, p. 1511)

IT infrastructure

Four studies discussed how inadequate IT infrastructure can negatively affect the utility of EP (Han et al. 2005, Kadmon et al. 2009, Lehmann et al. 2004, Upperman et al. 2005). It is notable that such issues were primarily discussed in the papers published earlier, suggesting that such problems may have been eliminated with advances in computer technology. The authors described two key issues in relation to IT infrastructure: the accessibility and availability of EP prescribing points and the capability of the computer system.

Access to computers was seen as a key problem in the Han et al. (2005) study, in which healthcare staff were observed being pulled away from the bedside in order to process an

order. The authors concluded that the system had thus the potential to reduce safety in two key ways. First, they felt that it reduced opportunities for face-to-face discussion between providers, which, they argued, reduced safety by reducing opportunities for other staff to review or contribute to the prescriber's decision (Han et al. 2005). Second, the authors felt that safety was compromised by reducing the availability of staff for patient care:

> Nurses must continue to spend significant amounts of time at the computer terminal and away from the bedside, effectively reducing staff-to-patient ratios during this critical period (Han et al. 2005, p. 1510)

Likewise, Lehmann et al. (2004) warned against the potentially harmful impact of a lack of computer terminals, specifying the need for sufficient numbers of computer terminals at convenient locations:

> We relied on the availability of public workstations in all clinical areas where providers might order TPN. If access to computers would have required travelling (even a short distance) or a waiting period, then we suspect that users' enthusiasm for this application would have been drastically diminished (Lehmann et al. 2004, p. 752)

Han et al. (2005) also commented on the potential problems caused by the inadequacy of the computer system in their hospital. In particular, they described experiencing insufficient 'communication bandwidth ... during peak periods', which slowed down the speed of the operating system, with the EP screen sometimes appearing 'frozen' (Han et al. 2005, p. 1509).

Han et al. (2005) and another study (Kadmon et al. 2009) also described glitches in the software system with the potential to reduce patient safety. Kadmon et al. (2009) described how alerts in their system did not continue to fire once a user had chosen to ignore one. Han et al. (2005) described users being blocked from the system when it was in use by another:

> When the pharmacist accessed the patient CPOE to process an order, the physician and the nurse were 'locked out,' further delaying additional order entry. (Han et al. 2005, p. 1509)

Upperman et al. (2005) concluded that the process of developing and maintaining computer software was 'incredibly important' in order to ensure 'elimination of computer system errors ... accommodation of the computer system to organizational changes; and ... efficiency in the system' (Upperman et al. 2005a, p. e637). Similarly Lehmann and colleagues emphasised the importance of a 'strong network structure and support' (Lehmann et al. 2005, p. 517).

Hospital policies and procedures

The Han et al. study (2005) also found their EP system to be significantly hampered by policies and procedures in operation within their hospital. In particular, they found that as their infrastructure resulted in a 'complete centralisation of pharmacy services', their system increased turn-around times by making it no longer possible to 'grab critical medications from a satellite medication dispenser located in the ICU' (Han et al. 2005, p. 1509). Another pre-implementation hospital policy designed to speed up the medications ordering process for emergency patients transported to their hospital was also overturned when EP was implemented:

> Before implementation of CPOE, after radio contact with the transport team, the ICU fellow was allowed to order critical medications/drips, which then were prepared by the bedside ICU nurse in anticipation of patient arrival ... After CPOE implementation, order entry was not allowed until after the patient had physically

> arrived to the hospital and been fully registered into the system. (Han et al. 2005, p. 1508)

As described above Han et al. (2005) acknowledged, however, that such issues were not weaknesses of EP per se. Indeed, Del Beccaro et al. (2006) described how they maintained similar policies for expediting medications ordering alongside EP:

> At our institution, emergency medications are able to be removed from the medication-dispensing system on each unit without the need for a preexisting order or pharmacy approval ... Our hospital also had a process for either preregistering patients who were being transported in (which predated CPOE) or would allow a quick registration process to facilitate order entry. (Del Beccaro et al. 2006, p.294)

Theme 5: Adapting the system: careful advance planning and development 'on the ground'

- Six studies recommend prolonged and careful pre-implementation planning.
- Fourteen studies recommend or imply the value of an iterative or 'suck it and see' post-implementation approach to development.
- Authors' views diverge with regard to the merits of pre-implementation planning and the cost-effectiveness of an iterative approach.

As indicated in development theme 1 on customisation, the common view among the studies was that having a system that is adapted to the needs of each hospital or setting is vitally important. Fourteen studies discussed implementation approaches to support the development of appropriately customised packages (Barnes 2009, Del Beccaro et al. 2006, Han et al. 2005, Holdsworth et al. 2007, Jani et al. 2010, Kadmon et al. 2009, Kazemi et al. 2011, Keene et al. 2007, Lehmann et al. 2004, Sullins et al. 2012, Upperman et al. 2005, Vardi et al. 2007, Walsh et al. 2008, Warrick et al. 2011). Two very different implementation approaches were described. All fourteen studies that discussed the issue recommended or implied the value of a 'suck-it-and-see' approach whereby the EP system was customised post-implementation based on user experience and identified needs. However, 6 of the 14 studies also recommended a long and careful pre-implementation planning phase (Del Beccaro et al. 2006, Han et al. 2005, Holdsworth et al. 2007, Jani et al. 2010, Keene et al. 2007, Upperman et al. 2005).

Careful advance planning

A long and careful planning and implementation phase in order to develop an appropriate bespoke system was recommended by six studies. All warned of the potential problems of a lack of planning. For example:

> The unique workflow issues in an ICU must be understood and mitigated before implementing CPOE, or the new processes of CPOE will only add increased complexity. (Del Beccaro et al. 2006, p.294)

Four of the studies were explicit in their view that the purpose of the exercise was to pre-empt potential problems, in particular problems arising from the IT system or the integration of EP into other existing hospital systems (Del Beccaro et al. 2006, Han et al. 2005, Jani et al. 2010, Upperman et al. 2005). In an additional article reporting on their 2010 study Jani et al. (2008) reported that:-

> Implementers need to give serious consideration to unforeseen errors that may arise after implementation of EP, either directly due to selection errors or indirectly due to how the system is set up. (Jani et al. 2008, p. 216)

Four studies were explicit that the preparatory phase should be prolonged (Del Beccaro et al. 2006, Holdsworth et al. 2007); two gave specific details of the length of their pre-implementation preparatory phase – Upperman et al. described it as 'more than one year before the actual live implementation' and Keene et al. (2007) noted it to be 'approximately 2 yrs rather than the 3 months described by Han and colleagues'. Three authors described what their preparation phase entailed. Upperman et al. (2005a)

recommended 'organization of stakeholders, leadership workshops, committee formation, employee education, and readiness assessments' (p. e637). Del Beccaro et al. (2006) described collaboration with another hospital with experience of EP: 'We were able to meet with administrative and clinical leadership, tour their hospital, and speak with clinical staff' (p.294). Keene et al. (2007) described observing implementation in other wards before implementing with children.

'Suck it and see': iterative approaches to implementation

Almost three quarters of all EP studies (n=14) recommended adopting a pragmatic and iterative approach to implementation which responds to issues and problems as they arise (the cyclical format of Figure 5.1 represents this issue). Whilst some authors recommended both a long pre-implementation phase and a responsive post-implementation phase, Jani and colleagues, for example, noted that whilst planning is important: 'Follow-up is also necessary because not all problems can be foreseen' (Jani et al. 2008, p. 216).

Others were of the view that a responsive approach should be adopted exclusively. Lehmann et al. (2004) warned that pre-implementation planning unnecessarily delays implementation and may result in an inferior product:

> An attempt to design a 'perfect' and completely error-free application from the start would have required considerable planning, consulting, and review before implementation, leading to long cycle times, which might have derailed the process long before completion. In addition, the desire to design the 'perfect' system might have resulted in an over-engineered product with additional features, complicating its use and making it unattractive to users. (Lehmann et al. 2004, p.752)

Similarly, there was divergence as to the cost-effectiveness of each approach. The continuous nature of the iterative approach was noted by Holdsworth et al. (2007) to require 'substantial resource commitment on an ongoing basis' (p. 1064). Lehmann et al. (2004) were of the opposite view:

> By limiting the number of people involved in the process of problem identification, development, testing, and deployment, the used resources such as time and manpower can be drastically reduced without losing effectiveness. By shortening the time interval between the birth of an idea and its implementation, we increased the speed of innovation. Although this approach carries a greater risk for software design flaws, in our opinion, this risk can be minimized by using participant/ observers in the development and is further offset by the significant gains through early implementation and cost reduction. (p. 752)

Authors described a number of prerequisites for accessing the benefits of an iterative approach to implementation:

- flexible and easily modifiable IT systems
- ongoing vigilance and monitoring of system impacts and problems
- timely and ongoing responsiveness to identified problems
- an onsite team or individual with the appropriate skills for innovative problem solving
- the communication of system updates and modifications to relevant staff.

Five authors indicated that flexible and easily modifiable IT systems were essential for responding to emerging problems (Barnes 2009, Del Beccaro et al. 2006, Lehman et al. 2004, Upperman et al. 2005, Warrick et al. 2011). For example:

> Modifications of TPN Calculator require minimal intervention, because any change made on the web server is immediately available to all users throughout the system. (Lehmann et al. 2004, p. 751)

Eight authors described constant vigilance and monitoring as an essential part of an iterative approach. For example, Walsh et al. (2008) recommended that hospitals must:

> Monitor, continually modify, and improve CPOE systems on the basis of data derived from their own institution. (Walsh et al. 2008, p. e427)

Authors were clear that monitoring systems should capture a range of impacts, including user-identified problems with the system (Upperman et al. 2005, Walsh et al. 2008, Warrick et al. 2011), the introduction of new types of error (Lehmann et al. 2004), resource utilisation (Lehmann et al. 2004), the impact on patient care (Han et al. 2005, Lehmann et al. 2004) and the impact on patient outcomes such as error and ADE (Han et al. 2005, Upperman et al. 2005). Indeed, Han et al. (2005) warned specifically that:

> Institutions should continue to evaluate mortality effects, in addition to medication error rates, for children who are dependent on time-sensitive therapies (p. 1512).

Eight authors expressed the view that ongoing and timely responses to identified problems were essential for success (Del Beccaro et al. 2006, Holdsworth et al. 2007, Kadmon et al. 2009, Lehmann et al. 2004, Sullins et al. 2012, Upperman et al. 2005, Walsh et al. 2008, Warrick et al. 2011). Studies emphasised both the need for swift action: 'Necessary modifications and prompt responses to complaints are vital' (Upperman et al. 2005a p.e640) and the continuous cycle of development: 'Constant surveillance with a search for innovative solutions is necessary' (Kadmon et al. 2009 p. 939).

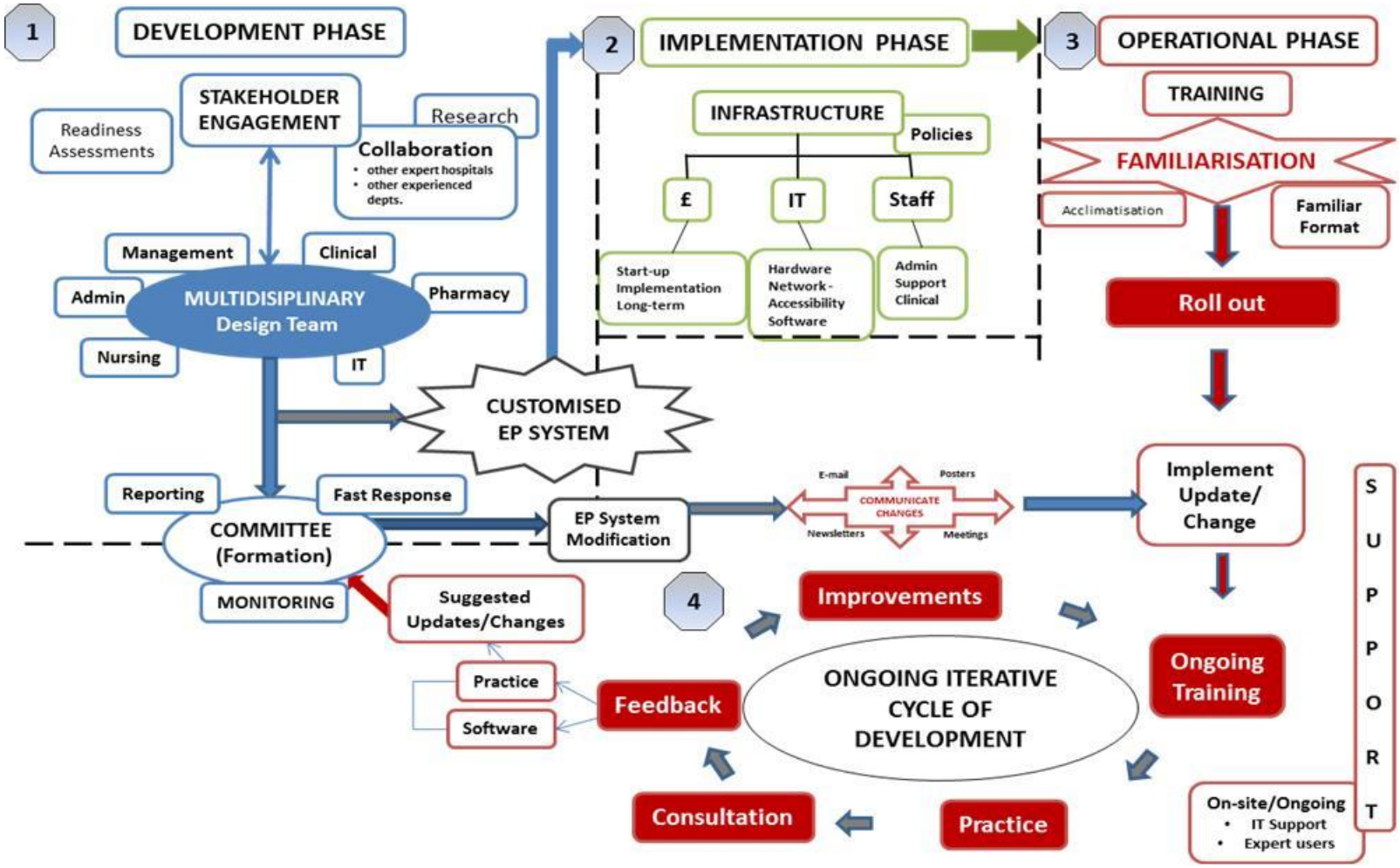
Five studies indicated the value of having an on-site team or individual with the requisite skills to respond creatively and swiftly to emerging problems (Holdsworth et al. 2007, Jani et al. 2010, Kadmon et al. 2009, Lehmann et al. 2004, Upperman et al. 2005):

> We were able to use a close-held, multitalented, small development group to develop a rapid solution in cooperation with local information services. (Lehmann et al. 2004, p. 751)

Lehmann et al. (2004) described using 'participant observers', i.e. prescribers and pharmacists as programmers, designers and testers of their EP system. Upperman et al. (2005) described having a dedicated physician to whom users could direct concerns, and who could facilitate modifications.

Three authors discussed the issue of communicating changes and updates to the EP system (Barnes 2009, Upperman et al. 2005, Walsh et al. 2008). Walsh et al. (2008) raise the problem of 'large-scale operator unfamiliarity' due to the need for hospitals to constantly update and tailor their EP systems. They suggested that this was problematic due to the high number of agency staff in the NHS. Barnes (2009) was of the view that keeping up to date remained the responsibility of users. Upperman et al. (2005) described ensuring that 'all hospital employees were informed and knowledgeable' regarding the current state of the system through staff meetings and via various media, i.e. newsletters, e-mails and posters. They also suggested that physician access to system design changes on an ongoing basis was critical to the continued success of the EP system.

Figure 5.1: Development and implementation of EP system



5.2 CDSTs

Five studies evaluated CDST interventions intended to simplify or streamline the process of prescribing, administering or formulating medication doses for children according to their size. In comparison to EP, the CDSTs evaluated are less complex, with fewer components; indeed, decision support tools were one element of most EP interventions. The CDST studies also differ from the EP set in that they are less comparable with each other. There is wide variation in the nature of the tools used, not least because of the different users (parents/carers and healthcare practitioners) and their different purposes (prescription, administration, formulation). We describe some of the features common to multiple CDST interventions in Section 5.2.1 below, and consider the authors' reflections on their strengths and weaknesses (5.2.2) and evidence on developing and implementing CDSTs (5.2.3).

5.2.1 CDSTs: intervention components

CDST packages varied according to whether they:

- targeted the prescription, administration or formulation points on the medicines' pathway
- were aimed at healthcare professionals or parents/carers
- involved a colour coding system to aid decision making
- were hand-held/pocket sized devices
- were computer-based interventions
- provided additional written information or instructions for use.

Variation in pathway points and users

Two of the studies evaluated interventions to support parents and caregivers in determining the correct dose for administration of medicines to children (Frush et al. 2004, Hixson et al. 2010). The remaining three studies evaluated interventions targeted at healthcare practitioners: two were aimed at supporting physicians to make prescription decisions (Hixson et al. 2009, Skouroliakou et al. 2005), and the third was an intervention to support student nurses' decision making around transcribing and administering medications (Burgess 2009).

Colour coding

Two studies evaluated colour-coding systems for parents/carers that aimed to simplify the procedure for determining and measuring an appropriate medication dose according to the size of their child (Frush et al. 2004; Burgess 2009). Frush et al. (2004) described a colour-coded method that helped caregivers to determine their child's weight based colour zone; weight was estimated based on the height of the child. A corresponding colour-coded measuring device enabled easy identification of an appropriate dose. Burgess (2009) evaluated the implementation of a web-based application for nursing students, Color Coding Kids (CCK), which also used the same method of weight estimation and colour coding.

Hand-held devices

Two studies evaluated hand-held devices designed to streamline the process of age- and weight-specific dose determination for clinicians (Hixson et al. 2009) and for caregivers (Hixson et al. 2010). Similar to the colour coding, both devices enabled the user to select a pre-calculated medication dose based on the size of the child. Hixson and colleagues (2009) evaluated the Paediatric Analgesia Wheel, a pocket-size device displaying pre-calculated doses of commonly used analgesic and anti-emetic drugs rounded to a volume that could be accurately administered for children from birth to 16 years of age (3-58 kg). The Parental Analgesia Slide, a simplified version of the Wheel, developed for caregivers,

displayed pre-calculated paracetamol administration information for children between one and 13 years old (10-44 kg) (Hixson et al. 2010).

Computer programs

Two interventions were delivered via computer program. The Burgess (2009) CCK system, described above, was an on-line tool. The other computer-based study evaluated the use of a program to support prescribing and preparing a protocol-based Total Parenteral Nutrition (TPN) formulation in a hospital setting (Skouroliakou et al. 2005). The TPN Formulation Automated Assistant (TFAA) provided recommended values for all TPN components and was linked to a dispensing and mixing device which prepared the final solutions automatically. The calculation tool appears similar to TPN interventions included in the EP synthesis (Lehmann et al. 2004, Maat et al. 2013); however, Skouroliakou et al. (2005) did not specify whether their computer program comprised order entry or was simply a decision aid.

5.2.2 CDSTs: strengths and weaknesses

Acceptability of CDSTs

Three studies assessed user satisfaction with the interventions (Frush et al. 2004, Hixson et al. 2009, 2010). Formal evaluation of acceptability was carried out in the two studies by Hixson et al. (2009, 2010). Clinician users of the wheel and parental users of the slide found them to be 'a good idea' and indicated that they would carry/use one if available. The majority of users in both studies also reported that they felt 'more comfortable' determining a dose when using the tools. Frush et al. (2004) reported informal feedback from participants but reported similar findings regarding increased confidence in determining a dose:

> as indicated by caregivers' comments, many felt more confident they could give an appropriate dose to their child when using color coded materials. (Frush et al. 2004 p.623)

Simplification of tasks

The main aim of all of the CDSTs was to simplify or streamline complex decisions. All authors attributed significant reductions in errors and turn-around times to having successfully streamlined decision making. For example, Skouroliakou et al. (2005) concluded that:

> The TFAA makes the complex task of prescribing and formulating TPN solutions easier. The benefits from using TFAA include greater speed and accuracy for conducting calculations ... TFAA streamlines pharmacists' and physicians' work on the formulation of TPN for pre-term and sick term neonates and may help prevent prescription and preparation errors. (Skouroliakou et al. 2005 p.309)

Similarly, Hixson et al. (2009) noted the increase in errors for heavier children in the control group, and suggested that avoidance of complex calculations, enabled by the wheel, improved accuracy for children weighing 23kg and over.

Dangers of oversimplification

However, some authors also warned of the potential dangers of oversimplification. First, the hand-held nature of some tools was found to reduce their comprehensiveness and thus their utility. Hixson et al. (2009) noted that the wheel's 'main limitation' was a result of its pocket-sized design and therefore limited space to provide comprehensive drug information. Neither the wheel (Hixson et al. 2009) nor the slide (Hixson et al. 2010) could cater for every age and weight combination, (e.g. children at a high centile for both height and weight but with normal body mass index). Hixson and colleagues attempted to address this issue by using the covering sleeve as a place to provide extra information, for example about dose frequency issues for clinicians (Hixson et al. 2009). However, as dose

frequency errors accounted for the majority of errors occurring with the use of the wheel, the authors speculated that clinicians might simply have overlooked this information when completing the prescription chart.

Second, some authors were concerned that simplifying such complex processes might lead to excessive confidence among parents, which might in turn lead to errors. For example, Hixson et al. (2010) were concerned that overconfidence may lead to paracetamol overdose if poorly labelled over-the-counter multi-component formulations were concurrently administered. They recommended that the sleeve of the slide was used to highlight additional drug safety information to minimise the risk of errors. Frush et al. (2004) noted that as the colour syringe needed to be directly correlated to a specific formulation of medicine (e.g. children's paracetamol[4], 160 g/5 mL), unwitting use of the syringe with a different formulation (e.g. infant paracetamol, 80 mg/0.8 mL) would cause a dosing error.

Simplicity not always achieved

Frush et al. (2004) were concerned that the slide was still too complex for use by parents/carers as it was developed using the same eight colour zone format used in a similar tool for clinicians (Broselow Paediatric Emergency Tape). The authors concluded that a less complex zoning system could further simplify home dosing. They also noted that the colour coded syringes could not be used by colour-blind caregivers.

Hixson et al. (2010) were also concerned that their tool for parents (the Slide) was still too complex as there was a problem with alignment of dose and the child's weight and age. The effect of these alignment errors was not large enough to prevent a reduction in dose errors, and the authors proposed that further improvements could be made with clearer instructions.

5.2.3 CDSTs: development and implementation issues

Scant information was provided regarding the development and implementation of CDSTs, although a small amount of data indicated some similar issues that arose from the EP synthesis, namely the importance of familiarisation with the intervention and the value of on-going or iterative development.

Familiarity with the intervention

Burgess (2009), in her evaluation of the Color Coded Kids system, attributed the non-significant difference between groups on turn-around times to the inexperience of users. Similar to the findings of Sowan et al. (2010) in the EP synthesis, observers in the Burgess study reported that the study participants reverted to standard practices for calculating doses, rather than following the instructions given by the system under trial. Lack of experience was also indicated when Burgess considered the below-standard hand-off communication, concluding that nurses' unfamiliarity with it contributed to the problem.

Hixson et al. (2010) considered that parents' and carers' lack of familiarity with the intervention impacted on their acceptability of it. They found that in comparison to other acceptability responses by parents about the slide (e.g. whether or not it was a good idea, and whether they would use it) fewer parents agreed that they felt more comfortable when using it (58 of 80 parents compared to over 70 of 80 parents for other responses). The authors hypothesised that familiarity with the tool would result in an improvement in response to the statement regarding comfort.

Iterative development

Three studies also implied the value of iterative development of CDSTs (Frush et al. 2004, Hixson et al. 2009, 2010) with constant vigilance and monitoring enabling them to address

[4] Known in the US as acetaminophen.

identified issues and problems. For example, as noted above Frush et al. (2004) concluded that further iterations of the colour coded instrument should be developed to further simplify it for parents and carers. Likewise, Hixson et al. (2010) indicate that they had learned lessons regarding sleeve information from their previous study (Hixson et al. 2009). They attributed greater improvements in drug intervals and frequencies resulting from the slide (Hixson et al. 2010) as compared to the wheel (Hixson et al. 2009) to the 'clarity of prescribing information presented on the outer sleeve'. Hixson et al. (2010) also proposed that 'further improvements could be made with clearer instructions' in response to their finding regarding difficulties with alignment of the slide, as noted above.

5.3 Education interventions

Although all six education studies described the interventions as 'brief', characterised by being delivered in a short, single session, two clear subgroups of interventions were evident in this dataset: those that targeted medication prescription and those that targeted medication administration.

5.3.1 Education interventions: intervention components

Education interventions varied according to whether they:

- were aimed at increasing prescribing knowledge of clinicians or administration knowledge of parents/carers
- were delivered on-line, face-to-face, or through pictographic information as part of written instructions
- were broad in scope or focused on a specific skill.

Paediatric prescribing education for clinicians

Three studies evaluated education interventions designed to improve the paediatric prescribing skills of healthcare practitioners (Frush et al. 2006, Gordon et al. 2011, Kozer et al. 2006). Two found statistically significant benefits from the education interventions; the third (Kozer et al. 2006) found a negligible non-significant trend towards reduced PME. The studies varied in the healthcare practitioners being targeted, the breadth of the prescribing education and the delivery format. Frush et al. (2006) focused on the use of on-line education to train clinicians (advanced practice nurses, doctors and paramedics) in a specific skill: the proper use of a paediatric dosing calculation aid. Very little detail was provided on the content of this intervention. The other two studies both evaluated broader education interventions on paediatric prescribing for junior doctors; the main content of both was common errors and key considerations for paediatric prescribing (e.g. age- and weight-based dosing). However, they differed in their format: Kozer et al. (2006) evaluated a short, 30-minute face-to-face tutorial and Gordon et al. (2011) evaluated a short e-learning education programme involving a PowerPoint presentation, videos and quizzes.

Pictographic liquid medication administration education for parents/carers

Three studies evaluated interventions aiming to improve a specific skill among parents and carers: the administration of paediatric liquid medications (Hu et al. 2013, Yin et al. 2008, 2011).

The use of pictographic information as part of the administration instructions was common to each intervention. This was described as including, for example, colourful photographs of medicine reconstitution steps and illustrations of storage equipment (Hu et al. 2013) or pictograms to convey information about medication name, indication, dose, dose frequency, length of treatment, preparation and storage (Yin et al. 2008). Both studies by Yin and colleagues focused on caregivers with low health literacy.

Two of the three studies (Hu et al. 2013 and Yin et al. 2008) examined whether providing a face-to-face instruction or demonstration of medicines administration by a trained

healthcare practitioner enhanced the impact of the pictographic information. In the study by Hu et al. (2013) a pharmacist explained how to reconstitute, use and store the medication. In the study by Yin et al. (2008) research staff referenced the sheets as they demonstrated dosing with a standardised instrument; parents then demonstrated to research staff how they planned to administer medication, a process referred to as 'teachback'.

5.3.2 Education interventions: strengths and weaknesses of intervention components

Strengths and weaknesses common to both clinician and parent/carer education

Acceptability

Only one of the six education studies provided any evidence regarding the acceptability of the intervention. Gordon et al. (2011) noted that informal feedback on the intervention was 'almost universally positive'. However, the authors of this study also noted a high drop-out rate between recruitment and first assessment, suggesting that a large number of participants who did not feed back may not have been so satisfied with the intervention.

Accessibility

Accessibility appeared to be a key feature of interventions to which authors attributed success. The two studies evaluating e-learning for clinicians (Frush et al. 2006, Gordon et al. 2011) noted that an on-line method of delivery made the intervention 'easily accessible' for users (Frush et al. 2006), as well as for staff developing the programme:

> The intervention was designed with a widely available and simple piece of software that allows educators to create most material in a familiar program ... updating is easy. (Gordon et al. 2011 p. 1194)

Accessibility was also discussed in the two studies by Yin and colleagues, who found that providing pictorial information was particularly helpful for participants with low health literacy. In their later study (Yin et al. 2011), they also found that pictographic instructions were helpful for bridging language barriers:

> Pictographic instructions, even when accompanied by English words, were beneficial for parents with low English proficiency (Yin et al. 2011 p.56)

Cost effectiveness

Four studies noted that the brief education interventions they evaluated were low cost (Frush et al. 2006, Gordon et al. 2011, Kozer et al. 2006, Yin et al. 2008). For example:

> In summary, a short e-learning module, taking less than 2h, is able to improve paediatric prescribing skills significantly. The intervention uses simple and low cost production. (Gordon et al. 2011 p.1194)

> The low resource requirements for this intervention, along with a large reduction in risk and a small number needed to treat, support its potential utility in clinical practice. (Yin et al. 2008 p.820)

Pictographic instructions

All three studies evaluating caregiver education found a statistically significant reduction in errors when pictographic instructions were incorporated into the intervention. Yin et al. (2011) compared the use of text instructions *with pictographic representation* to text instructions *alone* and found that pictographic dosing instructions significantly improved parent dosing accuracy, particularly among caregivers with low health literacy. The authors suggested that the use of pictographic dosing instructions proved particularly helpful in preventing large overdosing errors:

> The rate of large overdosing errors among those who received the text-only instructions was almost 10 times the rate of those who received text-plus-pictogram instructions (text plus pictogram 0.6%; text only 5.6%). Given these

> findings, consideration should be given to the routine inclusion of pictographic materials as part of medication dosing instructions. (Yin et al. 2011, p.55)

Face-to-face instruction

Both Hu et al. (2013) and Yin et al. (2008) found that a combination of pictograms and face-to-face demonstrations resulted in fewest administration errors. Hu et al. (2013) found that of three intervention groups (text instructions alone, text plus pictograms, text and pictograms plus pharmacist demonstration), those that received the additional level of pharmacist demonstration resulted in the 'highest accuracy rate' (p.39). They thus concluded that pharmacists should provide 'active education' and caregivers should not be left to read the package in isolation.

Face-to-face instruction in the Yin et al. (2008) study was also found to further reduce administration errors still found with pictographic instruction. However, the authors noted the additional time, and therefore resource, implications of face-to-face instruction: 'teachback' took 1.5 to 3 minutes to complete for each parent/caregiver 'depending on the complexity of the regimen'. Institutions looking to implement such interventions will need to balance the need for error reduction with the need for cost-effectiveness: essentially, pictographic instructions are cheap and reduce errors; face-to-face instruction reduces errors further but is more costly.

However, the Kozer et al. (2006) study, which evaluated the only face-to-face clinician education programme, was the only education study not to find reductions in error. This suggests that although face-to-face education can enhance learning, the format in itself is not sufficient for success; the content of the teaching and the supplementary materials (pictograms) evidently play a key role in success. Moreover, on reflecting on the failure of their intervention to reduce errors, Kozer et al. (2006) suggested that those doctors who took the tutorial may have been most anxious about their abilities, so the researchers could not discount that the course had had some effect. However, they were judged against those non-attenders who were more confident and possibly more competent, and so there was no difference between the two groups.

However, the small number of studies and the variation between them means that these findings should be considered uncertain. The lack of evidence on acceptability of these interventions, particularly with reference to parents and carers, is particularly disappointing.

5.3.3 Education interventions: development and implementation issues

In comparison to the EP studies, there is limited information regarding successful development and implementation strategies. There was a small amount of description of the methods, but very little commentary on the benefits of these approaches.

Developing course content

Five studies provided detail about developing the content of their course. In line with the stakeholder engagement theme identified in relation to successful implementation of EP, Frush et al. (2006) and Gordon et al. (2011) both sought advice from pharmacists in developing course content. The Kozer et al. (2006) study used data from their previous study, which examined the nature of prescribing error in their hospital, to develop their course content. None of the studies evaluating interventions for parents and carers described stakeholder engagement of any kind. The intervention evaluated in both the Yin et al. studies (2008, 2011) was developed using data from standard pharmaceutical references.

Evidence and theory-based educational approaches

A further three studies discussed deciding on the educational approach to use. Gordon et al. (2011) described the use of educational theories to develop the course structure, namely Gagné's Nine Events of Instruction and Cognitive Load Theory (Gagne 1985). Frush

et al. (2006) also sought educational theory input, again through stakeholder engagement, in the form of an advisory panel involving experts on educational theory, curriculum development and web-based learning. Both studies by Yin et al. (2008, 2011) used an evidence-informed approach in developing their intervention; they cite evidence on the efficacy of pictographic information and on the 'teachback' method.

E-learning: easy to produce and update

Just one study discussed barriers to or facilitators of implementation. As noted in the strengths and weaknesses section above, Gordon et al. (2011) felt that as the intervention was designed using simple software, it made the course easy to modify and update.

6. Discussion and conclusions

6.1 Key findings

- **Extent synthesis:** dose errors appear to be a common problem in both primary care (strong evidence) and acute care (promising evidence). However, an accurate and comprehensive picture of the rates and types of PME in the UK is not currently available, largely due to the fact that error reporting is often voluntary and there is significant inconsistency in the recording and categorising of errors.
- **Effectiveness synthesis:** international evidence on interventions to tackle PME shows strong evidence of effectiveness for electronic prescribing; evidence regarding the efficacy of CDSTs and education interventions is promising.
- **Intervention features synthesis:** evidence suggests that the way electronic prescribing systems are developed and implemented is crucial to their success; successful electronic prescribing systems require careful and considered development and implementation, should feature comprehensive decision support and should be customised for use with children.

6.1.1 Key findings on the nature and extent of paediatric medication error (PME) in the UK (extent synthesis)

Dose errors are a significant problem in primary care and acute care

National-level evidence from the UK identified for this review indicates that paediatric and neonatal patients are commonly prescribed or administered the wrong dose of medicine. Paediatric dose errors are a significant problem in the UK in both primary and acute care settings. Evidence on other error types, such as wrong drug or wrong frequency errors, is less clear. Fewer than half of the studies examined other error types, and those that did were hard to compare due to a lack of consistency in the error type categories they examined.

Paediatric dose errors have the potential to cause a significant amount of harm; reduced efficacy and treatment failure may result from underdosing, while overdosing may result in injury or harmful side-effects. Thus, the findings of this review that dose errors are common in the UK in both primary and acute care are of concern.

Similar findings regarding the extent of dose errors and off-label prescribing in primary care have been reported in other high income European countries (Bucheler et al. 2002; Lass et al. 2011) and in a review of worldwide evidence (Pandolfini and Bonati 2005). Evidence from Germany indicates that the risks of off-label *prescribing* may be compounded by off-label *use* of medicines among children in the home. Knopf et al. (2013) found that over two-fifths of all medicines prescribed to children aged 0-17 years in Germany were not taken according to the licensed recommendations; among children aged between three and six years, the rate of off-label use was almost half (49%).

With regard to acute care settings, this review found evidence that dose errors are currently the most common type of errors in the UK, and have remained so over several years. A systematic review of international evidence on paediatric dosing errors suggests that the problem has remained intractable for over a decade: Wong and colleagues concluded back in 2004 that the need to develop methods to address the problem was ‘urgent’ (p.669). A decade later, it would appear that the complexities of age- and weight-based dosing for paediatric and neonatal patients have not yet been overcome.

Perhaps one of the impediments to addressing the problem is that there is little evidence regarding the causes of dose errors. Although many of the included studies speculated on the causes, none provided direct evidence. The included studies identified that at least some portion of prescription dose errors is due to a lack of appropriate formulations

(Ekins-Daukes et al. 2004, Riordan et al. 2009). However, there are indications that other factors may account for the greater proportion of dose errors. A study not included in the review as it examined GPs' views regarding off-label prescribing, rather than measuring rates of off-label prescribing, found that 40 per cent of participants reported knowingly prescribing medicines off-label, most of whom indicated that this was due to prescribing medicines for a younger age-group than recommended (Ekins-Daukes et al. 2005). However, evidence gathered by the same authors and included in this review (Ekins-Daukes et al. 2004) indicates that the vast majority of off-label prescribing results from a failure to prescribe a dose in line with current recommendations, indicating that the bulk of off-label prescribing results from unintentional errors. The authors attribute such dose errors to the inconsistencies and lack of standardisation of age- and weight-based dosing recommendations relating to individual drug classes (Ekins-Daukes et al. 2003, 2004). Ekins-Daukes et al. (2005) also suggest that the 'clear disparity between perceived and actual reasons for off-label prescribing' indicates that informing GPs regarding the extent and nature of off-label prescribing may reduce its incidence. Grover et al. (2008) also indicated that knowledge deficits were causing prescription dose errors regarding PN prescribing in neonatal units 'leading to malnutrition that can only be termed *iatrogenic* malnutrition' (p. 143). However, one study indicated that an unbalanced approach to education and information giving may be a factor in high levels of underdosing in relation to certain drugs: 'It is possible that in the absence of reports relating to underdosing and treatment failure, primary care physicians have been sensitised by earlier reports of paracetamol overdosing and hepatotoxicity' (Kazouini et al. 2011, p. 503).

It is clear that there are likely to be multiple causes of paediatric dosing error, suggesting that a multipronged approach to addressing it is likely to be required.

6.1.2 Key findings on the efficacy of international interventions for reducing the incidence of PME (effectiveness synthesis)

Evidence from 20 international studies strongly indicates that electronic prescribing (EP) reduces PME, ADE and mortality.

The strongest evidence found for this review regarding interventions to reduce PME relates to EP. Of 15 studies examining the impact of EP on PME, nine found statistically significant reductions and a further four found non-significant trends towards reduced PME. Strong evidence was also found that EP reduces the harmful outcomes of ADE and mortality. As discussed below in the section on strengths and limitations, the size of this evidence base compensated for limitations relating to the less robust trial designs employed in most EP studies. Similar findings on the efficacy of EP are reported in systematic reviews not specific to children (Radley et al. 2013, Stürzlinger et al. 2009). However, evidence shows that despite the growing international evidence base regarding the efficacy of EP for use with children, and despite the growing prevalence of EP within English hospitals, specialist EP systems are employed in just 1% of paediatric wards and 1% of neonatal wards in English hospitals (Ahmed et al. 2013).

Promising evidence on CDSTs and educational interventions is available from smaller numbers of studies than is available for EP, but it is sufficient to indicate that they can reduce PME. Whilst the research designs evaluating these interventions are more robust than the HCT designs primarily employed in the EP studies, the differences between the different interventions evaluated within each intervention type and the smaller numbers of studies mean that the evidence is not as strong.

6.1.3 Key findings on successful development and implementation of effective interventions (intervention features synthesis)

The clearest findings regarding the successful development and implementation of effective interventions relate to EP. As noted in Chapter 5, there are a number of reasons

for this, including the volume of evidence, the comparability of EP interventions and the extent of author commentary on these development and implementation issues. It is likely that this last reason is due to the finding of increases in mortality found by one of the included studies (Han et al. 2005).

However, the findings which emerged from the plethora of informal evidence on EP development and implementation resulted in clear guidance about the features and components necessary for successful error reduction. Successful electronic prescribing interventions were typically customised for use with children and incorporated extensive decision support; conversely, in the three EP studies with negative findings, these features were largely absent. In addition, the evidence suggests that development and implementation of successful electronic prescribing involves customisation for use with child patients, engaging with a range of stakeholders during development, fostering a high level of familiarity with the system prior to use, ensuring adequate IT systems and compatibility with existing hospital systems and infrastructure, careful planning and ongoing iterative development post-implementation. Another systematic review on EP, largely focusing on adults but including some of the paediatric studies included in this review, reached similar conclusions regarding essential development and implementation features. Stürzlinger et al. (2009) concluded that EP systems are successful if the implementation is 'well planned and conducted', if 'sufficient training' is provided and if the system is 'adapted to the needs of the institution'. Corroborative evidence of this nature is particularly valuable given the untypical approach to generating these findings in this review.

The smaller evidence base and the lack of comparability among the CDST and education interventions mean that guidance about how to develop and implement these interventions successfully is less clear. However, corroborative evidence from adult interventions adds weight to the conclusion that colour coding systems for clinicians (Porat et al. 2009) and lay people (Hellier et al. 2010) may be useful features of CDSTs. However, whilst authors regarded pictographic instructions for caregivers as useful for overcoming language barriers, other evidence suggests that accuracy of interpretation of pictographic information is culturally bound (Kassam et al. 2004).

6.2 Strengths and weaknesses of the evidence base

- The review constitutes a uniquely comprehensive and holistic approach to understanding the issue of PME.
- The review provides a current assessment, providing new insights and making clear where ongoing issues and gaps remain.

One of the key strengths of this systematic review is that it is unique in taking a comprehensive and holistic approach to understanding the issue of PME in the UK, bringing together evidence on the rates and types of error in the UK, on the effectiveness of interventions and on the key features of successful interventions. Moreover, each different component of the review is unique in its approach. First, it is the only systematic review, as far as we are aware, that brings together different sources of national-level evidence from across the UK about rates and types of PME. Second, it is the first systematic review of which we are aware that brings together evidence about the efficacy of a range of interventions for reducing a range of error types, specifically among children. Third, it is the only systematic review which examines the key features of successful interventions for reducing PME in depth and which examines successful approaches for implementation and delivery.

The comprehensive overview of PME that this systematic review provides enables new insights both through the up-to-date assessment of each issue and by bringing together evidence examining the issue from different angles. Moreover, the holistic and

comprehensive nature of the assembled evidence base enables us to take stock, making clear what is known and what we still need to find out.

6.2.1 Strengths and weaknesses of the UK evidence on types and rates of error (extent synthesis)

Complementary evidence from prescription review and incident reports – but an accurate comprehensive evidence base is unavailable

As noted in Chapter 3, the findings on the extent and nature of error may be hampered by under-reporting of PME in voluntary reporting systems. There is currently a lack of agreement as to whether voluntary reporting produces an accurate evidence base. In their systematic review of incidents and errors in neonatal intensive care, Snijders et al. (2007) found that the total medication error rate was much higher in studies using voluntary reporting than in studies using mandatory reporting, and they concluded that voluntary, non-punitive error reporting systems were likely to generate valuable information on the type, aetiology, outcome and preventability of incidents. However, MacLennan and Smith (2011) noted that under-reporting was common in the UK due to a perceived lack of ownership of reporting systems, lack of feedback, lack of time and fear of blame (despite NRLS reports being anonymous). The accumulation of international research indicating significant under-reporting of patient safety incidents is also remarked upon in the National Patient Safety Agency (2009) report, as is, in particular, significant under-reporting to the NRLS from primary care settings.

In their systematic review examining the epidemiology, nature and interventions of hospital medication administration errors in paediatrics, Ameer et al. (2013) report overestimation and underestimation of errors, depending on the methodological approach used, and suggest that the use of a combination of methods may be desirable. Although no individual study using multiple data collection methods was identified, the inclusion of evidence from both voluntary reporting schemes and prescription review suggests that overall the range of studies may complement each other to provide a more robust picture. However, a comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities found that direct observation (by pharmacy technicians rather than nurses) was more efficient and accurate in detecting medication errors than both prescription or chart review and incident reports (Flynn et al. 2002). Whilst smaller-scale studies might be more reliable in terms of operationalisation, by definition they are not suitable for examining the picture at a national level, which was the aim of the review. Observational data from single sites may be influenced by differences in individual hospital infrastructure and processes, so the findings may skew or obscure the view in relation to the national picture. In any case, cross-verification of evidence from voluntary reporting schemes and prescription review was hampered by a lack of comparability between studies. For example, most voluntary reporting studies examined errors in acute care settings whilst prescription review occurred primarily in primary care settings.

Improvements in error detection and reporting systems are warranted

A lack of consistency in the approach to reporting errors is another significant weakness of the evidence base. For the evidence base to be truly comprehensive, and indeed, useful as a starting point for addressing the problem in the UK, consistent reporting of all features of errors is essential. The issue of good quality incident reporting and analysis featured as a key finding of two key reviews of the NHS in 2013. Sir Bruce Keogh's review of 14 hospital trusts in England concluded that across all trusts there was 'poor quality root cause analysis of incidents' (Keogh 2013, p. 21). Similarly Don Berwick's review on patient safety concluded that 'Most health care organisations at present have very little capacity to analyse, monitor, or learn from safety and quality information. This gap is costly, and should be closed.' (Berwick 2013, p. 27).

The authors of four studies within this review observed problems with the accuracy of reports (Bateman and Donyai 2010, MacLennan and Smith 2011, National Patient Safety Agency 2008, 2009) and indicated that a lack of consistency and definition of error types may be the cause of reports with insufficient detail and incorrect or miscoded errors. This finding led one study to conclude that 'better error detection and reporting systems' are needed (Bateman and Donyai 2010, p. 5).

Reporting of all key features, such as the pathway point, the error type and the error mechanism (knowledge based error or a mistake) is essential if PME is to be tackled. If evidence suggests that dose errors are the type most likely to occur but we do not know the reasons behind the relatively high rate of dose errors or at which point in the pathway they are most likely to occur, it then becomes difficult to identify appropriate interventions for addressing the problem. For example, if dose errors occur in the prescription of medicines due to miscalculation, then interventions such as electronic prescribing incorporating dose calculators may be of benefit. However, if wrong doses are being prescribed due to a lack of knowledge, then decision-support tools or prescriber training may be of most benefit. In another scenario, if the *correct dose is prescribed* but the error results from a *miscalculation at the administration stage*, then standardised paediatric concentrations or dose banding may be a more suitable area in which to invest time and resources.

Unfortunately, most of the included studies focused only upon a single point in the medicines pathway, predominantly prescription or administration. Others which covered multiple points did not examine at which points in the pathway errors occurred. The narrow focus of the studies in relation to the medicines pathway imposes two key limitations. First, no comparative evidence was available to examine at which points in the pathway medication errors were most prevalent. Second, since few studies examined errors occurring at pathway points other than prescription and administration, we were unable to assess the extent of, for example, dispensing or transcription errors. However, the limited available evidence regarding preparation errors in relation to PN and chemotherapy suggest that errors at this pathway point are minimal (Bateman and Donyai 2010).

Primary care and acute hospital care: evidence across and beyond these settings

Despite the relatively strong findings regarding underdosing and overdosing via off-label prescribing in the UK, there are still some gaps in our knowledge regarding this type of error. The single study covering multiple drug types is now a decade old and is specific to primary care in Scotland only; up-to-date national-level evidence from across the UK is needed to establish what the current overall rates of off-label prescribing are in primary care. Moreover, whilst the evidence we found indicates that this is a significant issue within primary care, we found no national-level assessment of off-label prescribing in other settings such as hospitals. An international review of evidence found that paediatric off-label prescribing in the hospital setting is common (Pandolfini and Bonati 2005) and a recent UK study found it to be associated with paediatric medication errors causing harm (Conroy 2011). Recent evidence from Germany also indicates that the home could be another significant arena in which off-label dose errors occur (Knopf et al. 2013). However, none of the evidence identified for this review covered the issue of errors occurring in the home.

In addition, whilst we do have evidence from both primary and acute care settings, none of the data sources provided a comprehensive overview of errors in both of these settings such that it would be possible to identify which setting constituted the greatest risk to children, and therefore which required the greatest level of intervention.

In conclusion, the evidence indicates areas of significant concern in relation to PME in the UK, namely dose errors in primary and acute hospital care. However, an accurate and comprehensive understanding of the relative importance of the range of error types,

pathway points and healthcare settings requires better and more extensive monitoring and reporting of errors.

6.2.2 Strengths and weaknesses of evidence on the efficacy of international interventions for reducing the incidence of PME (effectiveness synthesis)

Best evidence approach mitigates gaps in the evidence base

Overall, the quality of evidence was reasonable: 25 of the 37 intervention studies were found to be sound and 12 studies were RCTs, a design which evidence indicates is the most appropriate for examining the efficacy of interventions (Oliver et al. 2010). As noted above, the lack of RCTs in relation to EP, which is arguably the most key error-prevention intervention currently being employed, is disappointing. However, the adoption of a 'best evidence' approach meant that we were able to mitigate the dearth of RCTs on EP by examining a large number of less-robust studies – i.e. we were able to draw strength from quantity in the absence of quality. This approach was not effective in all circumstances, however; having identified a dearth of sound evidence regarding another key intervention, pharmacist involvement, we examined our database in an attempt to identify HTC studies for this intervention type, but no such studies were available.

A strong evidence base on EP would be enhanced by evaluations using robust trial designs, statistical meta-analysis and evaluation of EP in primary care

Although the data set on EP is large and has a reasonable level of consistency, it has several key weaknesses. First, the design of the vast majority of the studies (HCT) was less robust, which introduced a moderate risk of bias to each study employing this design. A second weakness was that differences between the studies meant that a pooled statistic was not calculable for any of the four outcomes examined. Third, the use of EP interventions in primary care was not evaluated. Whilst evidence indicates that EP is widely used in primary care in the UK (Ahmed et al. 2013) evidence gathered for the extent synthesis suggests that it is not preventing the high level of off-label prescribing of underdoses and overdoses to children. One possible explanation is that EP used in general practice may be largely generic off-the-peg systems not tailored for use with children, as suggested by the findings from the intervention features synthesis. Thus, evaluation of the impact of tailoring EP systems for use with children within primary care could potentially be a very valuable route to reducing PME.

The promising evidence regarding CDSTs and education interventions is limited by a lack of understanding of key features

Although data sets regarding education interventions and CDSTs largely comprised sound studies employing robust designs (RCT, nRCT) the evidence base for these interventions was much smaller than for EP. Moreover, the primary limitation of the evidence regarding these interventions is its diversity. The individual studies within each data set were very distinct, covering a range of intervention types (e.g. computerised or not) and targeting a range of users (clinicians or caregivers). Thus no strong recommendations can be made about which specific intervention options offer more potential than others. Likewise, with regard to all other intervention types the primary weakness lies in a lack of corroborative evidence; since evidence on each intervention type comes from just one study, the criteria for sufficiency and consistency cannot be met. Although we cannot draw firm conclusions about any of these interventions due to the lack of available evidence, the 'indicators' from sound studies signify areas of practice that should be evaluated more thoroughly.

A more consistent and comprehensive approach to measuring outcomes is needed

Similar to the findings on the extent and nature of PME in the UK in the extent synthesis, evidence on the efficacy of interventions to reduce error is hampered by a lack of consistency among the outcomes measured in the studies. As with the extent synthesis, the included intervention evaluations are primarily focused on either the prescribing or

administering stage of the medication pathway; there are therefore substantial gaps in our knowledge about whether interventions might work to reduce errors at different points in the pathway. Another significant weakness is the dearth of evidence on error-related harm outcomes. However, as noted earlier, it is possible that the lack of identified evidence on mortality and ADEs may represent a weakness in our search strategy, which focused on errors rather than mortality specifically. Other authors have noted the dearth of studies measuring the impact of interventions on mortality and the imperative to do so (Han et al. 2005). Few of the 37 studies reported evidence regarding the impact of the interventions on ADEs (n=6) or mortality (n=4). It is particularly frustrating that some studies were explicit that they measured ADE but did not provide data on it separately from that on PME such that it could be analysed independently. Future research into interventions aiming to reduce medication error and any resulting harm should examine and report evidence on these key outcomes.

In sum, there is strong evidence for the impact of EP and promising evidence for CDSTs and education interventions. However, the evidence base in relation to all interventions could be enhanced by additional rigorous evaluations with a consistent and comprehensive approach to outcomes measurement.

Evidence not published in the English language may enhance the evidence base

We acknowledge that restriction to studies published in the English language is a limitation of the effectiveness synthesis as we may have missed innovations from other countries. However, the significant resources required to conduct an unbiased search of evidence in other languages as well as translation of evidence identified in other languages precluded this.

6.2.3 Strengths and weaknesses of evidence on development and implementation of effective interventions (intervention features synthesis)

The benefits and limitations of drawing on informal evidence

The use of informal evidence, such as was used for the intervention features synthesis, is relatively uncommon in systematic reviews. However, a wealth of valuable information is often presented in the discussion sections of published reports, and the question for the reviewer is how to understand the warrant and utility of this type of knowledge.

It is not the outcome of a formal process evaluation, certainly, and so cannot be regarded as being equivalent to this form of knowledge. It does however reflect the considered opinion of the authors, in the light of their experiences in conducting their research. Can it therefore be regarded as being similar to the primary data collected as the result of, e.g., interviews and questionnaires? In terms of sampling strategy, there is a clear sampling frame, in that we have the views of a defined set of authors. However, the data may not be as complete as might be achievable through a separate study which sought the views of these participants, as not all may have felt the need to express 'process' opinions, and different journals may have different attitudes and requirements for the papers they accept. Arguably, the views presented may be biased, as they may be self-justifying; however, the same weakness can affect data collected through interviews as well, and moreover, these data may actually be more reliable in some ways, as they are the considered and distilled views of the authors, rather than their more instantaneous responses to an interview question. We therefore regard authors' views as being a valuable, if potentially incomplete, picture of their opinions, treated them as primary data and analysed them accordingly, rather than as the product of robust research for synthesis. However, we did find corroborative evidence from another source regarding the use of EP which underscores the validity of the findings. The COSMIC study by Wong et al. (2007) on dose calculation errors in the UK observed the use of EP in practice in three UK hospitals and sought the views of practitioners on their advantages and disadvantages. The main disadvantages reported by users at all three sites were related to the inadequacy of

IT systems and a lack of compatibility with existing hospital systems (Theme 4) thus implying the need for customisation (Theme 1) and ongoing development (Theme 5). The authors of the study also noted that the views of staff were 'important and should be taken into consideration' before implementation (Theme 2); where staff felt they had no influence on the roll out of the system it was seen to lead to 'resistance' (p.100). The study also emphasised the issue of familiarity with the system (Theme 3), concluding that adequate training was 'necessary for the successful maintenance of interventions' and that 'hospitals with clear guidelines and training were more receptive to maintaining Trust procedures' (p.100).

In addition, the findings of the review provide verification of the value of including this type of evidence and our approach to analysing it. The prime example relates to the seemingly critical nature of particular EP intervention features. Although the evidence regarding EP overwhelmingly indicated its efficacy for reducing errors and error-related harm, the negative impact on mortality identified in the study by Han et al. (2005) established that poorly designed or implemented EP may do more harm than good. The emergent findings regarding the key features and successful development and implementation approaches of EP identified that the EP system evaluated by Han et al. (2005) was qualitatively different from those showing positive findings – in particular, it had no decision-support functions and was not tailored for use with children. The validity of this evidence is underscored by the emergent approach to coding employed in the intervention features synthesis; we did not set out to explore differences between successful and less-successful interventions; rather, it became apparent as a result of emergent coding that the Han et al. (2005) intervention was qualitatively different from others. In sum, in order to prevent further harm, it was imperative that we identified what to avoid when designing and implementing EP, and the synthesis of informal evidence was able to provide clear findings with regard to this aim.

6.3 Implications for policy, practice and research

6.3.1 Implications for policy

- With regard to the nature and extent of PME in the UK, the review lends support to calls for improvements in error reporting and monitoring systems highlighted in recent NHS reviews.
- With regard to reducing errors, the strong findings regarding the benefits of EP for use with children, and the clear guidance regarding critical features and development and implementation processes, mean that policy makers should address the lack of EP systems being used in paediatric and neonatal units in hospitals England.

6.3.2 Implications for practice

- With regard to error detection and reporting, the review provides guidance for healthcare institutions regarding the need for a consistent approach to recording and reporting of error which captures both error type and pathway point.
- The review suggests that the development and implementation of EP in acute hospitals is warranted, as is the tailoring of EP within primary care for use with children in order to reduce the high level of dose errors resulting from unintentional off-label prescription.

6.3.3 Implications for research

- The evidence base for EP, CDSTs and education interventions would be enhanced by additional robust evaluations (i.e. RCTs); for other intervention types, additional evidence is essential.

- Evaluations of interventions aiming to reduce PME should adopt a consistent approach to outcome measurement and include error-related harm outcomes, i.e. ADE and mortality.

Part II: Technical description of the review

7. Detailed methods

This chapter describes in detail the methods used to conduct the review. Here we provide a transparent account of the explicit and rigorous methods used to identify, describe, appraise and synthesise the evidence. The review was conducted in two stages: a mapping exercise which described the characteristics of all relevant research for an interim report; and an in-depth review focusing on particular subsets of research identified by the UK Department of Health as being most relevant for its needs.

7.1 User involvement

For systematic reviews to be relevant to policy and practice, potential users of the review must be involved in key stages of the review process (Peersman et al. 1997, Rees and Oliver 2012). We worked closely with the review commissioners (CYPHO) throughout in order to ensure that the review is closely aligned with their needs and emerging programme, for example, in order to help us focus on those areas of most importance, and not to expend resources (and time) pursuing less significant avenues. In particular, we presented the results of some descriptive coding at an early stage in the review. As a result of this, we were able to identify in-depth review questions that were both relevant to their needs and answerable (i.e. we were certain that evidence was available to answer those questions). We also provided 'staged outputs' to ensure that the structure and content of the reports was sufficient for their needs – i.e., we submitted focused briefing reports on individual aspects of the review, thereby allowing their feedback to shape the nature of further reports. Relevant subject knowledge was also present within the review team itself, as it included several members with pharmaceutical and/or medical expertise.

Whilst we had hoped to get a range of responses regarding the scope and focus of the review, the policy timetable meant that we were unable to consult with young people in the earlier stages. Young people's input may be sought by consulting relevant children and young people stakeholder groups on the findings contained in this report, such as the Royal College of Paediatrics and Child Health (RCPCH) Youth Advisory Panel[5] and the Medicines for Children Research Network (MCRN) Young People's Panel.[6]

7.2 Review structure and questions

The review was conducted in two stages. First, the initial aim of the work was to create a systematic map describing the nature and breadth of research activity relating to PME. The purpose of this mapping stage was to support the development of answerable research questions and to avoid spending resources and time pursuing questions for which there was insufficient evidence. The initial question this review aimed to answer was:

> What empirical evidence is available regarding the issue of medication error in children? (**Systematic descriptive map)**

The findings of the systematic descriptive map were shared with the review commissioners to support identification of priority questions for in-depth review. The second part of the work, therefore, involved in-depth appraisal and synthesis of relevant subsets of research to answer the following questions:

> What is the nature and extent of PME in the UK? (**Extent synthesis)**

[5] http://www.rcpch.ac.uk/what-we-do/children-and-young-peoples-participation/youth-advisory-panel/youth-advisory-panel

[6] http://www.mcrn.org.uk

Which interventions are effective for reducing the incidence of PME? **(Effectiveness synthesis)**

What are the key features of effective interventions and how can they be successfully developed and implemented? **(Intervention features synthesis)**

7.3 Definitions for key concepts in the review

To ensure the coherence of the review and the consistency of application of eligibility criteria, we developed definitions for each of the key concepts examined in the review.

7.3.1 PME and related outcomes

Many issues surround a universally accepted definition of what constitutes medication error. This inconsistency in defining medication error is acknowledged to compromise the accuracy, quality and consistency of reporting of such errors (Lisby et al. 2010). Studies included in this review used different definitions of PME and related outcomes. However, we developed standard definitions and coded evidence according to these definitions to facilitate comparability (see Table 7.1). For example, in some studies, 'medication prescription error' was defined exclusively as illegible or incomplete prescriptions, whereas prescriptions with errors such as wrong dose or wrong drug were defined by the studies as 'potential ADEs'. By our definition (see below) both the former and the latter would be categorised as PME. In addition, authors often had more discrete categories of error than our own, for example, distinguishing between intercepted and non-intercepted errors, or serious and minor ADEs; usually however, authors provided an overarching category of total errors or total ADEs. In such a scenario, we opted use these higher-level categories to facilitate comparison across studies.

Table 7.1: PME and related outcomes as defined for this review

Term	Definition used for this review
Adverse drug event (ADE)	Actual harm resulting from medication error
Medication knowledge	Relevant medical knowledge (e.g. about appropriate dosing regimens, preparation and storage of medicines)
Mortality	Death rates - not necessarily explicitly connected with errors
Paediatric medication error (PME)	Errors administered but where any harmful impacts of errors were not reported OR errors detected before drug administration
Turn-around times	The time taken to prescribe, transcribe, dispense, administer or check medicine (e.g. time taken to calculate the correct dose)

Paediatric medication error (PME)

In defining PME, we drew on the work of Aronson (2009), who defined medication error as any 'failure in the treatment process that leads to, or has the potential to lead to, harm to the patient' (p. 599). Medications may be given incorrectly (or omitted) either unintentionally or in ignorance, i.e. a mistake or slip in the medication treatment process. No types of error were excluded from the review; however, we were confined to the way the studies defined and measured error. In this review, as in many of the included studies, we distinguished potential harm, which we defined as PME, and harm resulting from error, which we defined as ADE (see below for further details). PME was thus defined as errors administered but where any harmful impacts of error were not reported OR errors detected before drug administration.

Adverse drug events (ADE)

Whilst some definitions of ADE include adverse drug reactions, i.e. an unwanted or harmful response to a drug under normal conditions of use, for the purposes of this review, ADEs were defined as actual harm resulting specifically from medication error. Many studies distinguished between serious and minor ADEs, whilst others were specific about particular types, e.g. hypo- and hyperglycaemia. Where available, we captured evidence from the broadest available category – e.g. total ADEs.

Mortality

A small number of studies which examined EP interventions captured evidence regarding mortality. Studies compared the percentage of patients who died in the post-intervention period to the percentage of patients who died in the pre-intervention period. There was no assessment in these studies as to what proportion of these deaths was error related. For example, although the findings are considered to be directly attributable to EP they may have resulted from an impact on turn-around times or working practices rather than an increase or decrease in errors per se.

Knowledge

Medication knowledge was examined as an outcome in three of the studies examining education interventions. Studies explored whether educational interventions increased the extent or accuracy of medication knowledge among healthcare practitioners or parents and carers; the assumption being that increased knowledge would lead to reductions in errors.

Turn-around times

Evaluations of a range of interventions incorporated measures to determine whether interventions to reduce errors also resulted in reducing the amount of time required for decision making and delivery of medicines. Many of the studies examining this outcome were evaluating interventions in neonatal or critical care wards where both accuracy and timeliness of decision making are critical for good outcomes.

7.3.2 Medicines

Medicines were defined according to the Medical and Healthcare Products Regulatory Agency (MHRA) guidance based on the 2001 EC directive (MHRA 2012). We included research focusing on any substance or combination of substances presented as having properties for treating or preventing disease in human beings, and which may be used in or administered to human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (MHRA 2012). Thus we included both prescribed and non-prescribed medicines but excluded 'borderline' products such as cosmetics, toilet preparations, disinfectants, food, food supplements or beverages (MHRA 2012).

7.3.3 Children

To ensure a focus on issues specific to medication error in children, we sought studies which focused on children aged 0-12 years, as many adult medicines and preparations are suitable for children over the age of 12. However, since individual studies define 'children' in different ways we included studies which had a specific focus on paediatrics but where the definition of 'children' included those aged 0-18 years. Moreover, in the case of psychopharmaceuticals, we were specifically guided by the review commissioners to extend the age limit to include children aged 0-18 years because of the increased use of these types of drugs in recent years as well as concomitant concerns about both their short- and long-term safety (Vitiello et al. 2009).

7.3.4 Evidence relevant to current practices in the UK

In order to ensure that evidence is relevant to current practices and reflects recent technological and cultural changes within healthcare delivery, we only included reports of studies published in the last ten years. This decision was taken in discussion with the review commissioners. Following production of the map, it was clear that we had a high volume of research. Thus we felt able to include the most recent and therefore most relevant evidence, given the rapid pace of technology change.

To understand how best to address the issue of PME in the UK, it was felt important to establish the nature and extent of the problem. Thus we restricted the inclusion of research on the extent and types of errors to that conducted in the UK. However, with regard to evidence about interventions, we broadened the inclusion criteria to facilitate the inclusion of international evidence about recent innovations and cutting-edge practices. To ensure a reasonable level of relevance to practice in the UK, however, we only included studies reporting evidence about interventions from health systems in high-income and upper-middle-income countries as defined by the World Bank in 2012, i.e., health systems that are comparably well funded and facing similar issues to the UK.

7.3.5 Empirical evidence and rigorous research

In order to reduce the risk of bias in the included evidence, we needed to ensure that the primary studies themselves were well conducted. This requires explicit reporting of methodological issues in order for us to assess the extent to which they avoid methodological bias.

We felt that this was particularly important in relation to studies evaluating the efficacy of interventions. Evidence has shown that RCTs are the most robust form of evidence for evaluating interventions (Oliver et al. 2010). However, we were aware that much of the evidence evaluating such interventions was unlikely to be available from randomised trials. In order to minimise the risk of bias in the included effectiveness studies, whilst simultaneously avoiding an overly restricted or incomplete picture of potentially effective interventions, we specified that we would include the best available quality evidence. This meant restricting inclusion of evidence for each intervention type to studies employing a control or comparison group (i.e. randomised controlled trials (RCTs) or non-randomised controlled trials (nRCTs)) where these were available. Where no RCTs or nRCTs were identified in relation to a particular intervention type, the inclusion criterion was relaxed to include studies employing an historical control (HCT) design (i.e. a less-robust study that compares a group of participants receiving an intervention with a similar group from the past who did not). Whilst it is acknowledged that the inclusion of studies employing this less-rigorous design leads to more uncertainty about their findings, it was felt that the utility of the review would be undermined if available evidence on key intervention types was not included.

7.4 Identification of studies

7.4.1 Searching for studies

To identify relevant research studies, a comprehensive and systematic search strategy was developed in consultation with members of the Children and Young People's Health Outcomes Forum. Initial information provided by the commissioning team on the scope of the review was then developed into the comprehensive search strategy by our very experienced information specialist and other members of the review team, including those with medical and pharmaceutical backgrounds. Key research articles were also used as sources of search terms.

A broad range of electronic databases in the fields of medicine, biomedicine and nursing, as well as in the social sciences and economics, was systematically searched. Databases

specifically for reviews of research and for dissertations and theses were also searched in an attempt to ensure that research evidence not published in journal articles was identified. Topic-specific websites relating to paediatric medicines and medicine safety were also searched. The bibliographic database searches were undertaken in individual databases so that the controlled vocabulary within each database could be utilised. The full list of databases searched is available in Appendix 2. Reference lists of included studies were scanned and Google Scholar was used to identify papers citing included studies. A number of key authors in the field were contacted to ask if they had any further published or unpublished relevant research.

Electronic databases were searched using detailed strings of thesaurus and free-text terms for the three main concepts addressed in this review:

- **children** (example terms - neonates, infants, babies, toddlers, adolescents)
- **medicines** (example terms – medicines, drugs, doses, prescriptions, pharmacy)
- **error** (example terms - error, adverse events, risks, harms, safety)

Search strings for each of these concepts were combined such that the strategy identified research that focuses on children AND medicines AND error. An example of a search string is available in Appendix 1, illustrating the comprehensiveness of the approach and the broad range of search terms employed (e.g. terms relating to issues such as compounding, pharmacy and storage).

All records of research identified by searches were uploaded to the specialist systematic review software EPPI-Reviewer for duplicate stripping, screening for eligibility, data extraction and synthesis (Thomas et al. 2010).

7.4.2 Screening studies for relevance

Each paper identified in the searches was assessed for relevance. To be included in the systematic **descriptive map,** studies had to be:

- focused on medication error
- focused on children aged 0-12 years (or aged 0-18 years if specific to psychopharmaceuticals)
- empirical research
- published in or since 2003
- conducted in high-income or upper-middle-income countries
- published in the English language.

Additional criteria were applied to identify relevant studies for in-depth review. To be included in the **extent synthesis** on the nature and extent of error, studies had to:

- examine rates and types of error in UK settings
- be national-level evidence – i.e. report evidence on error rates/types for the whole of England, Wales, Scotland or Northern Ireland or for the UK as a whole.

For inclusion in the **effectiveness synthesis** on the effectiveness of interventions, studies had to:

- measure the impact of an intervention on outcomes relevant to PME (PME, ADE, mortality, turn-around times or knowledge)
- employ a rigorous research design involving the use of an appropriate control or comparison group (usually be randomised or non-randomised controlled trials).

For inclusion in the **intervention features synthesis** on the content, development and implementation of interventions, studies had to:

- evaluate an intervention with strong and/or promising evidence of effectiveness as identified in the effectiveness synthesis.

7.5 Describing studies: systematic descriptive map

A standardised coding system was developed for the initial mapping work to capture multiple characteristics of included research papers. Codes were developed to describe **key features** such as:

- The point(s) on the **medicines' pathway** with which the research is concerned (e.g. prescription, administration, dispensing, formulation, monitoring/checking)
- The **types of error(s)** that the research focuses on (e.g. wrong drug, wrong dose, wrong strength, wrong frequency, wrong time, wrong route)
- The **outcomes** focused on (e.g. errors, adverse events, mortality)

The detailed coding tool also captured contextual details of the research to reveal the full nature of the evidence base and any gaps, for example in particular age groups or in the UK. The full coding tool can be found in Appendix 3. Example codes include:

- **research design** (e.g. survey, intervention evaluation, observation, audit, qualitative interviews, systematic review)
- **setting** (e.g. hospital, GP practices, home, school, primary, secondary or tertiary care)
- **prescriber/ dispenser/ administrator** of medicines (e.g. pharmacist, doctor, nurse, parent/carer, teacher, self)
- **age range** of children with which the research is concerned (e.g. pre-term newborns <37 weeks gestation, neonates <28 days, infants and toddlers <24 months, children <13 years)
- **condition** (e.g. specific name and chronic/acute)
- **medicines** (e.g. name, main types, types of formulation, site of administration)
- **country** (name).

7.6 Extracting data from studies

Data were extracted from studies meeting the eligibility criteria for inclusion in the extent, effectiveness or intervention features syntheses. Frameworks to extract relevant information were specifically designed for this review and a separate framework was tailored for each synthesis (extent, effectiveness and intervention features). The frameworks for the extent and effectiveness syntheses were both designed to extract data on the study aims and rationale, the research design, the study population and methods of sampling, data collection, analysis and findings. The framework for the extent synthesis additionally captured details of whether studies examining rates or types of error captured data on specific drugs, populations, pathway points or error types. The framework for the effectiveness synthesis captured brief details of the nature of the intervention evaluated and the outcomes measured. The framework for the intervention features synthesis captured detailed information on the content of intervention packages. Data extraction for the intervention features synthesis also involved inductive coding of emergent themes regarding the strengths and weaknesses of individual intervention features and on the barriers to and facilitators of developing and implementing successful interventions.

7.7 Assessing the quality of studies

Bespoke quality appraisal tools were developed to appraise the soundness of evidence for each of the syntheses. For the extent and effectiveness syntheses, studies were assigned an **overall risk of bias** rating based on a) whether the study was **executed soundly** and b) the **appropriateness of the research design** employed. It should be noted that that inappropriate research designs were excluded at the screening stage; all included studies were deemed to employ either highly or moderately appropriate research designs. Table 7.2 provides an overview of the assessment criteria for the Extent and Effectiveness Syntheses.

For the **extent synthesis,** we drew on the quality assessment tool for systematic reviews of observational studies (QATSO) developed by Wong et al. (2008). Studies examining the extent and nature of PME in the UK were assessed as being **sound** if a) the methods for sampling the population were appropriate, b) reliable and valid measurement tools were used and c) appropriate methods for statistical analysis were employed. With regard to the **appropriateness of the research design**, studies were assessed as employing a highly appropriate research design where an active surveillance research design was employed (e.g. prescription review or survey) and a moderately appropriate research design where passive surveillance methods were used (i.e. voluntary reporting schemes), as they are susceptible to skewed reporting or under reporting.

For the **effectiveness synthesis,** we drew on the Cochrane Risk of Bias Tool (Higgins and Altman 2008); trials evaluating the efficacy of interventions were considered to be **sound** if a) the two comparators (intervention and control group) were equivalent on all key characteristics and b) there was no evidence of selective reporting bias (i.e. authors reported on all outcomes that they intended to measure as described in the aims of the study). For RCTs and nRCTs, there was an additional criterion that c) there should be no evidence of a substantial amount of attrition from the study or differential rates of attrition between the two groups. A study was considered not sound if any of the aforementioned forms of bias were present (selection bias, reporting bias, attrition bias). In relation to the **appropriateness of research designs**, RCTs were assessed as being the most appropriate design and rated 'Gold Standard' since they used concurrent allocation reducing the possibility of changes practice over time that could influence the results, and random allocation which ensures no systematic differences between groups. Trials using concurrent but non-random allocation (nRCTs) were assessed as being a highly appropriate design, since although they are susceptible to systematic differences between groups, we assessed whether equivalence between groups on major prognostic factors was reported. HCT designs were assessed as being moderately appropriate since they are susceptible to changes over time (i.e. in addition to the implementation of the intervention other changes in hospital working practices may have occurred which affected the findings). Evidence has shown that effect size tends to be more pronounced in historically controlled studies (Oliver et al. 2010).

For **the intervention features synthesis,** since only a small number of studies undertook formal process evaluations, and since we decided that it was inappropriate to attempt to appraise the soundness of informal evidence drawn from authors' reflections and informal observations, we do not present risk of bias ratings. The potential weaknesses of these informal data are acknowledged and attempts to mitigate them have been undertaken, as described below in the section on synthesis methods.

Table 7.2: Risk of bias assessments for the extent and effectiveness syntheses

Risk of bias criterion	Extent synthesis	Effectiveness synthesis
Is the study sound?	A study was rated as sound if: i. The methods for sampling the population were appropriate ii. Reliable and valid measurement tools were used iii. Appropriate methods for statistical analysis were employed	A study was rated as sound if: i. The two comparators (intervention and control group) were equivalent ii. There was no evidence of selective reporting bias iii. There was no evidence of a substantial amount of attrition from the study or differential rates of attrition between the two groups*

Is the research design appropriate?	Research designs were rated as: • highly appropriate - active surveillance design • moderately appropriate – passive surveillance	Research designs were rated as: • gold standard - RCT • highly appropriate - nRCT • moderately appropriate – HCT**
What is the overall risk of bias?	**Low risk of bias** = Sound studies employing gold standard or highly appropriate research design **Moderate risk of bias** = Sound studies employing moderately appropriate research design **High risk of bias** = Any study that is not sound	

* Applicable to RCTs and nRCTs only – attrition was not assessed for HCT studies

**HCT studies were only included in the absence of RCT or nRCT evidence

7.8 Quality assurance

Studies were screened independently by two reviewers at both the title/abstract and full-text screening stages in order to identify potential differences in interpretation of the criteria and to refine guidance for reviewers. Screening was conducted by single reviewers once an agreement rate of 90% was achieved.

For each included study, data extraction and quality appraisal was undertaken by two reviewers, who first worked independently and then compared their work to reach a consensus.

7.9 Synthesis methods

Drawing on previous reviewing experience, we developed a range of bespoke methods for synthesising each of the three different types of evidence.

7.9.1 Extent synthesis

Evidence on the rates and types of error in the UK for the extent synthesis was synthesised using a narrative approach. The reviewers looked across the set of studies and produced a descriptive summary of evidence relating to both the extent of error in the UK and the types of error commonly reported; the findings were grouped according to error types (e.g. dose errors) and pathway points (e.g. prescription errors, administration errors). The characteristics of individual studies were also presented in a structured tabular format.

The overall strength of conclusions regarding each finding is based on two considerations: the consistency and sufficiency of the evidence base.

- **Consistency** refers to the whether the studies agree about the direction of findings (GRADE Working Group 2004). A completely consistent evidence base would have 100% of included studies agreeing about the direction of findings (e.g. about the nature and extent of errors in the UK, or whether interventions reduce the number of errors or not). A moderately consistent evidence base would have 75-99% of studies agreeing about the direction of findings. An inconsistent evidence base would have fewer than 75% of studies agreeing on the direction of findings.
- **Sufficiency** refers to whether the *quality* and the *quantity* of available evidence is adequate for drawing overall conclusions (i.e. a minimum number of studies without a high risk of bias). Here we have stipulated that at least four studies without a high risk of bias must be present to draw strong conclusions.

Drawing on the GRADE approach for being explicit and transparent about the strength of recommendations (Guyatt et al. 2008) we developed an approach for grading the strength

of the evidence for each conclusion. The approach draws on assessments for consistency and sufficiency; Table 7.3 provides details of the grading system.

Table 7.3: System for grading the strength of the evidence for each finding

Grade	Criteria	Rationale
Strong	At least four studies with low or moderate risk of bias;* findings meet criterion for consistency	• Evidence corroborated by a large number of reliable studies • The pattern indicates that additional high-quality evidence would be very unlikely to contradict the overall conclusions • Even if an additional study with contradictory evidence were found, the overall consistency of the evidence base would probably remain above 75%
Promising	Two or three studies with low or moderate risk of bias;* findings meet criterion for consistency	• Reliable evidence corroborated by at least one other study • Patterns indicate that additional high quality evidence would be unlikely to contradict the overall findings • If an additional high-quality study with contradictory evidence were found, the overall consistency of the evidence base would probably fall below 75%
Tentative	Single study with low or moderate risk of bias	• Findings are reliable but uncorroborated • No patterns in the evidence can be determined • Identification of a high-quality study with contradictory evidence would change our overall conclusions
Inconclusive	Evidence only available from studies with a high risk of bias	• The findings are neither reliable nor corroborated • No overall conclusions can be drawn

*Supplementary evidence from studies with a high risk of bias may contribute to strong or promising findings where it is concordant with the overall direction of findings of the minimum stated number of studies with low/moderate risk of bias

7.9.2 Effectiveness synthesis

For the effectiveness synthesis, the findings from studies evaluating similar interventions (e.g. electronic prescribing) were grouped and synthesised. Where studies reported sufficient numerical information, effect size estimates were calculated to indicate a) whether the intervention reduced errors or not and b) the scale of any impact (Cooper et al. 2009). Where effect sizes could not be calculated, the authors' description of the findings was reported. Assessments were made to gauge the potential for combining the findings of multiple studies in a statistical meta-analysis; calculation of a pooled estimate of effect, however, was not found to be appropriate in relation to any intervention type.

The overall strength of conclusions regarding each intervention in relation to each relevant outcome is based on two considerations: the consistency and sufficiency of the evidence base as defined above. Using the same algorithm as for the extent synthesis, we graded the strength of the evidence as strong, promising, tentative or inconclusive.

7.9.3 Intervention features synthesis

We captured all available information about intervention components as described by the authors; the narrative synthesis comprises textual description and tabular representation. However, inconsistency in the level of detail provided and in the terminology and definitions used restricted our ability to provide a comprehensive and accurate picture of intervention packages. For example, whilst most studies provided detailed intervention descriptions, others provided more limited information, and one study simply named the intervention without describing the features of the system at all. Moreover, even in studies with at least some description of components, it remained unclear whether features that were not described were not present in the intervention or whether they were simply overlooked in the description. Inconsistency in the definition and description of features may have also caused inaccuracies in our summary; for example, studies appeared to have different understandings of structured order sets within EP packages. We have tried to mitigate this by coding and categorising the available descriptions according to a single definition so that we are, as far as possible, comparing like with like; again, differing levels of detail hampered this process.

In capturing evidence on **intervention strengths and weaknesses, development and implementation**, we have taken a broader definition of evidence than is typical for systematic reviews, balancing the need for insight with the need for rigorously collected, and therefore trustworthy research data. A small number of the included studies provided **formal evidence** about process and implementation issues gathered using robust research methods. This formal evidence related exclusively to the issue of acceptability of or satisfaction with the intervention. However, the vast majority of studies also provided a wealth of **informal evidence** in the nature of rich description about the experience of developing, using and implementing interventions. Such evidence included authors' reporting of informal feedback from users, authors' observations of the impact of interventions on working practices, and authors' hypothetical conclusions regarding associations between intervention features and the success (or otherwise) of the intervention. Thematic analysis of this qualitative data enabled us to identify key strengths and weakness of interventions and the barriers to and facilitators of development and implementation. However, though this evidence provides vital insight into the systems under study, since formal research methods designed to reduce inherent biases were not employed, it must be recognised that this evidence is at risk of being partial or biased in some way. Attempts to mitigate this weakness included a) being explicit about the extent of data on a particular issue and the consistency of opinion across the studies and b) checking if the emergent themes are corroborated by evidence in the effectiveness synthesis.

Figure 7.1: Flow of studies through the review

Criteria on which reports excluded:

Systematic map criteria

1 - LANGUAGE: Not English

2 - DATE: Not published in/after 2003

3 - GEOGRAPHY: Not in higher or upper middle income countries

4 - TOPIC: Not medication error

5 - POPULATION: Not children aged 0-12 years/(0-18 psychopharmaceuticals)

6 - EMPIRICAL: Not empirical research

Error extent synthesis criteria

A1 – AIM & CONTEXT: Not on rates/types of error in UK setting

A2 – NATIONAL LEVEL: Not national-level evidence

Intervention effectiveness synthesis criteria

B1 – PME INTERVENTION: Not evaluating intervention impact on PME outcomes

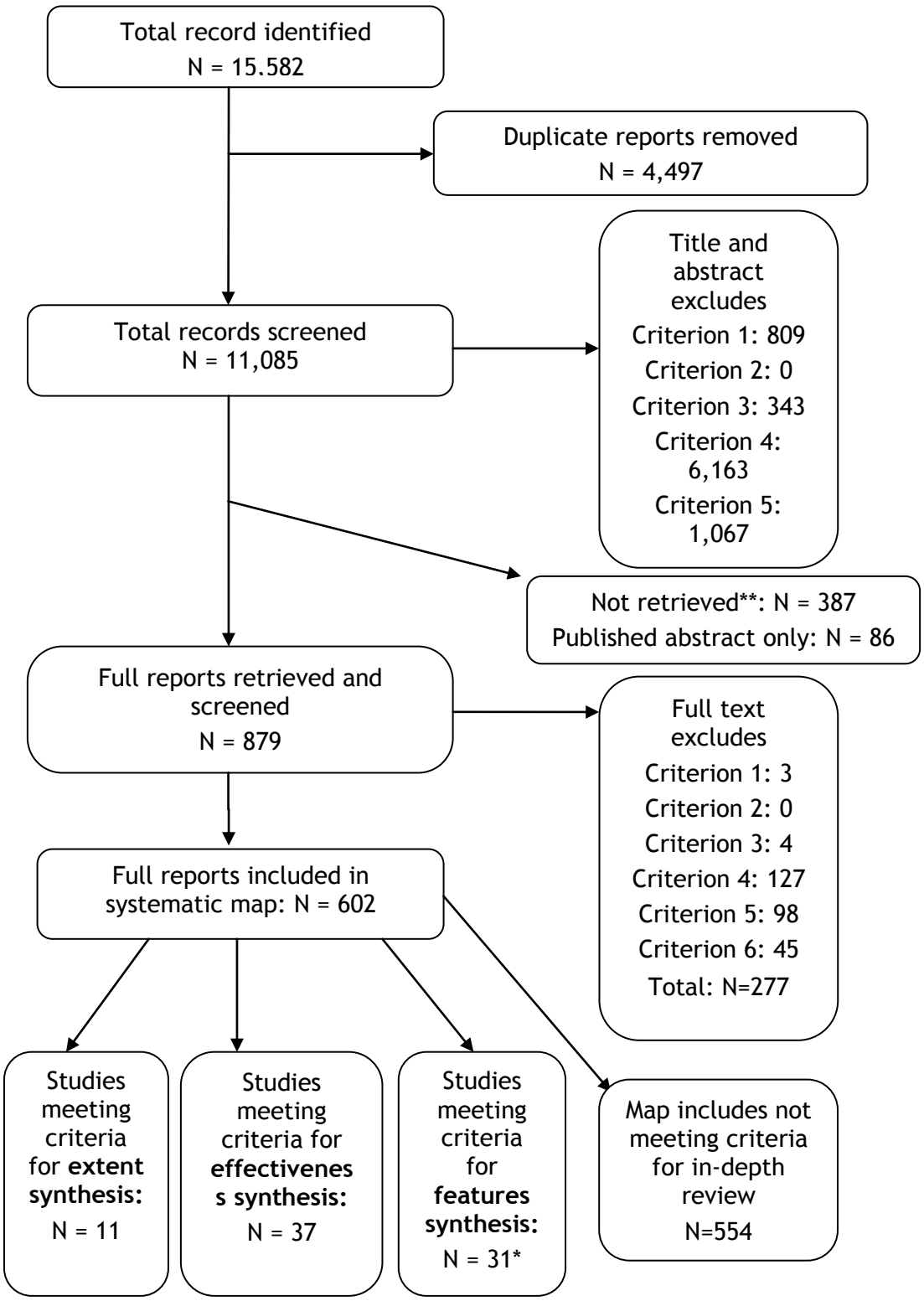
B2 – RESEARCH DESIGN: No control or comparison group

Intervention features synthesis criteria

C1 – STRONG/PROMISING INTERVENTION: Not strong/promising intervention as identified in the effectiveness synthesis

*The 31 studies included in the intervention features synthesis are drawn from the set included in the effectiveness synthesis.

**We were unable to retrieve a small number of papers despite extensive effort – the majority were intentionally not retrieved as retrieval was ceased for certain study types following identification of in-depth review questions



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Appendices

Appendix 1: Example search strategy

Search history - MEDLINE in EBSCO host, date 23 May 2013

Notes – All search = S92 (n=9,330); 1990 onwards (n=7,688); 2000 onwards, S95 (n=5,882)

= no or one character

N = proximity regardless of the order in which they appear

* = truncation

#	Query	Limiters/Expanders	Results
S95	S94	Limiters - Date of Publication from: 20000101-20131231 Search modes - Boolean/Phrase	5,882
S94	S92 NOT S93	Search modes - Boolean/Phrase	9,258
S93	PT Editorials OR Comments OR News	Search modes - Boolean/Phrase	152,338
S92	S91 AND S24	Search modes - Boolean/Phrase	9,330
S91	S28 OR S32 OR S43 OR S44 OR S53 OR S50 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S61 OR S60 OR S62 OR S63 OR S64 OR S65 OR S66 OR S71 OR S90 OR S80 OR S79 OR S82 OR S81 OR S78 OR S77 OR S84 OR S83 OR S87 OR S88	Search modes - Boolean/Phrase	58,610
S90	(S67 OR S68) AND (S72 OR S73 OR S74 OR S76)	Search modes - Boolean/Phrase	6,036
S89	S28	Search modes - Boolean/Phrase	10,162
S88	AB (problems N8 dosing) OR TI (problems N8 dosing)	Search modes - Boolean/Phrase	133
S87	S85 AND S86	Search modes - Boolean/Phrase	6,780
S86	TI (problem#) NOT TI ("mental health problem#" OR "behavio#r* problem#")	Search modes - Boolean/Phrase	166,995
S85	TI (medicament# OR medicine# OR drug# OR dosing OR pharmacovigilance OR medication# OR prescription# OR prescribed OR prescribing OR dosage# OR dose# OR pharmaceutical#)	Search modes - Boolean/Phrase	615,578
S84	AB ("risk assessment" OR "checking system" OR "checking systems" OR "due diligence" OR incident# OR "double checking" OR "automated checking" OR	Search modes - Boolean/Phrase	1,202

#	Query	Limiters/Expanders	Results
	"patient adherence" OR "patient compliance" OR "patient use" OR "patient usage" OR "safe production" OR "safe administration") N2 (medicament# OR medicine# OR dosing OR pharmacovigilance OR medication# OR prescription# OR prescribed OR prescribing OR dosage# OR dose# OR dosing OR pharmaceutical#)		
S83	TI ("risk assessment" OR "checking system" OR "checking systems" OR "due diligence" OR incident# OR "double checking" OR "automated checking" OR "patient adherence" OR "patient compliance" OR "patient use" OR "patient usage" OR "safe production" OR "safe administration") AND (medicament# OR medicine# OR dosing OR pharmacovigilance OR medication# OR prescription# OR prescribed OR prescribing OR dosage# OR dose# OR dosing OR pharmaceutical#)	Search modes - Boolean/Phrase	5,862
S82	TI "effective prescribing practice" OR "effective prescribing practices"	Search modes - Boolean/Phrase	1
S81	AB "effective prescribing practice" OR "effective prescribing practices"	Search modes - Boolean/Phrase	6
S80	TI unsafe N1 (dose OR dosage OR dosing OR doses OR dosages)	Search modes - Boolean/Phrase	0
S79	AB unsafe N1 (dose OR dosage OR dosing OR doses OR dosages)	Search modes - Boolean/Phrase	15
S78	TI (safety OR safe OR safely OR unsafe OR unsafely OR "risk management" OR checking OR validation) N2 (prescribing OR prescription# OR dispensing OR dispensary)	Search modes - Boolean/Phrase	210
S77	AB (safety OR safe OR safely OR unsafe OR unsafely OR "risk management" OR checking OR validation) N2 (prescribing OR prescription# OR dispensing OR dispensary)	Search modes - Boolean/Phrase	534
S76	S75 NOT ((MH"Suicide+") OR S46)	Search modes - Boolean/Phrase	3,569
S75	TI ((unintentional* OR accidental* OR drug#) N1 (overdose# OR poison* OR overdosing)) OR AB((unintentional* OR accidental* OR drug#) N1 (overdose# OR poison* OR overdosing))	Search modes - Boolean/Phrase	4,297
S74	AB ((reduc* OR decreas*) N1 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepenc* OR malpractice OR incident# OR event# OR negligen* OR disparit* OR lapse# OR omission#))	Search modes - Boolean/Phrase	12,082

#	Query	Limiters/Expanders	Results
S73	TI (literacy AND (error# OR mistake#)) OR AB (literacy AND (error# OR mistake#))	Search modes - Boolean/Phrase	172
S72	TI ((reduc* OR decreas*) N1 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepenc* OR malpractice OR incident# OR event# OR negligen* OR disparit* OR lapse# OR omission#))	Search modes - Boolean/Phrase	1,420
S71	S69 AND S70	Search modes - Boolean/Phrase	5,510
S70	AB ((administer* OR administration OR preparation OR "patient history" OR "medical history" OR mathematical OR equipment# OR calibration# OR calculation# OR checking OR interpret* OR dilution# OR diluting OR formulation# OR formulating OR storage OR storing OR label#ing OR practice OR medical OR clinical OR polypharmacy OR transcription# OR transcribing OR "chart review" OR charting OR production OR manufactur* OR practictioner# OR professional) N1 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepenc* OR malpractice OR incident# OR event# OR negligen* OR disparit* OR lapse# OR omission#)) OR TI ((administer* OR administration OR preparation OR "patient history" OR "medical history" OR mathematical OR equipment# OR calibration# OR calculation# OR checking OR interpret* OR dilution# OR diluting OR formulation# OR formulating OR storage OR storing OR label#ing OR practice OR medical OR clinical OR polypharmacy OR transcription# OR transcribing OR "chart review" OR charting OR production OR manufactur* OR practictioner# OR professional) N1 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepenc* OR malpractice OR incident# OR event# OR negligen* OR disparit* OR lapse# OR omission#))	Search modes - Boolean/Phrase	20,866
S69	S67 OR S68	Search modes - Boolean/Phrase	2,290,974
S68	TI (dosing OR dosage# OR dose# OR medication# OR medicine# OR medicament# OR prescription# OR prescribing OR drug# OR pharmaceutical#)	Search modes - Boolean/Phrase	613,846
S67	AB (dosing OR dosage# OR dose# OR medication# OR medicine# OR medicament# OR prescription# OR prescribing OR drug# OR pharmaceutical#)	Search modes - Boolean/Phrase	1,985,263

#	Query	Limiters/Expanders	Results
S66	AB (polypharmacy OR pharmacovigilance OR posology OR dispensing OR dispensary OR pharmacy OR pharmacist#) N2 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepenc* OR malpractice OR incident# OR event# OR negligen* OR disparit* OR lapse# OR omission#)	Search modes - Boolean/Phrase	479
S65	TI (polypharmacy OR pharmacovigilance OR posology OR dispensing OR dispensary OR pharmacy OR pharmacist#) N2 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepenc* OR malpractice OR incident# OR event# OR negligen* OR disparit* OR lapse# OR omission#)	Search modes - Boolean/Phrase	190
S64	AB "underdosing" OR "under dosing" OR "underdose" OR "under dose"	Search modes - Boolean/Phrase	677
S63	TI "underdosing" OR "under dosing" OR "underdose" OR "under dose"	Search modes - Boolean/Phrase	53
S62	AB ((dosing OR dosage# OR dose# OR medication# OR medicine# OR medicament# OR prescription# OR prescribing) N1 (erroneous* OR wrong* OR inappropriat* OR incorrect* OR misuse OR misusing OR improper* OR inadequat* OR misdose# OR misdosing OR excess*)) OR TI ((dosing OR dosage# OR dose# OR medication# OR medicine# OR medicament# OR prescription# OR prescribing) N1 (erroneous* OR wrong* OR inappropriat* OR incorrect* OR misuse OR misusing OR improper* OR inadequat* OR misdose# OR misdosing OR excess*))	Search modes - Boolean/Phrase	5,329
S61	AB ("medication difference" OR "medication differences" OR "prescribing difference" OR "prescribing differences" OR "prescription difference" OR "prescription differences") OR TI ("medication difference" OR "medication differences" OR "prescribing difference" OR "prescribing differences" OR "prescription difference" OR "prescription differences")	Search modes - Boolean/Phrase	52
S60	AB ((medication# OR prescribing OR prescription#) N1 (omission# OR disparit* OR event#)) OR TI ((medication# OR prescribing OR prescription#) N1 (omission# OR disparit* OR event#))	Search modes - Boolean/Phrase	973
S59	TI excess* N1 (dosing OR dosage# OR dose#)	Search modes - Boolean/Phrase	120
S58	AB excess* N1 (dosing OR dosage# OR dose#)	Search modes - Boolean/Phrase	1,344
S57	TI misdose# OR misdosing OR "mis dose#" OR "mis dosing"	Search modes - Boolean/Phrase	1

#	Query	Limiters/Expanders	Results
S56	AB misdose# OR misdosing OR "mis dose#" OR "mis dosing"	Search modes - Boolean/Phrase	11
S55	AB (dosing OR dosage# OR dose# OR medication# OR medicine# OR medicament# OR prescription# OR prescribing OR drug# OR pharmaceutical#) N2 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation OR miscalculations OR misadventure OR misadventures OR mishap OR mishaps OR discrepenc* OR malpractice OR negligen* OR incidents OR incident OR accident* OR erroneous* OR wrong* OR inappropriat* OR incorrect* OR misuse OR misusing OR improper* OR inappropriat* OR iatrogenic)	Search modes - Boolean/Phrase	9,956
S54	TI (dosing OR dosage# OR dose# OR medication# OR medicine# OR medicament# OR prescription# OR prescribing OR drug# OR pharmaceutical#) N2 (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation OR miscalculations OR misadventure OR misadventures OR mishap OR mishaps OR discrepenc* OR malpractice OR negligen* OR incidents OR incident OR accident* OR erroneous* OR wrong* OR inappropriat* OR incorrect* OR misuse OR misusing OR improper* OR inappropriat* OR iatrogenic)	Search modes - Boolean/Phrase	4,468
S53	(S51 OR S52) AND (S41 OR S47)	Search modes - Boolean/Phrase	8,213
S52	AB (error# OR mistake OR mistakes OR miscalculation# OR misadventure# OR mishap# OR discrepency OR discrepencies OR malpractice OR negligence OR negligent OR erroneous* OR misuse OR misusing OR misdos* OR (excess* N1 dose#) OR (excess* N1 dosag*) OR (excess* N1 dosing) OR "under dosing" OR underdosing OR underdose OR "under dose" OR iatrogenic OR omission#)	Search modes - Boolean/Phrase	211,277
S51	TI (error# OR "near miss" OR "near misses" OR mistake OR mistakes OR miscalculation OR miscalculations OR misadventure OR misadventures OR mishap OR mishaps OR discrepency OR discrepencies OR malpractice OR negligence OR negligent OR erroneous* OR incorrect* OR misuse OR misusing OR improper* OR inadequat* OR misdos* OR (excess* N1 dose#) OR (excess* N1 dosag*) OR (excess* N1 dosing) OR "under dosing" OR underdosing OR underdose OR "under dose" OR iatrogenic OR unintentional* OR omission#)	Search modes - Boolean/Phrase	55,373
S50	S49 NOT (S45 OR S46)	Search modes - Boolean/Phrase	9,117
S49	S47 AND S48	Search modes - Boolean/Phrase	9,308

#	Query	Limiters/Expanders	Results
S48	(MH "Safety-Based Drug Withdrawals") OR (MH "Patient Safety") OR (MH "Risk Assessment") OR (MH "Risk Management") OR (MH "Safety Management") OR (MH "Safety") OR (MH "Risk Reduction Behavior") OR (MH "Malpractice+") OR (MH "Accident Prevention+") OR (MH"risk factors") OR (MH "risk")	Search modes - Boolean/Phrase	797,523
S47	(MH "Drug and Narcotic Control") OR (MH "Drug Approval") OR (MH "Drug Industry") OR (MH "Drug Monitoring") OR (MH "Drug Recalls") OR (MH "Legislation, Drug+") OR (MH "Drug Discovery+") OR (MH "Drug Labeling") OR (MH "Medication Reconciliation") OR (MH "Pharmacoepidemiology") OR (MH "Product Surveillance, Postmarketing") OR (MH "Technology, Pharmaceutical") OR (MH "Drug Compounding") OR (MH "Drug Repositioning") OR (MH "Drug Overdose" NOT MH "Suicide+") OR (MH "Off-Label Use") OR (MH "Dosage Forms") OR (MH "Drug Prescriptions") OR (MH "Drug Dosage Calculations") OR (MH "Drug Substitution") OR (MH "Drug Packaging+") OR (MH "polypharmacy")	Search modes - Boolean/Phrase	193,733
S46	(MH "Alcohol Drinking+") OR (MH "Street Drugs+")	Search modes - Boolean/Phrase	55,309
S45	(MH "Transportation+") OR (MH "Accidents, Traffic") OR (MH" Automobile Driving+") OR (MH "Alcohol Drinking+") OR (MH "Street Drugs+")	Search modes - Boolean/Phrase	138,103
S44	S30 AND (S33 OR S34 OR S35 OR S37 OR S38 OR S39 OR S40)	Search modes - Boolean/Phrase	878
S43	S41 AND S42	Search modes - Boolean/Phrase	973
S42	((MH "Iatrogenic disease+") OR (MH "Medical Errors"))	Search modes - Boolean/Phrase	23,647
S41	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S30	Search modes - Boolean/Phrase	454,421
S40	(MH "Drug Therapy/AE/CT") OR (MH "Drug Toxicity/PC")	Search modes - Boolean/Phrase	7,632
S39	(MH "ADVERSE DRUG REACTION REPORTING SYSTEMS+")	Search modes - Boolean/Phrase	5,161
S38	(MH "Drug Packaging+")	Search modes - Boolean/Phrase	8,991
S37	(MH "drug substitution+") OR (MH "Pharmacovigilance") OR (MH "Polypharmacy") OR (MH "Drug interactions+")	Search modes - Boolean/Phrase	137,253

#	Query	Limiters/Expanders	Results
S36	(MH "Drug Dosage Calculations")	Search modes - Boolean/Phrase	770
S35	(MH "pharmaceutical preparations")	Search modes - Boolean/Phrase	45,618
S34	(MH "prescription drugs+")	Search modes - Boolean/Phrase	2,288
S33	(MH "drug prescriptions") OR (MH "dosage forms+") OR (MH "off-label use+")	Search modes - Boolean/Phrase	258,420
S32	S30 AND S31	Search modes - Boolean/Phrase	67
S31	(MH "Dentist's Practice Patterns+") OR (MH "Nurse's Practice Patterns+") OR (MH "Physician's Practice Patterns+") OR (MH "Medical History Taking")	Search modes - Boolean/Phrase	55,715
S30	(MH "Drug Overdose+") NOT ((MH"Suicide+") OR (MH "Street Drugs+") OR (MH "Alcohol Drinking+")) OR (MH "Drug Dosage Calculations")	Search modes - Boolean/Phrase	6,125
S29	(MH "Observer Variation+") OR (MH "Iatrogenic disease+") OR (MH "Medical Errors") OR (MH "Dentist's Practice Patterns+") OR (MH "Nurse's Practice Patterns+") OR (MH "Physician's Practice Patterns+") OR (MH "Medical History Taking")	Search modes - Boolean/Phrase	107,948
S28	S25 OR S26 OR S27	Search modes - Boolean/Phrase	10,162
S27	(MH "Prescription Drug Misuse")	Search modes - Boolean/Phrase	130
S26	(MH "medication errors")	Search modes - Boolean/Phrase	9,664
S25	(MH "Inappropriate Prescribing+")	Search modes - Boolean/Phrase	420
S24	S11 OR S23	Search modes - Boolean/Phrase	3,104,802
S23	S20 OR S22	Search modes - Boolean/Phrase	1,417,856
S22	S21 NOT S18	Search modes - Boolean/Phrase	1,417,854
S21	S12 OR S13 OR S14 OR S15 OR S19	Search modes - Boolean/Phrase	1,619,921
S20	S18 AND S19	Search modes - Boolean/Phrase	2
S19	(MH "Pregnancy in Adolescence+")	Search modes - Boolean/Phrase	6,363
S18	S16 OR S17	Search modes - Boolean/Phrase	677,232

#	Query	Limiters/Expanders	Results
S17	(MH "Pregnancy+") NOT (MH "Pregnancy in Adolescence+")	Search modes - Boolean/Phrase	676,475
S16	(MH "Maternal exposure+")	Search modes - Boolean/Phrase	4,589
S15	(MH "Infant+") OR (MH "Infant, Premature+") OR (MH "Infant Welfare") OR (MH "Infant, Newborn+")	Search modes - Boolean/Phrase	897,070
S14	AF neonat* OR SO neonat*	Search modes - Boolean/Phrase	37,762
S13	AB child OR children OR infant# OR babies OR baby OR neonat* OR newborn#	Search modes - Boolean/Phrase	883,762
S12	TI child OR children OR infant# OR babies OR baby OR neonat* OR newborn#	Search modes - Boolean/Phrase	689,712
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	Search modes - Boolean/Phrase	2,711,363
S10	SO paediatr* OR peadiatr* OR pediatr*	Search modes - Boolean/Phrase	440,910
S9	AF (paediatr* OR peadiatr* OR pediatr*)	Search modes - Boolean/Phrase	325,598
S8	AB pediatric OR pediatrics OR preadolescent OR preadolescents OR prepubescence OR prepubescent OR puberty OR pubescence OR pubescent OR schoolchild OR schoolchildren OR teenagers OR toddler OR toddlers OR paediatric OR paediatrics OR peadiatric OR peadiatrics OR "pre adolescent" OR "pre adolescents" OR "pre pubescence" OR "pre pubescent" OR "school pupil" OR "school pupils" OR "school student" OR "school students" OR "young people" OR adolescent OR adolescents OR boys OR girls OR juvenile	Search modes - Boolean/Phrase	361,926
S7	TI pediatric OR pediatrics OR preadolescent OR preadolescents OR prepubescence OR prepubescent OR puberty OR pubescence OR pubescent OR schoolchild OR schoolchildren OR teenagers OR toddler OR toddlers OR paediatric OR paediatrics OR peadiatric OR peadiatrics OR "pre adolescent" OR "pre adolescents" OR "pre pubescence" OR "pre pubescent" OR "school pupil" OR "school pupils" OR "school student" OR "school students" OR "young people" OR adolescent OR adolescents OR boys OR girls OR juvenile	Search modes - Boolean/Phrase	244,020
S6	(MH "child, preschool+")	Search modes - Boolean/Phrase	713,505
S5	(MH "child welfare+")	Search modes - Boolean/Phrase	46,747

#	Query	Limiters/Expanders	Results
S4	(MH "pediatrics+")	Search modes - Boolean/Phrase	41,292
S3	(MH "Child+")	Search modes - Boolean/Phrase	1,471,490
S2	(MH "Adolescent+")	Search modes - Boolean/Phrase	1,516,618
S1	(MH "Adolescent Medicine+")	Search modes - Boolean/Phrase	1,256

Searching 'key' of items searched for and the lines:

		Exclusions
S24	pediatrics	
S28	Mesh Medication Errors	
S32	Mesh medical practice And drug overdose/ drug calculations	NOT suicide NOT alcohol drinking NOT street drugs
S43	Mesh Medical Errors/iatrogenic disease AND drugs	
S44	Mesh drug overdose/ drug calculations AND drugs	
S53	Mesh drug prescriptions/ Mesh drug control/ mesh adverse effects toxicity etc AND Free-text errors	NOT transportation/ driving / suicide NOT alcohol drinking NOT street drugs
S50	Mesh drug control AND Safety management	NOT transportation/ driving NOT alcohol drinking NOT street drugs
S53	Mesh drug control AND free text errors	
S54 OR S55	Free text - drug NEAR errors	
S56 OR S57	Free text - misdosing	
S58 OR S59	Free text excess dosing	
S61 OR S60	free text prescribing differences/ medication differences	
S62	free text - dosing/ prescribing NEAR errors	
S63 OR S64	free text underdosing	
S65 OR S66	free text dispensing/pharmacy NEAR errors	
S71	free text dosing/prescribing NEAR production/calculation/ admin errors	

S90	free text dosing/prescribing NEAR reducing/ decreasing errors	
S80 OR S79	free text unsafe dosages	
S82 OR S81	free text effective prescribing practices	
S78 OR S77	free text safety NEAR prescribing/dispensary	
S84 OR S83	free text checking/compliance/ saftey/ unsafe NEAR drugs/prescriptions	
S87	free text TITLE Only problems AND drugs/prescriptions	
S88	free text Abstract Dosing NEAR/8 problems	
S90	free text literacy AND error/mistakes AND medication	
S90	free text accidental overdose/poisoning AND medication	NOT suicide/ street drugs (MESH)

Appendix 2: List of databases searched

British Nursing Index (BNI)

Cochrane Central Register of Controlled Trials (CENTRAL)

CINAHL

Cochrane reviews

DARE

Dart-Europe

Designing Out Medical Errors Project (DOME)

Economic evaluations

EMBASE

Electronic Theses Online Service (EThOS)

European Agency for the Evaluation of Medicinal Products

Google Scholar

Global Research in Paediatrics (GRIP)

Health Management Information Consortium (HMIC)

Index to Theses

Institute for Healthcare Improvement

Institute for safe medication practices

Institute of Medicine – National Academy of Sciences

International Pharmaceutical Abstracts (IPA)

Medicines and Healthcare Products Regulatory Agency

Medline

National Patient Safety Agency

New York Academy of Medicine Grey Literature report

NHS Evidence

Neonatal and Paediatric Pharmacists Group (NPPG)

Open Grey

PsychInfo

Royal Pharmaceutical Society

World Health Organization (WHO) - medicines for children - resources, progress, scientific publications

ZETOC

Appendix 3: Systematic descriptive map: tool for coding studies

1) LEVEL OF DATA
   a) Primary research
   b) Systematic review

2) COUNTRY
   a) UK
   b) Non-UK

3) TYPE OF EVIDENCE
   a) Extent of errors/associations with errors
   b) Intervention evaluation
   c) Views research (qualitative or survey)
      (Any research which collects the views of people about experiences of Paediatric Medication Error (PME), their views on the causes, context of PME etc.)
   d) Cost/economic data
   e) Case report (Not strictly applying the empirical inclusion criterion for this type of evidence)
   f) Case series study
   g) non-evaluated interventions (i.e. descriptions of relevant interventions)
   h) Other (Specify)

4) **CONDITION FOCUS** - Does the paper focus on children with a specific condition? (specify)
   a) Yes (specify)
   b) No (paper does not focus on specific condition(s)

5) **DRUG FOCUS** - Does the paper focus on drug or type of drug? (specify)
   a) No – no focus on drugs/drug types (move to next question)
   b) Yes - multi drug focus (NOW CODE TYPES)
      Yes - single drug focus (NOW CODE TYPES BELOW)
   c) **DRUG TYPES** (code if answered YES above)
      i) Anaesthesia
      ii) Antibiotics (Anti-bacterials only)
      iii) Antimicrobials (All antimicrobials EXCEPT FOR ANTIBIOTICS i.e. antifungals, antivirals, antiprotozoals)
      iv) Off label drug use
      v) Opioids
      vi) Paracetamol
      vii) Parenteral feeding
      viii) 'Specials' (Create-your-own formulation)
      ix) Unlicensed drugs
      x) anticonvulsants/antiepileptics
      xi) psychopharmaceuticals
      xii) Other type of drug (specify)

6) **SETTING FOCUS** - Does the paper focus on a particular setting? (SETTING = site in which error occurred)
   a) No - no setting focus (GO TO NEXT QUESTION)
   b) Yes - multi setting focus (NOW CODE BELOW)
   c) YES- Single setting focus (NOW CODE BELOW)
   d) **SETTING TYPES** (Code if answered YES above)
      i) Acute hospital - Emergency department
      ii) Acute hospital - intensive care unit (ICU, PICU, NICU)

iii) Acute hospital - general ward (clinical or surgical e.g. neonatal or paediatric wards)
iv) Acute hospital - not further specified
v) Community hospital (Community hospitals offering a range of healthcare services such as minor surgery, physio and respite care)
vi) Community nursing, medical and therapy service (nursing provided in the home/health visitors etc.)
vii) Pharmacy – community
(i.e. high street pharmacies where patients can collect medicines ordered on doctors' prescriptions or buy medicines over the counter)
viii) Pharmacy – hospital
(Hospital pharmacies are responsible for the purchase, manufacture, dispensing, quality testing and supply of all the medicines used in their hospital)
ix) Dental practice
x) General practice (GPs and family physicians)
xi) Home (use this for patient or carer administration of own medicines)
xii) Other setting (e.g. care home, school)

7) PATHWAY FOCUS - Does the paper focus on a specific point in the medicines pathway?
a) No - no pathway focus (GO TO NEXT QUESTION)
b) Yes - Multi pathway focus (NOW CODE)
c) Yes - Single pathway focus
d) PATHWAY TYPES
i) Prescribing (errors in the decision making around which/how much drug to give)
ii) Transcribing (errors in the writing of information)
iii) formulation/preparation (errors in the drawing up/mixing of drug)
iv) Dispensing (errors in the gathering of drugs to fill a prescription/the handing over of drugs)
v) Administering (errors in the act of putting the drug inside the body)
vi) Monitoring/checking (Any systems or checks that should be in place to make sure the right type/amount etc. of medication is given)
vii) Other pathway type

8) ERROR FOCUS - Does the paper focus on a specific type of error?
a) No - no specific error focus (GO TO NEXT QUESTION)
b) YES - multi error focus (NOW CODE BELOW)
c) YES - single error focus (NOW CODE BELOW)
d) **ERROR TYPES** (Code if answered YES above)
i) Wrong drug
ii) Wrong dose (For 10 fold errors (or other multiplication errors) use '10 fold errors' option below)
iii) Wrong strength/concentration
iv) Wrong frequency (Drug doses are administered either too close together or too far apart)
v) Wrong time (Drug is administered early, late or at the wrong time of day)
vi) Wrong duration (length of time that the drug course lasts i.e. days, weeks or months)
vii) omitted medicine/ingredient
viii) wrong formulation/preparation
ix) wrong patient
x) Expired/out of date drug
xi) Wrong route (e.g. drug had been administered intravenously rather than orally).

xii) Wrong site (e.g. anaesthetising the wrong tooth.)
xiii) 10 fold errors
xiv) Duplication (when the same medication is inadvertently prescribed twice)
xv) Other type of error (Specify)

9) PROVIDER FOCUS - Does the paper focus on errors administered by a specific type of provider?
a) No - no PROVIDER focus (GO TO NEXT QUESTION)
b) YES - multi-provider focus (NOW CODE BELOW)
c) YES - Single provider focus (NOW CODE BELOW)
d) **PROVIDER TYPES** (Code if answered YES above)
i) anaesthetist
ii) child/patient
iii) nurse
iv) parent/guardian
(including grandparents etc.)
v) pharmacist
vi) physician
vii) dentist
viii) Other provider

10) OUTCOME FOCUS - what types of outcomes are measured in the study?
a) Death resulting from medication error
b) Adverse events resulting from medication error
c) Medication error not further specified
d) Potential errors/near misses
e) No harm resulting medication error
f) Other outcome type(s) - SPECIFY

11) AGE FOCUS - Which age group(s) of child patients does the paper focus on? (tick all that apply)
a) neonates <28 days
b) infants and toddlers 29 days - <24 months
c) children 2 - ≤12 years
If the age group extends beyond 12 years (e.g. 6-14yrs) and the proportion of over-12s exceeds 20% please record the proportion of under-12s in the study. N.B. Only use 13-18 category for psychopharmaceuticals.
d) children 13 < 18 years
This category only to be used for psychopharmaceuticals.
e) Not specified

12) STUDY TYPE FURTHER DETAILS
THIS SECTION ONLY NEEDS COMPLETING FOR EXTENT OF/ASSOCIATIONS WITH ERROR OR INTERVENTION EVALUATIONS
a) N/A - not extent of error OR intervention evaluation
(case studies, qualitative studies and other types do not need further codes)
b) EXTENT OF ERROR/ASSOCIATIONS WITH ERROR
i) Level of data set?
(1) Multi-site (specify)
e.g. participants are recruited from 2 or more healthcare settings
(2) National (specify country)
(3) Single site (specify)
(Single hospital or health care setting is used)
(4) Not specified/not applicable (SR)

ii) Which factors are explored in relation to medical error?
(1) None - the paper does not explore associated factors
(2) EQUIPMENT error/failure
(3) PROVIDER COMMUNICATION (both written and spoken communication - e.g. poor handwritten instructions)
(4) KNOWLEDGE Inadequacy/inexperience
(5) Labelling
(6) MISCALCULATION
(e.g. factors 10 errors)
(7) SYSTEM safeguards failure/inadequacy
(8) Workload/staffing levels
(include fatigue)
(9) look alike/sound alike medicines
(10) Accuracy of dose measurement
(11) Other factor (please specify)

iii) How is the data collected?
(1) Chart review
(2) Observation of practice
(Including simulations)
(3) Records audit
(4) Survey
(5) Voluntary error reporting system
(6) Mandatory error reporting system
(7) Reporting system - not further specified
(8) Other data collection method (please specify)
(9) Data collection method not specified

iv) When was the data collected?
(1) Prospectively
(2) Retrospectively
(3) Timing of data collection not specified

c) INTERVENTION EVALUATION

i) **Type of intervention**
For each intervention type please copy and paste a brief (1 sentence max) description of the intervention
(1) Education
(2) CPOE - Computerised Physician Order Entry (details)
(3) EMR - Electronic medical records
(4) Pharmacist involvement/checking of prescriptions
(5) CDST/CDSS - Clinical decision support tools/systems
(Can be electronic devices/or reference books etc. which provide healthcare providers with convenient access to paediatric medicines information at point of care)
(6) Other intervention type
(7) Smart pumps/smart devices
(8) Systemic Change
(e.g. practice guidelines or system protocols)
(9) Standardised concentrations/doses
(10) Workload scheduling
(Reducing hours of practitioners to reduce tiredness and improve performance)

ii) Evaluation method
(1) RCT
(2) nRCT
(3) Before and after (no control)

(4) Other evaluation method (please specify)
(5) Not specified (i.e. SR)

Appendix 4: Extent synthesis: table of studies and structured summaries of studies on rates and types of error

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
Bateman and Donyai (2010) Quality rating: MODERATE RISK OF BIAS	To provide an understanding of the errors being made and reported to the National Aseptic Error Reporting Scheme (NAERS) database.	UK Hospital Pharmacies. National Aseptic Error Reporting Scheme (NAERS). 4,691 reports from 43 participating hospital pharmacies.	Voluntary self-reporting. Jan 2004 – Dec 2007	Age not specified.	Injectables: Paediatric Cytotoxic Medicines Paediatric Parenteral Nutrition (PN)	Transcribing Formulation/ Preparation Monitoring/ Checking Calculation Wrong drug Diluent Dose/strength Expiry date Labelling.	0.49% items associated with at least one error: 4691 out of an estimated 958532 items made during study period. Of 4691 reports, 2.7% (129) error reports relate to paediatric cytotoxic preparations and 3.9% (184) to paediatric PN. Transcription: 8.5% and 19% of errors in the preparation of paediatric cytotoxic medications and paediatric PN respectively. Labelling: 44.2% and 11.4% of errors in the preparation of paediatric cytotoxic medications and paediatric PN respectively.
Ekins-Daukes et al. (2003) Quality rating: LOW RISK OF BIAS	To identify the extent of dose-related off-label antibiotic paediatric prescribing and to identify any potential clinical effects.	GP practices, Scotland. General Practice Administration System for Scotland (GPASS). Antibiotic prescribing data for 23,911 children from 158 general practices.	Retrospective review of prescribing records. 1 Nov 1999 - 31 Oct 2000	0-16 years: 0-4 years 5-11 years 12-16 years.	Antibiotics	Prescribing; Dose.	19.2% (4,582) prescribed antibiotic at lower than Summary of Product Characteristics (SPC) recommended dose. 1.6% (373) prescribed antibiotic at higher than SPC recommended dose. Prescribing at less than the recommended dose increased with age from 11.8% (1,154) in those aged 0–4 years to 30.0% (1,827) in the 12–16 years age group.

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
							Prescribing lower than recommended dose occurred most often at ages where an SPC dose increase was advised.
Ekins-Daukes et al. (2004) Quality rating: LOW RISK OF BIAS.	To investigate the extent and pattern of off-label prescribing to children in primary care throughout Scotland.	GP practices, Scotland. General Practice Administration System for Scotland (GPASS). Prescribing data for 167,865 children from 161 general practices.	Retrospective review of prescribing records. 1 Nov 1999 - 31 Oct 2000	0-16 years: 0-4 years 5-11 years 12-16 years.	All medicines 215 medicines were assessed for off-label use, representing 93.5% of all medicines prescribed to 0-16 year olds.	Prescribing Formulation/ Preparation Dose.	Off-label prescription was issued to 17,715 children (26.1% of those issued a prescription), giving an overall population prevalence of 106/1,000 registered children. Lower than recommended dose accounted for 39.2% of off-label prescribing in 0-4 year olds, 51.9% in 5-11 years olds and 52.1% in 12-16 year olds. Higher than recommended dose accounted for 35% of all off-label prescribing. Off-label prescribing due to formulation accounted for 5-10% of off-label prescribing. Off-label prescribing due to age accounted for 6-16% of off-label prescribing. Antibiotics were the most frequently prescribed off-label medicines in all age groups (26%). 80-95% of antibiotic off-label prescribing was due to lower than recommended dose.

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
							Antihistamines accounted for 12% of off-label prescribing with 36.0%, 60.2% and 84.7% due to the use of a lower than recommended dose in 0-4, 5-11 and 12-16 year olds respectively.
Elkout et al. (2009) Quality rating: LOW RISK OF BIAS	To determine the extent and pattern of off-label inhaled steroid (ICS) prescribing to children in primary care.	GP practices, Scotland. Scottish Practice Team Information (PTI) database. 48,490 ICS prescriptions issued to 7,092 children.	Retrospective review of prescribing records Sep 2001 – Aug 2006	0-18 years	Inhaled Corticosteroids (ICS)	Prescribing Formulation/ Preparation Dose.	16% (8032) prescriptions off-label. 14% (980) of all children issued an ICS were prescribed off-label. Off-label prescribing due to higher than recommended dose for 638 children (65%), due to formulation for 323 children (33%) and due to age for 157 children (16%). Over the 5-year period, off-label prescribing due to dose decreased (from 79% to 49%); it increased due to age (from 9% to 22%) and formulation (from 20% to 40%).
Grover et al. (2008) Quality rating:	To ascertain current practice regarding neonatal parenteral	Tertiary neonatal units with 5 or more intensive care cots in England, Scotland	Questionnaire Survey Oct 2005 – Mar 2006	Neonates (1-10 days old)	Parenteral nutrition (PN)	Prescribing Dose.	Compared to recommended intake, median prescriptions lead to calorie and protein deficits over the first 10 days of life.

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
LOW RISK OF BIAS	nutrition prescription in the early postnatal period in the United Kingdom.	and Wales. Survey data. 48 of 64 neonatal pharmacists serving level 3 and major level 2 units in the UK.					
Kazouini et al. (2011) Quality rating: LOW RISK OF BIAS	To assess the level of paracetamol off- label prescribing in the community and the potential for paracetamol under- or overdosing.	GP practices, Scotland. Scottish Practice Team Information (PTI) database. 4,423 Paracetamol prescriptions issued to 2761 children from 40 general practices.	Retrospective review of prescribing records. 1 Jan 2006 - 31 Dec 2006	0-12 years: 1-3 months 4-11 months 1-5 years (48.9%) 6-12 years.	Paracetamol	Prescribing Dose.	17.9% (793) prescriptions off-label. 11.3% (502) prescriptions classified as underdose. 2.9% (127) prescriptions classified as overdose. 15.2% (673) prescriptions without clear dosage instructions. Non-BNFc recommended prescriptions issued to 22.7% (626) of all children prescribed paracetamol.
MacLennan and Smith (2011) Quality rating: MODERATE	To identify and analyse critical incidents relating to paediatric anaesthesia from the	Hospitals, England and Wales. National Reporting and Learning System	Voluntary self-reporting. 1 Jan 2006 – 31 Dec 2008	<16 years	Analgesic (84%) Antibiotic (12%)	Prescribing Formulation/ Preparation Dispensing (supply)	Medication incidents constituted 35.6% (216/606) critical incidents relating to paediatric anaesthesia. 77.3% (167/216) of errors occurred during administration.

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
RISK OF BIAS	National Reporting and Learning System (NRLS) in England and Wales.	(NRLS). 606 paediatric anaesthesia incidents.				Administration.	34.7% (75/216) of errors were due to duplicated dose. 10.2% (22/216) prescription errors. 4.6% (10/216) supply errors. 2.3% (5/216) preparation errors.
National Patient Safety Agency (2008) Quality rating: MODERATE RISK OF BIAS	To identify any underlying themes relating to the safety of childhood vaccination.	NHS, England and Wales. National Reporting and Learning System (NRLS). Random sample of 200 (62 mis-coded) from total of 949 incidents involving vaccinations in children.	Voluntary self-reporting. 2007	Patients from children's specialties or <18 years.	Vaccines	Administration Wrong drug Wrong time (delayed vaccination) Documentation error.	42.8% (59/138) reports involved the wrong vaccination. 27.5% (38/138) documentation error. 12.3% (17/138) delayed vaccination.
National Patient Safety Agency (2009) Quality rating: MODERATE	To highlight patient safety issues for children, young people and their families, outline current NPSA	NHS, England and Wales: 79% acute 10% mental health 7% 'other' 4% primary care.	Voluntary self-reporting. 1 Oct 2007 – 30 Sep 2008	Neonates: (0-27 days) Child: (27 days-17yr)	All medicines	Dose/strength; Wrong frequency; Omitted medicine/ ingredient.	Medication incidents constituted 17% of patient safety incidents for children and 15% for neonates. In approximately 24% of medication incidents, the error type was not specified. Administration of incorrect

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
RISK OF BIAS	partnership work streams and identify key actions for stakeholders.	NRLS 19,307 incidents in neonates and 42,029 incidents in children.					dose/strength constituted 23% and 18% of medication incidents in children and neonates respectively. Omission of a medicine or ingredient constituted 10% and 18% of medication incidents in children and neonates respectively. Wrong frequency of treatment constituted 8% and 13% of medication incidents in children and neonates respectively.
Riordan et al. (2009) Quality rating: LOW RISK OF BIAS	To describe the use of tenofovir disoproxil fumarate (TDF) in a national UK and Ireland based cohort of HIV-1 infected children.	Setting not specified. Collaborative HIV Paediatric Study (CHIPS) cohort. 159 children taking TDF of 1,253 in CHIPS cohort.	Dosage information recorded in cohort study. 2001- 2007	0-17 years	Anti-retroviral: tenofovir disoproxil fumarate (TDF)	Dose	18% (23) of children receiving the recommended adult daily dose were first dosed at >120% of the suggested dose for their age/weight. Of those taking a portion of the adult daily dose 37% (14) were receiving <80% of the suggested dose for their age/weight.
Rosario (2013) Quality rating: MODERATE RISK OF BIAS	A review of patient safety incident reports from the National Reporting and Learning System	NHS, England and Wales: Primarily acute hospital-based incidents. NRLS Medication Incidents: 12,233	Voluntary self-reporting. 1 Oct 2009 – 30 Sep 2012	Neonates (0-27 days) Children (27 days - 17 years)	All medicines	Omitted medicine/ ingredient Wrong/unclear dose or strength Wrong frequency	For paediatric patients the highest proportion of errors aside from 'others' was wrong dose or strength (20%). For neonates, the largest proportion of errors other than those categorised as 'other' were in relation to omitted medicines/ingredients (18%).

Study	Objective	Setting/ dataset/ sample	Data collection and period	Age range of children	Drug/ medicine	Reported types of error	Overall results
		neonatal and 33,019 paediatric medication incidents				Wrong quantity Wrong drug	

Bateman and Donyai (2010)

Aims and setting: To provide an understanding of the errors being made and reported to the National Aseptic Error Reporting Scheme (NAERS) database.

Drug type: Chemotherapy and parenteral nutrition.

Methods: Analysis of error reports from hospital pharmacies participating in the NAERS. Reports of potential errors associated with the preparation of aseptic injectables for both adults and paediatrics were examined (n= 4,691), of which 313 were explicitly associated with paediatric medicines. (Of the total number, only 24 incidents reached the patient and it is not stated whether adult or paediatric medicines were involved.

Study quality: The absolute number of incidents is small for the relevant paediatric drug categories and the NAERS is a voluntary reporting system and therefore not suitable for providing accurate information regarding rates of medication incidents. The majority of reports submitted to NAERS relate to near-misses, and therefore the data may reflect effective error detection and reporting processes rather than highlighting real problem areas that escape detection and reporting. Quality rating: MODERATE RISK OF BIAS

Findings: Most errors were detected before reaching patients, with only 24 of 4,691 detected during or after administration.

Table A4.1: Chemotherapy and parenteral nutrition errors recorded according to type

Error type	**Paediatric chemotherapy**	**Paediatric parenteral nutrition**
Transcription	11 (8.5%)	35 (19%)
Calculation	4 (3.1%)	18 (9.8%)
Drug	1 (0.8%)	23 (12.5%)
Dose/strength	10 (7.8%)	12 (6.5%)
Diluent	4 (3.1)%	4 (2.2%)
Final volume	3 (2.3%)	17 (9.2%)
Label	57 (44.2%)	21 (11.4%)
Expiry	13 (10.1%)	7 (3.8%)
Container	1 (0.8%)	6 (3.3%)
Other	25 (19.4%)	41 (22.3%)
Total	129	184

Author conclusions: This study highlights scope for examining current arrangements for checking and releasing products, certainly for paediatric cytotoxic and paediatric parenteral nutrition preparations within aseptic units, but in the context of resource and capacity constraints.

Ekins-Daukes et al. (2003)

Aims and setting: To identify the extent of dose-related off-label antibiotic paediatric prescribing and to identify any potential clinical effects.

Drug type: Antibiotics

Methods: Analysis of data from the General Practice Administration System for Scotland (GPASS) relating to antibiotic prescribing for 23,911 children from 158 general practices.

Study quality: It should be noted that there is overlap between the dataset examined in this paper and that examined in Ekins-Daukes et al. (2004) as both examine prescribing data from the GPASS for the period 1 November 1999 to 31 October 2000. We have included Ekins-Daukes (2003) within this review in order to provide more detailed findings relating to the prescription of antibiotics in primary care. Quality rating: LOW RISK OF BIAS.

Findings: A total of 4,582 (19.2%) children were prescribed an antibiotic dose of less than that recommended in the Summary of Product Characteristics (SPC). The number of children prescribed an antibiotic at less than recommended dose increased with age from 1,154 (11.8%) aged 0–4 years to 1,827 (30.0%) in the 12–16 years age group. Age trends for lower than recommended dose prescribing were apparent for each of three antibiotic classes: penicillins, cephalosporins and macrolides. For each antibiotic, prescribing lower than the recommended dose occurred most frequently at those ages at which a dose increase was recommended in the SPC. Antibiotic prescribing at doses higher than recommended occurred less frequently (1.6%) and decreased steadily with age.

Author conclusions: Off-label prescribing of antibiotics at less than the recommended dose in children is common in primary care and occurs primarily as the result of a failure to increase antibiotic dosage with age in line with SPC recommendations. Adoption of a uniform approach to SPC age banding for antibiotic dose increments would reduce the frequency of dose-related off-label antibiotic prescribing in children.

Ekins-Daukes et al. (2004)

Aims and setting: To investigate the extent and pattern of off-label prescribing to children in primary care throughout Scotland.

Drug type: All types

Methods: Analysis of data from the General Practice Administration System for Scotland (GPASS) relating to prescribing for 167,865 children from 161 general practices.

Study quality: It should be noted that there is overlap between the dataset examined in this study and that examined in Ekins-Daukes et al. (2003), as both examine prescribing data from the GPASS for the period 1 November 1999 to 31 October 2000. Quality rating: LOW RISK OF BIAS.

Findings: At least one off-label prescription was issued to 17,715 children aged 0-16 years (26.1% of those issued a prescription) . The most common cause for off-label prescribing was the prescription of a lower than recommended dose, accounting for 39.2% of all off-label prescribing in 0-4-year olds and approximately 52% in 5-11-year and 12-16-year olds. Off-label prescribing due to higher than the recommended dose was the next most common form, accounting for between 32.3% and 38.0% of all off-label prescribing. Off-label prescribing due to age was most common amongst 0-4 year olds, accounting for 16.1% of all off-label prescribing in this age group. Off-label prescribing with respect to formulation was the least common form, accounting for 6.7%, 10.3% and 5.1% in the 0-4, 5-11 and 12-16 year age groups respectively.

Medicines within the ten drug classes most commonly prescribed off-label accounted for 81.9%, 84.3% and 79.3% of all off-label prescribing to 0-4-, 5-11- and 12-16-year olds, respectively. Antibiotics were the most frequently prescribed off-label medicines for 0-4 year olds and 12-16 year olds. Antihistamines were also commonly prescribed off-label (36.4%, 56.8% and 8.6% in the 0-4-, 5-11 and 12-16 year age groups, respectively). β_2-agonists were the third most commonly prescribed off-label drug in all three age bands. Aside from antihistamines, the highest proportion of children with off-label prescriptions for a particular medicine was found for laxatives (with 35.2% of 0-4 years olds receiving an off-label prescription), anti-migraine drugs (with 47.1% of 12-16 year olds receiving an off-

label prescription) and systemic decongestants (with 58.4% of 0-4 year olds receiving an off-label prescription).

In the youngest age group (0-4 years), off-label prescription for some drugs was largely due to lower than recommended dose, as for antibiotics (80.4%) whereas for other drugs, it was largely due to a higher than recommended dose, as for non-opioid analgesics (84.0%), laxatives (76.4%) and systemic decongestants (70.8%). Antihistamines, however, were frequently prescribed at both a higher than recommended dose (29.6%) and a lower than recommended dose (36.0%) in the 0-4 year age group. Off-label prescription due to formulation was less common accounting for less than 2% of off-label prescribing in the 0-4 age band for all drug classes except laxatives (4.3%), inhaled corticosteroids (10.7%) and β_2-agonists (57.6%).

For 5-11 year olds, off-label prescription for some drugs was largely due to lower than recommended dose, as for antibiotics (88.5%), topical anti-infectives (79.8%) and cough preparations (81.7%), whereas for other drugs it was largely due to a higher than recommended dose, as for topical corticosteroids (69.6%), β_2-agonists (88.2%), laxatives (73.3%) and inhaled corticosteroids (83.3%). For antibiotics, off-label prescribing was consistently due to prescription of a lower than recommended dose, accounting for 80.4%, 88.5% and 95.4% of off-label prescriptions in the 0-4, 5-11 and 12-16 year age groups respectively. In contrast, β_2-agonist off-label prescribing was largely due to higher than recommended dose in the 5-11 age group (88.2%) and the 12-16 age group (95.3%); however, off-label prescribing was due to higher than recommended dose in only 22.3% of 0-4 year olds, where off-label prescribing due to formulation (57.6%) was prevalent.

Author conclusions: This is the largest and most detailed study to date of paediatric off-label prescribing in primary care within the UK. Such off-label prescribing probably occurs as the result of several factors, including a failure to update licensing information with currently accepted practice and confusion or unawareness of the licensing recommendations, further compounded by a lack of clinical trials data and suitable formulations for medicines commonly prescribed to young children and adolescents.

Elkout et al. (2010)

Aims and setting: To determine the extent and pattern of off-label inhaled steroid prescribing to children in primary care.

Drug type: Inhaled corticosteroids (ICS)

Methods: Retrospective observational survey of primary care prescribing data for children aged 0-18 years prescribed at least one asthma medication between September 2001 and August 2006 using the Scottish Practice Team Information (PTI) database. Children issued one or more ICS prescriptions were identified and their mean daily dose calculated. The licensed recommendations applicable at the time of ICS prescription issue were obtained from the summary of product characteristics and The British National Formulary. A prescription was considered off-label if it was for a formulation, age group, or dose not licensed for use in children.

Study quality: LOW RISK OF BIAS.

Findings: During the five-year study period, 48,490 ICS prescriptions were issued to 7,092 children, 16% (8,032) of which were off-label. Of all children prescribed an ICS, 14% (980) were issued with at least one off-label prescription. Higher than recommended dose was the main reason for an off-label ICS prescription in 65% (638) of children. Formulation and age were the cause of off-label prescribing in 33% (323) and 16% (157) of children respectively. Over the five-year study period, there was a decrease in off-label prescribing due to dose and an increase in off-label prescribing due to age and formulation.

Author conclusions: During the five-year study period, the proportion of children prescribed off-label ICS has remained constant. However the reasons for an ICS prescription being off-label demonstrated a significant change over time.

Grover et al. (2008)

Aims and setting: The objective of this study was to ascertain current practice regarding neonatal parenteral nutrition (PN) prescription in the early postnatal period in the United Kingdom.

Methods: A study questionnaire was e-mailed to neonatal pharmacists serving level 3 and major level 2 units in the United Kingdom between October 2005 and March 2006. Fifty-two (81%) units responded to the questionnaire; 4 units were excluded for incomplete data. Calories and amino acids intakes were compared with the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations and deficits were calculated over the first 10 days.

Study quality: LOW RISK OF BIAS.

Findings: In comparison to recommended intake of calories and amino acids, the current median prescription would result in a cumulative deficit over the first 10 days of 420 kcal/kg and 11.9 g/kg respectively.

Author's conclusions: There is a wide disparity in PN prescription in major neonatal units in the United Kingdom. Current PN prescription leads to significant nutrient deficits in very low birth weight infants in early postnatal life.

Kazouini et al. (2011)

Aims and setting: To assess the level of paracetamol off-label prescribing in the community and the potential for paracetamol under- or overdosing.

Drug type: Paracetamol

Methods: Analysis of data from the Scottish Practice Team Information (PTI) database relating to 4423 paracetamol prescriptions issued to 2761 children from 40 general practices.

Study quality: LOW RISK OF BIAS.

Findings: A total of 17.9% (793) of prescriptions were outside BNFc recommendations while 15.2% (673) were classified as unpredictable (no clear dosage guidance recorded). Prescriptions outside BNFc recommendations were issued to 22.7% (626) of all children prescribed paracetamol. Analysis of prescriptions in terms of age and dosage outcomes revealed that 11.3% (502), and 2.9% (127) of prescriptions were for an underdose or overdose respectively. Children aged 1–3 months were at the highest risk of being overdosed (21.8%), while older children (6–12 years old) were at the highest risk of being underdosed (19.4%). The likelihood of being issued with a prescription recommending a potential overdose decreased significantly with increasing age (chi-square for linear trend = 149.68, $P < 0.001$), while underdosing increased significantly with age (chi-square for linear trend = 134.73, $P < 0.001$).

Author conclusions: Paracetamol off-label prescribing is common in primary care, with relatively high levels of potential overdosing in the youngest children and potential underdosing in the oldest children.

MacLennan and Smith (2011)

Aims and setting: To analyse critical incidents relating to paediatric anaesthesia from the National Reporting and Learning System (NRLS) in England and Wales.

Drug type: Anaesthesia

Methods: Analysis of 606 paediatric anaesthesia critical incidents, of which 216 were medication incidents, reported to the NRLS between 1 January 2006 and 31 December 2008.

Study quality: The absolute number of incidents is small and a voluntary reporting system cannot be used to give an accurate assessment of incidence of errors. The failure to record age in many of the reports may have led to the exclusion of a number of otherwise eligible records. In many reports, sufficient detail was lacking for a full understanding of what had happened. Many reports appeared to have been compiled by non-specialists.

Findings: Medication incidents (n = 216) were the most common form of paediatric anaesthesia critical incident, forming 35.6% of events. There were 167 (77.3%) administration incidents, 75 (34.7%) of which were due to unintentional additional dose of medication with an anaesthetist being one of the health professionals involved. Double dosing often occurred as a result of medications and fluids being prescribed in more than one setting. Analgesic (84%) and antibiotic (12%) medications were the drugs most often involved. There were 22 (10.2%) prescription errors, 10 (4.6%) supply errors and 5 (2.3%) preparation errors.

Author conclusions: Anaesthetists should be encouraged to contribute high-quality descriptions of incidents to national systems. Drugs and fluids given during anaesthesia which may also be given on the ward, especially analgesics and antibiotics, should be documented on a prescription chart used by the ward in addition to the anaesthetic record.

National Patient Safety Agency (2008)

Aims and setting: To identify any underlying themes relating to the safety of childhood vaccination.

Methods: A random sample of 200 NRLS incidents was reviewed in detail. Of these, 62 incidents were excluded which were not found to relate to vaccinations.

Study quality: The NRLS is a voluntary reporting system and therefore not suitable for providing accurate information regarding rates of medication incidents. There is also significant under-reporting from primary care settings within the NRLS relative to the volume of healthcare provided. Thirty-one per cent of the random sample examined was found to have been mis-classified and did not relate to vaccination incidents. Quality rating: MODERATE RISK OF BIAS.

Findings: Reports involving the wrong vaccination numbered 59 (42.8%). Reports involving a documentation error numbered 38 (27.5%). Delayed vaccination accounted for 17 (12.3%) of reports.

Author's conclusions: Vaccination incidents are an important theme within patient safety for children and neonates. Incidents reported to the NRLS suggest that vaccination incidents most commonly involve an incorrect vaccination being given to the patient, which could be prevented through improving systems for checking patient records to ensure that the patient has not already been given the intended vaccination and recording administered vaccinations more consistently in patient records.

National Patient Safety Agency (2009)

Aims and setting: To highlight patient safety issues for children, young people and their families, outline current National Patient Safety Agency (NPSA) partnership work streams, and identify key actions for stakeholders in the NHS in England and Wales.

Drug type: All types.

Methods: Analysis of the 19,307 neonatal and 42,029 paediatric incidents reported to the NRLS between 1 October 2007 and 30 September 2008.

Study quality: The NRLS is a voluntary reporting system and therefore not suitable for providing accurate information regarding rates of medication incidents. There is also significant under-reporting from primary care settings (just 4%) in relation to the volume of patient care undertaken in this sector. Almost a quarter (approximately 24%) of medication incidents were not categorised by error type. Quality rating: MODERATE RISK OF BIAS.

Findings: Medication incidents constituted 17% of patient safety incidents for children and 15% for neonates. Approximately 24% of medication incidents were not specified. Administration of incorrect dose/strength constituted 23% of medication incidents in children and 18% of medication incidents in neonates. Omission of a medicine or ingredient constituted 10% of medication incidents in children and 18% of medication incidents in neonates. Wrong frequency of treatment constituted 8% of medication incidents in children and 13% of medication incidents in neonates.

Author conclusions: As the vast majority of children receive their healthcare in the community, improved reporting from primary care is essential to improving analysis of patient safety issues for children and subsequent learning.

Riordan et al. (2009)

Aims and setting: To describe the use of tenofovir disoproxil fumarate (TDF) in a national UK and Ireland based cohort of HIV-1 infected children.

Methods: 159 children ever prescribed TDF and followed in the Collaborative HIV Pediatric Study cohort (n = 1,253) since 2001 were included in analyses of dosing, adverse events and virologic and immunologic response.

Study quality: The main focus of this paper was not upon dosing errors. Although the sample size is small in terms of absolute numbers, the sample represents all children prescribed TDF in the UK among those in a cohort representing 92% of all children being treated for HIV in the UK and Ireland. Quality rating: LOW RISK OF BIAS.

Findings: 18% (23) of children receiving the recommended adult daily dose (n=122) were first dosed at >120% of the suggested dose for their age/weight. Of those taking a portion of the adult daily dose (n=37) 37% (14) were receiving <80% of the suggested dose for their age/weight. There is a gradual decline in dose by weight as age increases, with a slight jump from lower to higher dose by weight at approximately 10 years of age, when many children increase from a half tablet to a full tablet (recommended daily adult dose) per day.

Author's conclusions: With only adult dose TDF tablets available dosing anomalies were demonstrated. Considerable underdosing and overdosing occurs. Deviations from recommended TDF dose are probably caused by lack of availability of an appropriate formulation for children.

Rosario 2013

Aims and setting: A review of patient safety incident reports from the National Reporting and Learning System database for the period 1 October 2009 – 30 September 2012.

Drug type: All types.

Methods: Analysis of the 12,233 neonatal and 33,019 paediatric medication incidents reported to the NRLS between 01 October 2009 – 30 September 2012.

Study quality: The NRLS is a voluntary reporting system and therefore not suitable for providing accurate information regarding rates of medication incidents. There is also

significant under-reporting from primary care settings relative to the volume of healthcare provided. Almost a quarter (25% in neonates and 23% in paediatric patients) of medication incidents were not categorised by error type. There is often overlap and miscoding within the categories 'wrong dose or strength', 'wrong frequency' and 'wrong quantity'.

Findings: Table A4.2 delineates the type of medication incidents reported for neonates and paediatric patients. For neonates, the largest proportion of errors other than those categorised as 'other' were in relation to omitted medicines/ingredients (18%). For paediatric patients, the highest proportion of errors aside from 'others' was wrong dose or strength (20%). The proportions across the two age groups ranked identically for all other error types.

Table A4.2 Types of medication incidents among neonates, paediatrics and overall

Medication error category	**Neonates**	**Paediatrics**	**Total**
	Frequency (%)	**Frequency (%)**	**Frequency (%)**
Other	3,063 (25)	7,732 (23)	10,795 (24)
Omitted medicine/ingredient	2,200 (18)	3,992 (12)	6,192 (14)
Wrong/unclear dose or strength	1,948 (16)	6,628 (20)	8,576 (19)
Wrong frequency	1,679 (14)	3,156 (10)	4,835 (11)
Wrong quantity	860 (7)	2,567 (8)	3,427 (8)
Wrong drug/medicine	424 (3)	2,074 (6)	2,498 (6)
Wrong/omitted/passed expiry date	356 (3)	921 (3)	1,277 (3)
Wrong/transposed/omitted medicine label	-	840 (3)	-
Total medication incidents	12,223	33,019	45,242
Categories with 2% or less not shown			

Author conclusions: None.

Appendix 5: Effectiveness synthesis: EP table of studies and structured summaries

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
Barnes (2009)	Error: Effect size not calculable. The authors report no significant impact on medication error rate. Pre-EP 82 patients - 38 errors reached patient Post-EP 87 patients – 29 errors reached patient.	Design: Historical control Sound: No RoB: High	Setting: PICU Country: USA	Software: EPIC system, DocConnect Decision support: Yes Implementation: Not reported	Not stated	PP: Prescription ET: dose and time errors	CT = 82 IV = 87 (Patients)
Cordero et al. (2004)	Error: Significant reduction in dose prescription errors post-EP – (RR 0.041, 95% CI 0.002 – 0.671) Mortality: Fewer deaths following EP but finding not significant (RR 0.624, 95% CI 0.289 – 1.349) Time: Authors report statistically significant (p <0.01) reductions in medication turn-around times post-EP (pre-EP n=41, mean 10.5±9.8 SD hours, post-EP n=48, mean 2.8+/- 3.3 SD hours).	Design: Historical control Sound: Yes RoB: Moderate	Setting: NICU Country: USA	Software: Invision 24, Siemens Decision support: Yes Implementation: Training for clinicians, nurses and clerical staff	Handwritten orders	PP: Prescription ET: dose errors (for mortality outcome not specified)	CT = 111 IV = 100 (Patients)

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
Del Beccaro et al. (2006)	Mortality: Fewer deaths following EP but finding not significant (RR 0.819, 95% CI 0.554–1.212)	Design: Historical control Sound: Yes RoB: Moderate	Setting: PICU Country: USA	Software: Millennium Powerchart, Cerner Decision support: Yes Implementation: Staff training and on-site support	Handwritten orders	PP: Prescription ET: Not specified	CT = 1,232 IV = 1,301 (Patients)
Han et al. (2005)	Mortality: Significantly more deaths post-EP than pre-EP (RR 2.348, 95% CI 1.509 – 3.654)	Design: Historical control Sound: Yes RoB: Moderate	Setting: Children's hospital Country: USA	Software: Millennium Powerchart, Cerner Decision support: Yes Implementation: Training	Handwritten orders	PP: Prescription ET: Not specified	CT = 1,394 IV = 548 (Patients)
Holdsworth et al. (2007)	Error: Significant reduction in prescription errors post-EP (RR 0.368, 95% CI 0.252 – 0.539) ADE: Significant reduction in preventable adverse events post-EP (RR 0.559, 95% CI 0.348 – 0.898)	Design: Historical control Sound: Yes RoB: Moderate	Setting: PICU and general paediatric units Country: USA	Software: Eclipsys System 2000 - modified from the commercial product Decision support: Yes Implementation: 15 months' user acclimation	Handwritten orders	PP: Prescription ET: Total errors	CT = 1,197 IV = 1,210 (Drugs given)
Jani et al. (2010)	Error: Significant reduction in dose errors post-EP (RR 0.533, 95% CI 0.383 – 0.742) ADE: Effect size not	Design: Historical control Sound: No	Setting: Children's hospital Country: UK	Software: JAC Computer Services Ltd Decision support:	Handwritten orders	PP: Prescription ET: Dose errors	IV = 3,939 CT = 4,784 (Orders)

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
	calculable. The authors report significant reduction in minor/moderate ADE; non-significant reduction in severe ADE (minor ADE reduced from 0.89% to 0.44% p<0.009, moderate ADE from 1.17% to 0.69% p<0.019, severe ADE from 0.18% to 0.06% p<0.11)	RoB: High		'basic clinical decision support' Implementation: None reported			
Kadmon et al. (2009)	Error: Significant reduction in total errors post-EP (RR 0.534, 95% CI 0.389-0.734)	Design: Historical control Sound: No RoB: High	Setting: PICU Country: Israel	Software: Metavision, iMDsoft, Decision support: 'limited decision support' Implementation: None reported	Handwritten orders	PP: Prescription ET: Total errors	IV = 1,250 CT = 1,250 (Orders)
Kazemi et al. (2011)	Error: Effect size not calculable – the authors report significantly reduced rate of non-intercepted medication errors, dose errors and frequency errors post-EP (total errors pre-EP 53%, post-EP 34% p<0.001; dose errors pre-EP 41%, post-EP 22% p. <0.001; frequency errors pre-EP 25%, post-EP 20% p. <0.001)	Design: Historical control Sound: Yes RoB: Moderate	Setting: Neonatal ward Country: Iran	Software: Sayan-HIS Decision support: Yes (study examines both with and without) Implementation: Training for physicians	Handwritten orders	PP: Prescription ET: Dose and frequency errors	IV = 1,080 CT = 1,249 (Orders)
Keene et al. (2007)	Mortality: Fewer deaths following EP implementation	Design: Historical	Setting: PICU and NICU	Software: PHAMIS LastWord Online	Handwritten orders	PP: Prescription ET: Not specified	CT = 917 IV = 374

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
	but finding not significant (RR 0.761, 95% CI 0.364 – 1.592)	control Sound: Yes RoB: Moderate	Country: USA	Medical Record System Decision support: No Implementation: Training for nurses and physicians. On-site support for first 3 weeks of implementation.			(Patients)
King et al. (2003)	Error: Significant decrease in total error post-EP (OR 0.903, SE 0.111 p<0.01). Non-significant increase in prescription errors post-EP implementation (RR 1.155, 95% CI 0.338–3.945) ADE: Very small non-significant increase in error-related adverse events post-EP (RR 1.011, 95% CI 0.092 – 11.147)	Design: non RCT Sound: Yes RoB: Low	Setting: Children's hospital Country: Canada	Software: Sunrise Clinical Manager, Eclipsys Decision support: No Implementation: Not reported	Handwritten orders	PP: Prescription ET: Not specified	IV = 5,786 CT = 11,699 (Patients)
Lehman et al. (2004)	Error: Significant reduction in errors post TPN Calculator (RR 0.394, 95% CI 0.241-0.644) and at two years after the implementation (RR 0.113, 95% CI 0.055-0.235)	Design: Historical control Sound: No RoB: High	Setting: NICU Country: USA	Software: TPNcalculator Decision support: No Implementation: Brief 10-minute training	Written orders	PP: Prescription ET: Wrong strength/ concentration Omitted medicine/ ingredient Other type: insufficient fluids calculation	IV = 471 orders (intervention 1); 656 orders (intervention 2) CT= 557 orders

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
Lehman et al. (2006)	Error: Significantly fewer orders with one or more errors than handwritten orders (RR 0.208, 95% CI (0.1-0.431).	Design: Historical control Sound: Yes RoB: Moderate	Setting: Children's hospital Country: USA	Software: Implemented on ColdFusion application Decision support: Yes Implementation: Informal on-demand training	Written orders	PP: Prescription ET: One or more errors	IV = 142 orders CT= 129 orders (phase A)
Maat et al. (2013)	ADE: Small non-significant decrease in ADE (hypo- and hyperglycaemias) after EP: Hypoglycaemias 4.0 (95% CI, 3.2-4.8) pre-EP and 3.1 (2.7-3.5) post-EP, p = 0.88 Hyperglycaemias 6.0 (4.3-7.7) pre-EP and 5.0 (3.7-6.3) post-EP, p = 0.75. Time: Significant reduction turn-around times post EP: 16% time reduction (1.3 minutes, 0.3-2.3) for simple and 60% (8.6 minutes, 95% CI 5.1-12.1) for complex calculations.	Design: Historical control Sound: Yes RoB: Moderate	Setting: NICU Country: The Netherlands	Software: In-house software Decision support: Yes Implementation: No	Written orders	PP: Prescription ET: Wrong doses	Interrupted Time series IV = 970 CT= 1,070 (Patients) Simulation (a cross-over, n= 7)
Potts et al. (2004)	Error: Significant decrease in error post-EP (RR 0.58, 95% CI 0.446–0.753)	Design: Historical control Sound: Yes RoB: Moderate	Setting: PICU Country: USA	Software: WizOrder Decision support: Yes Implementation: Training provided.	Handwritten orders	PP: Prescription ET: All error types	CT = 6803 IV = 7025 (Orders)

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
Sowan et al. (2010)	Error: Effect size not calculable. The authors report that 'computerized orders saved nurses time but did not improve ability to detect errors'. Using EP orders, 26 (72%) of 36 nurses failed to identify one or more infusions with errors compared with 24 (67%) of 36 nurses using handwritten orders (p = 0.82).	Design: Historical control Sound: Yes RoB: Moderate	Setting: PICU Country: USA	Software: Not stated, developed in-house Decision support: Yes Implementation: Not stated	Handwritten orders	PP: Prescription ET: Dose and concentration errors	CT = 36 IV = 36 (Nurses – scenario study)
Sullins et al. (2012)	Error: Effect size not calculable. Authors report non-significant decrease in total errors (OR, 1.18; p=0.24) Findings by error type (documentation, prescription and administration) all show increases.	Design: Historical control Sound: No RoB: High	Setting: Children's hospital Country: USA	Software: Not stated Decision support: Not stated Implementation: Not stated	Handwritten orders	PP: Prescription, administration, documentation ET: Wrong dose/wrong strength	CT = 1,000 IV = 1,000 (Drugs delivered)
Upperman et al. (2005)	ADE: Effect size not calculable. The authors report that EP 'would prevent 1 ADE every 64 (95% CI 25-100) patient days'.	Design: Historical control Sound: No RoB: High	Setting: Children's hospital Country: USA	Software: Not stated Decision support: Yes Implementation: Clinicians and ancillary personnel received 2-3 hours training	Handwritten orders	PP: Prescription ET: dose errors	CT = Not reported IV = Not reported (Doses)

Study	Outcomes	Risk of bias (RoB)	Setting	EP intervention details	Comparison	Pathway point (PP) and error type (ET)	Sample size
Vardi et al. (2007)	Error: Significant decrease in total errors post-EP (RR 0.04, 95% CI 0.002–0.773)	Design: Historical control Sound: No RoB: High	Setting: PICU Country: Israel	Software: 'Visual Basic' Decision support: Yes Implementation: Not stated	Handwritten orders	PP: Prescription ET: Total errors	CT = 13,124 IV = 46,970 (Orders)
Walsh et al. (2008)	Error: Non-significant decrease in non-intercepted serious errors post-EP (RR 0.891, 95% CI 0.559 – 1.418) ADE: Non-significant decrease in preventable adverse events post-EP (RR 0.818, 95% CI 0.362 – 1.849)	Design: Historical cohort Sound: Yes RoB: Moderate	Setting: NICU, PICU, and inpatient paediatric wards Country: USA	Software: Eclipsys Decision support: Paediatric weight-based calculator + alerts Implementation: 2- to 3-hour training session	Handwritten orders	PP: Prescription ET: Dose and frequency errors	CT = 1,848 IV = 1,386 (Patient days)
Warrick et al. (2011)	Error: Non significant reduction in prescribing errors (RR 0.928, 95%CI 0.472,1.826, at immediately after implementation; RR 0.53, 95% CI 0.52-1.117, at 6 months after the implementation)	Design: Historical cohort Sound: No RoB: High	Setting: PICU Country: UK	Software: Intellivue Clinical Information Portfolio Decision support: No Implementation: Yes, a training session on the system one week before the implementation	Paper charts	PP: Prescription ET: All prescribing errors and omitted doses	CT = 159 IV = 208 (period 1); 257 (period 2) Doses CT = 528 IV = 216 (period 1); 278 (period 2)

Notes: RCT = randomised controlled trial; IV = intervention group; CT = control group.

Barnes (2009)

Aims and setting: This US-based PhD thesis aimed to examine the effect of EP on medication error rates, types of medication errors and severity of errors in a paediatric intensive care unit.

Methods: Hospital prescription data for 169 patients were collected in the two months before and the two months following implementation of an EP system; the impact on dose and time errors was explored. The EP system was named as the EPIC System from DocConnect and described as involving some level of decision support. Implementation issues such as training and support were not reported.

Study quality: This historical cohort study was found to be not sound. Equivalence between those receiving care before and after EP implementation was not examined, although the limited evidence that is available indicates some differences between groups. The study has a high risk of bias.

Findings: An effect size was not calculable for this study; however the authors report that there was no significant impact on error rates.

Author conclusions: 'It appears that the implementation of EP does not have a statistically significant impact on medication error rate'.

Cordero et al. (2004)

Aims and setting: To study the impact of EP on selected neonatal intensive care unit (NICU) practices in nursing units in an academic health system in the USA.

Methods: A retrospective review of medication error rates (accuracy of gentamicin dose) and initiation to completion time intervals for pharmacy orders in 111 very low birth weight (VLBW) infants born consecutively in the six months prior to EP implementation and 100 VLBW infants born in the six months after EP implementation. The EP system implemented included decision support, and training was provided for clinicians, nurses and clerical staff.

Study quality: This historically controlled study was found to be sound. Baseline characteristics were reported for each group and the intervention group and historical comparison group were judged to be equivalent. The study has a moderate risk of bias.

Findings: There was a significant reduction in gentamicin dose prescription errors post-EP implementation (RR 0.041, 95% CI 0.002–0.671). There were fewer deaths following EP implementation but this finding was not found to be statistically significant (RR 0.624, 95% CI 0.289–1.349). The study authors also reported statistically significant ($p < 0.01$) reductions in medication turn-around times post-EP implementation (pre-EP n=41, mean 10.5+/-9.8 SD hours, post-EP n=48, mean 2.8+/-3.3 SD hours).

Author conclusions: 'The implementation of CPOE in our NICU resulted in a significant reduction in … medication errors for selected drugs. In spite of the complexities of medication orders in pediatric populations, commercially available software programs for CPOE can successfully be adjusted to accommodate NICU needs and to beneficially impact clinical practice.'

Del Beccaro et al. (2006)

Aims and setting: To determine if there were any changes in risk-adjusted mortality after the implementation of EP in a tertiary care PICU in the USA.

Methods: A retrospective review of crude mortality and paediatric risk-adjusted mortality in 1,232 infants born prior to EP implementation and 1,301 infants born in the 13 months after EP implementation. The Cerner software EP system included decision support; staff training and on-site support were also provided.

Study quality: This historically controlled study was found to be sound. Baseline characteristics were reported for each group and the intervention group and historical comparison group were judged to be equivalent. The study has a moderate risk of bias.

Findings: There were fewer deaths following EP implementation, but this finding was not found to be statistically significant (RR 0.819, 95% CI 0.554–1.212).

Author conclusions: 'Implementation of a computerized provider order entry system, even in the early months after implementation, was not associated with an increase in mortality.'

Han et al. (2005)

Aims and setting: This study examined mortality rates among US children who were admitted to a hospital via inter-facility transport before and after EP implementation, testing the hypothesis that patient outcome would improve after this intervention.

Methods: Demographic, clinical, and mortality data were examined for all children who were admitted to a hospital for specialised, tertiary-level care during an 18-month period from 1 October 2001, to 31 March 2003. An EP system had been fully implemented at the hospital and staff trained in its use by 29 October 2002. A total of 1,394 admissions occurred during the 13 months before EP implementation and 548 admissions occurred during the 5 months after EP implementation.

Study quality: This historically controlled study was found to be sound. The study has a moderate risk of bias.

Findings: This study found significantly more deaths following the implementation of EP than before implementation (RR 2.348, 95% CI 1.509 – 3.654). Overall, 75 children died during the study period; the unadjusted mortality rate increased from 2.80% (39 of 1,394) before EP implementation to 6.57% (36 of 548) after EP implementation (p=0.001).

Author conclusions: 'In this current study … we observed an unexpected increase in mortality coincident with CPOE implementation. Our unanticipated finding suggests that when implementing CPOE systems, institutions should continue to evaluate mortality effects, in addition to medication error rates, for children who are dependent on time-sensitive therapies.'

Holdsworth et al. (2007)

Aims and setting: This study aimed to determine the impact of an EP system with substantial decision support on the incidence and types of adverse drug events in hospitalised children in the USA.

Methods: 2,407 children admitted to a PICU or paediatric ward of a large metropolitan tertiary care centre between 1 April and 5 October 2005 were included in this prospective study. Baseline data were used from a previously published study on these same units during the pre-EP period from September 2000 to May 2001. The study, which measured PME and ADE, allowed a 15-month user acclimation period before data collection. The EP system (Eclipsys System 2000) included decision support and was modified from the commercial product.

Study quality: This historically controlled study was found to be sound. The study has a moderate risk of bias.

Findings: Significant reductions in prescription errors were found after the implementation of EP (RR 0.368, 95% CI 0.252 – 0.539). Significant post-EP reductions in preventable ADE were also found (RR 0.559, 95% CI 0.348 – 0.898). The study also identified reductions for all of those events rated as serious or life-threatening between the two time periods (pre-EP [n=13] and post-EP [n=3]; RR: 0.23; 95% CI: 0.07–0.80).

Author conclusions: 'This study demonstrated that a CPOE system with substantive decision support was associated with a reduction in both ADE and potential ADE among pediatric inpatients'.

Jani et al. (2010)

Aims and setting: The study aimed to examine the incidence and severity rating of dose prescribing errors before and after the implementation of a commercially available electronic prescribing system at a tertiary care children's hospital in the UK.

Methods: 8,723 prescriptions were reviewed to identify dose errors over a 13-month period from July 2005 to July 2006. Errors were categorised according to potential patient harm on a scale of 0-10, where 0 represents a case with no potential effect and 10 a case that would result in death. Severe outcomes (mean score greater than 7) were categorised as ADEs for the purposes of this review. The JAC Computer Services Ltd EP system was implemented in October 2005. The study did not report whether training was provided.

Study quality: This before and after study was found to be not sound due to significant differences between mean age of patients in the before and after implementation groups, which could have influenced the findings. The study has a high risk of bias.

Findings: This study found a significant reduction in dose errors post-EP implementation (RR 0.533, 95% CI 0.383 – 0.742). An effect size was not calculable for ADE; the authors report that severe ADEs were reduced, but the finding was non-significant (reduction from 0.18% to 0.06%, p <0.11). Minor adverse outcome rates were reduced from 0.89% to 0.44% (95% CI -0.8% to -0.11%, p <0.009) and moderate adverse outcome rates from 1.17% to 0.69% (95% CI -0.91% to -0.08, p <0.019).

Author conclusions: 'Our findings are consistent with the literature, as they show that EP can reduce dosing errors, even in the absence of dose related advance clinical decision support … The small but significant reduction is an important change.'

Kadmon et al. (2010)

Aims and setting: This study investigated the change in prescription error rates with the introduction of EP with and without a clinical decision support system (CDSS) in a PICU in Israel.

Methods: This report examines the difference in error rates between no EP and the implementation of EP with CDSS among 2,500 prescriptions examined over a three-year period, September 2004 to September 2007. The analysis focused on potential adverse drug events, medication prescription errors and rule violations, and also total errors – a combination of all of these error types. The EP system was Metavision, from iMDsoft, Tel Aviv, Israel. The study did not report whether training was provided.

Study quality: This historically controlled study was found to be not sound because the characteristics of the patients for whom the prescriptions were made were not described, and there was no analysis of whether differences existed between patients at the two different time periods that could have altered the findings. The study has a high risk of bias.

Findings: The study found significant reduction in total errors following the implementation of EP (RR 0.534, 95% CI 0.389-0.734).

Author conclusions: 'The present study indicates that, in our PICU, CPOE implementation reduced the prescription error rate only slightly. After the addition of CDSS tools that limited medication doses according to weight, the rate of prescription errors dropped significantly.'

Kazemi et al. (2011)

Aims and setting: This study investigated the effect of EP with and without a decision support system on reducing medication dosing errors of antibiotics and anticonvulsants in an Iranian neonatal ward. This report focuses on the findings regarding EP with decision support.

Methods: 248 neonates who received antibiotics for infectious diseases or anticonvulsants for seizure were included in the study. Order books were retrospectively reviewed to assess pre-implementation errors. Post-EP implementation, the researchers explored the nature of ignored warnings generated by the EP system. The study, conducted between May 2007 and December 2007, examined total errors, dose errors and frequency errors. The EP system was identified as Sayan HIS; training for physicians was provided.

Study quality: This historically controlled study was found to be sound. The study has a moderate risk of bias.

Findings: It was not possible to calculate an effect size for this study as the number of errors identified was based on warnings generated by the EP system and appeared qualitatively different from outcomes explored in other studies. However, the study authors reported a significantly reduced rate of total non-intercepted medication errors after implementation of EP with decision support compared to no EP (pre-EP 53% post-EP 34% $p<0.001$). They also reported significant reductions in dose errors from 41% to 22% ($p <0.001$) and in frequency errors from 25% to 20% ($p <0.001$).

Author conclusions: 'In the neonatal ward physician order entry without decision support functionality does not reduce non intercepted dose and frequency medication errors of antibiotics and anticonvulsants. However, when paired with a dose decision support system, it is capable of reducing these errors.'

Keene et al. (2007)

Aims and setting: To determine whether mortality increased after the initiation of EP in a paediatric population that was directly admitted to neonatal and paediatric intensive care units in a US hospital.

Methods: A retrospective review of mortality in 917 infants born in the 6 months prior to EP implementation and 374 infants born in the 6 months after EP implementation. The PHAMIS LastWord Online Medical Record System was used; a four-hour training session for nurses and a two-hour session for physicians were provided. On-site support was available for the first 3 weeks of implementation.

Study quality: This historically controlled study was found to be sound. Baseline characteristics were reported for each group and the intervention and historical comparison groups were judged to be equivalent. The study has a moderate risk of bias.

Findings: There were fewer deaths following EP implementation but this finding was not found to be statistically significant (RR 0.761, 95% CI 0.364 – 1.592).

Author conclusions: 'Mortality did not increase during CPOE initiation.'

King et al. (2003)

Aims and setting: To assess the impact of EP on medication errors and adverse drug events (ADE) in paediatric inpatients on three medical and two surgical wards in a tertiary care paediatric hospital in Canada.

Methods: A controlled trial in which the intervention group consisted of the 2 medical wards on which EP was implemented and the control group consisted of 1 medical and 2 surgical wards that continued to use handwritten orders. Data on errors and ADE were drawn from 17,485 patients over the course of this 6-year study. The commercially

available EP system, developed by Eclipsys, did not involve any form of decision support and the paper does not report whether training or support were provided.

Study quality: This non-randomised controlled trial was judged to be sound. Baseline characteristics were reported for each group and the intervention and control groups were judged to be equivalent. The study has a low risk of bias.

Findings: There was a non-significant increase in prescription errors post EP implementation (RR 1.155, 95% CI 0.338–3.945). However, the authors report that for total error, the post-EP rate was 40% lower on the intervention than on the control wards (ratio = 0.60; 95% CI = 0.48, 0.74). In relation to ADE, there was a very small, non-significant increase post-EP implementation (RR 1.011, 95% CI 0.092–11.147).

Author conclusions: 'The introduction of a commercially available physician computer order entry system was associated with a significant decrease in the rate of medication errors but not ADEs in an inpatient pediatric population.'

Lehmann et al. (2004)

Aims and setting: To describe the development of a medical information system that reduces errors in the ordering of total parenteral nutrition (TPN) in a newborn intensive care unit in USA.

Methods: Data were collected during a pre-intervention period (6 weeks from 2 October 2000, to 14 November 2000, n=557) and during the post-implementation periods - period 1 (8 weeks, from 15 November 2000 to 31 December 2000), n= 471, and period 2 (6 weeks from 27 August 2002 to 13 October 2002), n = 656.

Study quality: This study was found to be not sound as equivalency between groups at baseline could not be established. The study has a high risk of bias.

Findings: This study found a significant reduction of error rate at immediately after the TPN calculator implementation (RR 0.394, 95% CI 0.241-0.644) and at two years after the implementation (RR 0.113, 95% CI 0.055-0.235).

Author conclusions: 'Low-cost, pragmatic approaches using Internet technology in the design of medical information systems can reduce medical errors and might pose a viable option for the prevention of adverse drug events.'

Lehmann et al. (2006)

Aims and setting: To evaluate the effect of a web-based calculator and decision support system on infusing ordering errors in a children's hospital at an academic medical centre in USA.

Methods: Data collection on all infusion orders and errors was carried out at before and after the intervention implementation. During Phase A (February-March 2003), before the implementation, 129 orders were collected; 162 orders were collected during Phase B (February-April 2004), after the implementation. To control the differences between prescribers, data were collected at similar times during the academic year. The calculation and decision support was implemented on a distributed ColdFusion application.

Study quality: This HCT study was found to be sound. The study has a moderate risk of bias.

Findings: This study found that calculator-generated infusion orders contained significantly fewer orders with one or more errors than handwritten orders (RR 0.208, 95% CI 0.1-0.431).

Author conclusions: 'A Web-based calculator reduced significantly the total number of errors and eliminated all high-risk errors in the prescribing process for continuous

pediatric infusions. With no observed errors in pharmacy preparation, this study provides data to support the use of computerized ordering as an independent safe and viable method for ordering continuous pediatric infusions.'

Maat et al. (2010)

Aims and setting: To evaluate the impact of an EP system and clinical decision support (CDS) for glucose control and prescribing time in a neonatal intensive care unit at a children hospital in the Netherlands.

Methods: A historically controlled study was carried out over six years (2001-2007) to examine the effect of EP on glucose control conditions in patients (n = 2,040, 12 pre- and 12 post-EP intervals, EP implemented from April 2004). Glucose measurement results were collected from the Utrecht Patient Oriented Database. A crossover simulation study was carried out to determine the impact of EP on prescribing time (time needed to calculate glucose intake for NICU patients). Seven clinicians were randomly selected to calculate glucose intake both manually and with EP. The system was a home-grown EP.

Study quality: The study was found to be sound, as baseline main characteristics between groups were judged to be equivalent or further investigated during data analysis. The study has a moderate risk of bias.

Findings: Effect sizes were not calculable for this study; however, the authors report no significant difference between pre- and post-EP mean incidences of hypo- and hyperglycaemias per 100 hospital days of patients at risk in every 3-month period: hypoglycaemias, 4.0 (95% CI, 3.2-4.8(pre-EP and 3.1 (2.7-3.5) post-EP, p = 0.88; hyperglycaemias, 6.0 (4.3-7.7) pre-EP and 5.0 (3.7-6.3) post-EP, p =0.75. The findings suggested that EP led to a significant time reduction of 16% (1.3 minutes, 0.3-2.3) for simple and 60% (8.6 minutes, 95% CI 5.1-12.1) for complex calculations.

Author conclusions: 'CPOE including a special CDS tool preserved accuracy for calculation and control of glucose intake and increased prescribing time efficiency.'

Potts et al. (2004)

Aims and setting: The objective of this study was to evaluate the impact of EP on the frequency of errors in the medication ordering process in a paediatric critical care unit (PCCU) in the USA.

Methods: A total of 13,828 medication orders were reviewed to examine medication error rates. Data were collected for two months pre-implementation and for two months post-implementation. The WizOrder EP system, including decision support and training, was provided.

Study quality: This historically controlled study was found to be sound. The study has a moderate risk of bias.

Findings: EP implementation resulted in a significant decrease in error (RR 0.58, 95% CI 0.446 – 0.753). The authors reported that overall, EP resulted in a 95.9% (P=0.001) reduction in all types of errors associated with medication ordering.

Author conclusions: 'In this study, CPOE significantly reduced all categories of errors ... In addition, during the study, there were no reports of errors caused by the CPOE system, including no reports of orders being entered on the wrong patient.'

Sowan et al. (2010)

Aims and setting: This study examined the effect of using computerised orders for continuous infusions as compared to using handwritten orders on nurse ability to detect infusion pump programming errors, time required to verify pump settings and user satisfaction. The study was undertaken in a PICU in the USA.

Methods: 36 nurses were involved in this historically controlled crossover trial, with each being involved in both the intervention and control conditions. Nurses were required to verify the infusion pump settings against the continuous drug infusion orders (handwritten and EP) and to indicate whether the infusion pump settings correctly matched those in the medication orders. The outcomes measured were rates of error and time taken to complete tasks. The bespoke EP system included decision support; the study did not report whether training was provided.

Study quality: This historical control study was found to be sound. The study has a moderate risk of bias.

Findings: It was not possible to calculate effect sizes for this study. The authors reported a non-significant reduction in medication error. Using EP orders, nurses failed to detect dose or concentration errors in 27 (37%) of 72 infusions with deliberate errors, as compared with 28 of (39%) 72 infusions using the handwritten orders ($p = 0.68$). They also reported a significant reduction in the time taken to check the accuracy of orders (EP orders 6 minutes 18 seconds ± 2 minutes 26 seconds, handwritten orders 8 minutes 47 seconds ± 3 minutes 6 seconds; $p < 0.0001$). In addition the authors reported that nurses were significantly more satisfied with EP orders than with handwritten orders ($p < 0.0001$).

Author conclusions: 'The computerized orders saved nurses time but did not improve their ability to detect infusion pumps programming errors. Nurses preferred computerized orders.'

Sullins et al. (2012)

Aims and setting: The study examined the impact of two different interventions: EP and electronic medication administration records (eMAR). The authors aimed to determine the effectiveness of each and whether the order of implementation, EP first or eMAR first, would impact on the medication error rate. The study examined implementation in two different sites, one paediatric and one adult. For the purposes of this synthesis, we are only interested in the findings regarding EP in the paediatric population.

Methods: All patients admitted to a paediatric hospital during the designated data collection periods (20 January – 18 February 2009 EP first and 30 May – 28 June 2009 after the second intervention (eMAR) was added) were eligible for inclusion. 1,000 medication administrations were evaluated at each time period (baseline, EP). The primary outcome was change in medication error rate before and after EP implementation. Secondary outcomes included evaluating final medication error rates and the severity and origin of errors. The EP system used was not named and training and implementation issues were not reported.

Study quality: This historically controlled study was found to be not sound; baseline characteristics of the pre- and post-EP groups were not reported and the authors stated that there were differences in baseline error rates (p. 868). The study has a high risk of bias.

Findings: Effect sizes were not calculable for this study. The authors reported a non-significant decrease of 13.3% in total errors post-EP implementation (OR, 1.18; $p=0.24$). However, when the findings were broken down by error type, the three most common types of error (out of four examined) all increased post-EP implementation: documentation errors increased by 25%, prescription errors increased from 20 to 23 and administration errors of omission and of delays increased by 240% and 50% respectively. The authors did not indicate whether these findings were statistically significant. Nevertheless, it is unclear how these contradictory findings can be reconciled; that is to say, the authors reported an overall (non-significant) decrease in total errors but increases in all of the three most common types of error.

Author conclusions: 'CPOE was associated with higher rates of prescribing errors … and sufficient physician education must be completed prior to implementing this system. Specifically, prescribers may need additional education on first dose timing, product selection, and route of administration, as these are new elements they have not previously completed.'

Upperman et al. (2005)

Aims and setting: To determine whether hospital-wide EP in a tertiary care US paediatric hospital would lead to a decrease in medication errors.

Methods: An evaluation of inpatient discharge and usage and adverse drug event (ADE) rate data pre- and post-EP introduction. Over the 9-month study period, there were 45,615 inpatient days. Clinicians and ancillary personnel received 2-3 hours training prior to the implementation of the commercially available customised EP system. The authors did not name the software used.

Study quality: This historically controlled study was not found to be sound. Baseline characteristics were not reported for each group and it was not possible to judge whether the intervention and historical comparison groups were equivalent. The study has a high risk of bias.

Findings: Effect sizes were not calculable for this study; however, the authors reported a non-significant decrease in total ADEs post-EP implementation (reduction from 0.3 ± 0.04 per 1,000 doses pre-EP to 0.37 ± 0.05 per 1,000 doses post-EP p =0.3). When looking just at harmful ADEs, a statistically significant post-EP reduction was found (pre-EP 0.05 ± 0.017 per 1,000 doses, post-EP 0.03 ± 0.003 per 1,000 doses p =0.05). The authors also reported that their calculations demonstrated that EP would prevent 1 ADE every 64 patient days (95% CI 25-100).

Author conclusions: 'CPOE decreases harmful ADEs in a pediatric hospital, thus leading to increased patient safety.'

Vardi et al. (2007)

Aims and setting: To evaluate the impact of computerised physician order entry with a clinical decision support system (EP+CDSS) on (1) the frequency of errors in ordering resuscitation (CPR) medications and (2) the time for printing out the order form, in an 18-bed paediatric critical care department in a tertiary-care children's hospital.

Methods: A comparison of number of errors and time to fill in forms before and after implementation of EP + CDSS. A total of 60,094 orders were examined. The software system was developed using 'Visual Basic'; the report does not specify whether training was provided.

Study quality: This historically controlled study was not found to be sound. Baseline characteristics were not reported for each group and it was not possible to judge whether the intervention and historical comparison groups were equivalent. The study has a high risk of bias.

Findings: There was a significant decrease in total errors post-EP implementation (RR 0.04, 95% CI 0.002–0.773). The authors report that there were three reported incidents of errors among 13,124 CPR medications orders during the year preceding implementation of EP + CDSS. These represent errors that escaped the triple check by three independent staff members. There were no errors after EP + CDSS was implemented. Time to completion of drug forms dropped from 14 minutes 42 seconds to 2 minutes 14 seconds (p <0.001).

Author conclusions: 'CPOE+CDSS completely eliminated errors in filling in the forms and significantly reduced time to completing the form.'

Walsh et al. (2008)

Aims and setting: The study evaluated the effect of EP on the rate of inpatient paediatric medication errors. It was carried out in an urban hospital with 4 PICU beds, 15 NICU beds and 40 surgical and medical paediatric ward beds in the USA.

Methods: The research team reviewed 627 admissions to the paediatric inpatient wards, PICU and NICU, which consisted of 12,627 prescriptions written over 3,234 days. Forty patients per month were randomly selected for inclusion in the study. All components of the inpatient record were reviewed for possible medication errors and adverse drug events by paediatric nurses. They presented a description of possible errors to two paediatricians, unaware of whether these errors had taken place before or after the implementation of the system. These doctors then classified the error as an ADE (injury), a serious medication error without injury, an error without harm, neither an error nor ADE. They examined the rates of overall errors, serious medical errors, non-intercepted serious medical errors and preventable adverse drug events. The study was conducted between September 2001 and March 2002 (pre-EP) and between September 2002 and May 2003. The EP system was the Sunrise Clinical Manager EP system by Eclipsys.

Study quality: This before and after study was found to be sound since the patients before implementation were comparable to those after. The greatest difference was between number of admissions to the NICU which was higher after implementation, but not significantly so ($p = 0.055$). The study has a moderate risk of bias.

Findings: This study found a 7% decline in the rate of non-intercepted serious medication errors and no change in the rate of injuries as a result of error after the implementation of a commercially available EP system. There was no statistically significant change in the outcomes. The rate of errors per 1,000 days for all errors was: pre-EP 44.7, post-EP 50.9, IRR (incident rate ratio) 1.14 (95% CI 0.80-1.51); for serious medical errors: pre-EP 31.7, post-EP 33.0, IRR 1.04 (95% CI 0.70-1.54); for non-intercepted serious medical errors: pre-EP 23.1, post-EP 20.6, IRR 0.89 (95% CI 0.69-1.87); for preventable adverse drug events: pre-EP 7.9, post-EP 6.5 IRR 0.83 (95% CI 0.37-1.87).

Author conclusions: 'This study, which focused on children who were cared for in a general hospital, found that a commercial CPOE system caused a 7% decline in non-intercepted serious error rates and had no effect on pediatric injuries caused by error. CPOE has potential to accelerate the momentum of pediatric health care systems change but may require additional improvements to support complex medication ordering better to prevent more effectively errors in hospitalized children.'

Warrick et al. (2011)

Aims and setting: To determine the effect of electronic prescribing (EP) with a clinical information system on prescribing errors and omitted doses in a paediatric intensive care unit (PICU) in a UK hospital.

Methods: Data on prescribing errors and omitted doses were collected prospectively from charts of all patients over a 96-hour period: a) before EP system implementation; b) one week after EP system implementation; and c) six months after EP system implementation. The clinical information system was the Intellivue Clinical Information Portfolio by Phillips, UK. The system was implemented in March 2009.

Study quality: This study was found to be not sound as equivalency between groups could not be established. The study has a high risk of bias.

Findings: This study found no significant reduction in prescribing errors between pre-EP system implementation and immediately after implementation (RR 0.928, 95% CI 0.472-1.826) and at six months after implementation (RR 0.53, 95% CI 0.52-1.117). The authors

reported that the prevalence of omitted doses significantly decreased at six-month follow up ($p<0.05$).

Author conclusions: 'EP within a clinical information system increases medication safety in a PICU.

Appendix 6: Effectiveness synthesis: education interventions table of studies and structured summaries

Study	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
Frush et al. (2006)	**Error:** Significantly lower simulated dosing error in the web-based education group compared to controls (p = 0.0002) **Other outcomes reported:** Use of the Broselow Paediatric Emergency Tape; comparison of dosing time	**Design:** RCT **Comparison:** Usual practice (free to use any dosing calculation aid) **Sound:** Yes **RoB:** Low	**Research setting:** Unclear/ not specified **Setting in which the error is proposed to occur:** Acute hospital - Emergency department Tertiary care - specialist unit or clinic Paramedic situations **Country:** USA	**Intervention type:** Web-based education about correct use of a medication dosing tool Who received the intervention? Nurses Physicians Paramedics who were credentialed to order medicines **Drug types targeted:** No focus on specific drug types **Factors explored in relation to medical error:** Clinical decision tool incorrect use Knowledge of dosing tool Miscalculation	**PP:** Prescribing **ET:** Wrong dose	IV= 43 CT= 44
Gordon et al. (2011)	**Knowledge:** Significantly higher prescribing knowledge in the e-learning intervention group compared to controls (d = 1.24, 95% CI 0.87-1.60)	**Design:** RCT **Comparison:** Inactive control **Sound:** Yes **RoB:** Low	**Research setting:** University setting **Setting in which the error is proposed to occur**: Unclear/ not specified	**Intervention type:** 1-2 hour e-learning tutorial about prescribing **Who received the intervention?** Junior doctors **Drug types targeted:** No focus on specific drug types **Factors explored in relation to medical**	**PP:** Prescribing **ET:** Wrong drug; wrong dose; wrong strength/ concentration	IV= 76 CT= 86

Study	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
	Other outcomes reported: Confidence scores; satisfaction with teaching		**Country:** UK	**error:** Knowledge inadequacy/ inexperience Miscalculation Practitioner confidence		
Hu et al. (2013)	**Knowledge:** Significantly higher knowledge about administration of antibiotics in face-to-face instruction group compared to the controls (OR = 139.46, 95% CI 17.45 to 1114.51) **Other outcomes reported:** Time spent for each group	**Design:** non-RCT **Comparison:** Usual care (standard medication packaging instructions) **Sound:** Yes RoB: Low	**Research setting:** Acute hospital - outpatient clinic Setting in which the error is proposed to occur: Home **Country:** Taiwan	**Intervention type:** Face-to-face instruction by pharmacist about administration Who received the intervention? Parent/caregiver **Drug types targeted:** Antibiotics (augmentin syrup; zithromax powder) **Factors explored in relation to medical error:** Accuracy of dose measurement Knowledge inadequacy/ inexperience Mode of information provision	**PP:** Administering **ET:** Wrong strength/ concentration; wrong time; wrong formulation/ preparation; expired/ out of date drug; storage	IV group 1= 50 IV group 2= 50 CT= 50
Kozer et al. (2006)	**Error:** There was no difference between actual prescribing errors in the tutorial intervention group compared to controls (OR = 0.97, 95% CI 0.65 to 1.45).	**Design:** non-RCT **Comparison:** Usual practice (standard training) **Sound:** No **RoB:** High	**Research setting:** Tertiary care – paediatric clinic that is a training site for a nearby university **Setting in which**	**Intervention type:** 30-minute tutorial on appropriate methods for prescribing Who received the intervention? Trainee physicians **Drug types targeted:** No focus on specific drug types	**PP:** Prescribing **ET:** Wrong dose; wrong strength/ concentration; wrong frequency; wrong	IV = 13 CT = 9

Study	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
			the error is proposed to occur: Acute hospital emergency department **Country:** Canada	**Factors explored in relation to medical error:** Knowledge inadequacy/ inexperience Miscalculation	formulation/ preparation; wrong route; wrong unit of measure (e.g., mg instead of mml)	
Yin et al. (2008)	**Error:** Significantly higher dosing accuracy was evident in the medication counselling plus pictogram intervention group compared to the controls (OR = 0.15, 95% CI 0.08-0.26) **Knowledge:** Knowledge of appropriate preparation and frequency of administration were reported as higher in the intervention group. **Other outcomes reported:** Adherence	**Design:** RCT **Comparison:** Usual care (standard medication counselling) **Sound:** Yes **RoB:** Low	**Research setting:** Acute hospital emergency department **Setting in which the error is proposed to occur:** Home **Country:** USA	**Intervention type:** Medication counselling using plain language, pictogram-based medication instruction sheets **Who received the intervention?** Parent/ caregiver **Drug types targeted:** No focus on specific drug types **Factors explored in relation to medical error:** Accuracy of dose measurement Knowledge inadequacy/ inexperience Adherence	**PP:** Administering **ET:** Wrong dose; wrong frequency; wrong duration; wrong formulation/ preparation; storage	IV = 113 CT = 114

Study	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
Yin et al. (2011)	Error: Significantly fewer dosing errors for the text-plus-pictogram instructions compared to the text-only instructions (OR = 0.54, 95% CI 0.34-0.86).	**Design:** RCT **Comparison:** Alternative intervention (text-only version of the dosing information) **Sound:** Yes **RoB:** Low	**Research setting:** Acute hospital - paediatric outpatient clinic **Setting in which the error is proposed to occur:** Home **Country:** USA	**Intervention type:** administration instruction - pictographic dosing diagram **Who received the intervention?** Parent/ caregiver **Drug types targeted:** Infant paracetamol **Factors explored in relation to medical error:** Accuracy of dose measurement Health literacy and language of choice for instructions	**PP:** Administering **ET:** Wrong dose	IV = 155 CT = 144

Note. RCT = randomised controlled trial; IV = intervention group; CT = control group.

Frush et al. (2006)

Aims and setting: The study aimed to evaluate whether a web-based education program on correct use of the Broselow Pediatric Emergency Tape could reduce medication dosing errors and time to determine dose. It was conducted in paediatric emergency settings in the USA.

Methods: 89 emergency providers (nurses, physicians and paramedics who were credentialed to order medicines) participated in a videotaped, simulated stabilisation scenario. They were then randomly assigned to a control or education group; the latter consisted of a 30-minute web-based tutorial on the correct use of the tape. All participants undertook another simulation after the intervention for assessment purposes. The primary outcome was dosing accuracy; dosing time was also measured.

Study quality: This RCT study was assessed to be sound. The study has a low risk of bias.

Findings: The authors reported a significant (p = 0.0002) difference between the median dosing deviation of the education intervention group (median of 7.1% deviation from the required dosage) and the control group (median of 20.1% deviation from the required dosage), favouring the intervention group. The education group also had lower median dosing times than the controls.

Author conclusions: 'The Web-based education program on the proper use of the Broselow Emergency Resuscitation Tape could improve dosing accuracy and reduce dosing time.'

Gordon et al. (2011)

Aims and setting: This study sought to evaluate an e-learning resource for paediatric prescribing to improve junior doctors' prescribing skills. It was conducted in a university setting in the UK.

Methods: 162 volunteer junior doctors were randomised into control (n = 86) and intervention (n = 76) groups. The 1-2 hour e-learning intervention, which was developed by the researchers, covered four main categories of prescribing knowledge: drug selection, prescribing calculations for children, discussing therapies, and sources of error. The primary outcome was prescribing assessments; secondary outcomes were confidence in prescribing and satisfaction with the course.

Study quality: This RCT was found to be sound. The study has a low risk of bias.

Findings: This study found a statistically significant difference in prescribing skills for hypothetical situations in the intervention group compared to the control (d = 1.24, 95% CI 0.87-1.60). This difference in favour of the intervention group was reduced but still significant at three-month follow-up (d = 0.87, 95% CI 0.48 to 1.26). Physician prescribing confidence was also higher in the intervention, and satisfaction with the teaching on the course was high.

Author conclusions: 'This short e-learning resource significantly improved the paediatric prescribing skills of junior doctors. Outcomes were maintained at 3 months ... However, the direct impact on patient outcomes following this intervention has yet to be determined.'

Hu et al. (2013)

Aims and setting: This study aimed to assess the effectiveness of education programmes for parents of paediatric patients on administering oral antibiotic suspension medications. It was conducted in an outpatient clinic in Taiwan.

Methods: 150 caregivers were allocated into three education programmes: Group 1 read the package insert; Group 2 read a photograph-designed educational sheet; and Group 3

received a face-to-face medication education from a pharmacist with the photograph-designed educational sheet. The primary outcome was caregiver's accuracy of medication knowledge as measured by 12 questions covering dose concentration, timing, formulation, expiration and storage conditions. The time spent by caregivers in each group was also measured.

Study quality: This non-RCT was found to be sound. The study has a low risk of bias.

Findings: This study found that the caregivers who received the face-to-face education from the pharmacist were significantly more likely than caregivers who only received the standard medication package instructions to have no errors on the 12-item dose administration assessment (OR = 139.46, 95% CI 17.45-1114.51). The results also indicate that the face-to-face education took less time than written information.

Author conclusions: '…when compared to reading a package insert or education sheet, a pharmacists verbal education with photographic education materials was significantly more effective and time-saving in providing caregivers with the correct knowledge of oral antibiotic suspensions in pediatrics.'

Kozer et al. (2006)

Aims and setting: This study aimed to determine whether a short educational intervention reduced prescribing errors among trainees in a paediatric emergency department. It was conducted in a tertiary care paediatric clinic that is a training site for a nearby university in Canada.

Methods: All trainees in an emergency department were invited to attend a 30-minute tutorial focusing on appropriate methods for prescribing medications, followed by a written test. Of the 22 trainees, 13 attended the tutorial and therefore formed the intervention group. The actual medical charts in the trainees' emergency department were evaluated for medication errors as the primary outcome.

Study quality: This non-RCT was found to be not sound due to a risk of bias resulting from the intervention and control groups not being equivalent at baseline. The authors noted that the more experienced trainees were likely to opt out of the tutorial. The study also only had a small sample of trainee physicians. The study has a high risk of bias.

Findings: This study found that trainees who undertook a brief tutorial had similar medication error rates to trainees who did not attend the tutorial (OR = 0.97, 95% CI 0.65-1.45).

Author conclusions: 'A short tutorial, followed by a written test, administered to trainees before entering their rotation in the pediatric ED, did not appear to reduce prescribing errors.'

Yin et al. (2008)

Aims and setting: The purpose of this study was to evaluate the efficacy of a pictogram-based health literacy intervention to decrease liquid medication administration errors by caregivers of young children. The study was conducted in the USA in a paediatric emergency department which serves primarily low socio-economic groups.

Methods: 245 caregivers were randomised to the intervention (medication counselling using plain language with pictogram-based medication instruction sheets, n = 113) or control condition (standard medication counselling, n = 114). Dosing accuracy (defined as within 20% of the required dose), knowledge about administration and adherence were assessed through self-report or observation by the research team.

Study quality: This RCT was found to be sound. The study has a low risk of bias.

Findings: When error rates (i.e., ≥20% deviation above/below the required dose) were combined across both daily dose and as-needed medication types and included both self-report and observed error rates, the intervention group had significantly better dosing accuracy compared to the control group (OR = 0.15, 95% CI 0.08-0.26). Knowledge of appropriate preparation, knowledge of frequency and adherence were also higher in the intervention compared to control conditions.

Author conclusions: 'A plain language, pictogram-based intervention used as part of medication counselling resulted in decreased medication dosing errors and improved adherence among multiethnic, low socioeconomic status caregivers whose children were treated at an urban pediatric emergency department.'

Yin et al. (2011)

Aims and setting: This study aimed to test whether a pictographic dosing diagram could improve parent ability to dose infant paracetamol, and to determine whether pictogram benefit varies by health literacy level. The study was conducted in the USA in a paediatric outpatient clinic which serves primarily low socio-economic groups.

Methods: Caregivers were randomised to the control condition, which consisted of a standard infant paracetamol dropper with text-only instructions (n = 144) or the intervention, which consisted of text-plus-pictogram instructions (n = 155). The primary outcome, dosing error, was defined as 20% deviation above/below the required dose, with large overdosing error defined as ≥1.5 times the recommended dose. The authors also measured health literacy.

Study quality: This RCT was found to be sound. The study has a low risk of bias.

Findings: This study found that there were significantly fewer dosing errors (20% deviation above/below the required dose) for caregivers who received the text-plus-pictogram instructions compared to those who received text-only instructions (OR = 0.54, 95% CI 0.34-0.86). When health literacy was taken into account, the authors report that the intervention was effective for low health literacy caregivers but there was no significant difference between instruction types for caregivers with high health literacy.

Author conclusions: 'Inclusion of pictographic dosing diagrams as part of written medication instructions for infant acetaminophen may help parents provide doses of medication more accurately, especially those with low health literacy. High error rates, even among parents with adequate health literacy, suggest that additional study of strategies to optimize dosing is needed.'

Appendix 7: Effectiveness synthesis: CDST table of studies and structured summaries

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
Burgess (2009)	**Error - administering:** Significantly lower simulated administering error in the CCK group compared to controls (d = 0.87, 95% CI .37-1.37). **Other outcomes reported:** Completeness of documentation; time to turnaround patient	**Design:** RCT **Comparison:** Usual practice ('traditional medication administration') **Sound:** Yes **RoB:** Low	**Research setting:** Urban nursing school simulation lab Regional simulation hospital **Setting in which the error is proposed to occur:** Acute hospital emergency department **Country:** USA	**Intervention type:** Color Coding Kids (CCK) system developed by Broselow and Luten for standardising dosages **Who received the intervention?** Nursing students **Drug types targeted:** No focus on specific drug types **Factors explored in relation to medical error:** None - the paper does not explore associated factors	**PP:** Transcribing Administering **ET:** Wrong drug Wrong dose Wrong time Wrong patient Wrong route Transcription errors Assessment errors Documentation errors Evaluation errors Failure to provide education to the patient's family	IV= 34 CT= 34
Frush et al. (2004)	**Error – administering:** Significantly lower simulated administration error (dose determination) in the colour-coded	**Design:** RCT **Comparison:** Usual practice ('conventional dosage measurement	**Research setting:** Paediatric emergency centre at a tertiary care medical centre **Setting in which**	**Intervention type:** Colour-coded method to determine and measure a dose of paracetamol **Who received the intervention?** Parent/ caregiver **Drug types targeted:**	**PP:** Formulation/preparation Administering **ET:** Wrong dose	IV= 50 CT= 50

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
	method group compared to controls (RR = 0.16, 95% CI 0.06-0.43). **Other outcomes reported:** Dose measuring accuracy	methods') **Sound:** Yes **RoB:** Low	**the error is proposed to occur:** Home **Country:** USA	Paracetamol **Factors explored in relation to medical error:** Accuracy of dose measurement		
Hixson et al. (2009)	**Error - prescribing:** Significantly lower simulated total prescribing error in the Paediatric Analgesia Wheel group compared to controls (d = 2.90, 95% CI 2.10-3.69) **Other outcomes reported:** Unlicensed use of drugs; acceptability of intervention; time taken to complete prescription.	**Design:** RCT **Comparison:** Alternative intervention (access to the 2006 BNFC and a calculator) **Sound:** Yes **RoB:** Low	**Research setting:** Acute hospital **Setting in which the error is proposed to occur:** Acute hospital **Country:** UK	**Intervention type:** Paediatric Analgesia Wheel, which provides pre-calculated doses of commonly used analgesic and anti-emetic drugs rounded to a volume that can be accurately administered. **Who received the intervention?** Anaesthetist Physician **Drug types targeted:** Analgesics (intravenous ondansetron, intravenous morphine and oral oramorph, oral and intravenous paracetamol, rectal diclofenac and oral ibuprofen) Factors explored in relation to medical error: Accuracy of dose measurement	**PP:** Prescribing **ET:** Unlicensed use of the drug Wrong dose Wrong frequency Wrong interval	IV= 27 CT= 25

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
				Miscalculation Time taken to complete prescriptions		
Hixson et al. (2010)	**Error – administering:** Significantly lower simulated administering error in the Parental Analgesia Slide group compared to controls (effect size not calculable; authors report difference significant at p <0.001). **Other outcomes reported:** Recorded dose interval (in hours), frequency (maximum number of doses per day), and demonstrated drug volume.	**Design:** RCT **Comparison:** Usual practice (product information leaflets) **Sound:** No **RoB:** High	**Research setting:** Acute hospital - general ward **Setting in which the error is proposed to occur:** Home **Country:** UK	**Intervention type:** Parental Analgesia Slide, which provides parents with pre-calculated drug administration information **Who received the intervention?** Parent/caregiver **Drug types targeted:** Paracetamol **Factors explored in relation to medical error:** Miscalculation	**PP:** Administering **ET:** Wrong dose	IV= 80 CT= 80

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
Skouroliakou et al. (2005)	**Error - prescribing:** Significantly lower total prescribing error for machine-calculated formulations compared to controls (RR = 0.02, 95% CI .00-0.29). **Other outcomes reported:** Time taken to prepare the parenteral nutrition solutions	**Design:** Non-RCT **Comparison:** Usual practice (manual calculation and formulation) **Sound:** No **RoB:** High	**Research setting:** Gynaecology hospital **Setting in which the error is proposed to occur:** Gynaecology hospital **Country:** Greece	**Intervention type:** Computer programme developed to assist in prescribing and preparing/ formulating parenteral feeding in neonates **Who received the intervention?** Pharmacist Physician **Drug types targeted:** Parenteral feeding **Factors explored in relation to medical error:** Miscalculation	**PP:** Prescribing Formulation/preparation **ET:** Error types not specified, although appear to relate to calculation errors	IV= 941 CT= 941

Notes: RCT = randomised controlled trial; IV = intervention group; CT = control group.

Burgess (2009)

Aims and setting: This study aimed to compare the effectiveness of traditional nursing medication administration with the computerised Color Coding Kids (CCK) system (developed by Broselow and Luten for standardising dosages) to reduce paediatric medication errors. It was conducted in simulation laboratory settings in the US.

Methods: 68 nursing students were randomly assigned to a control (traditional medication administration) or intervention (CCK system) condition. The CCK system determines a colour-coded category based on a child's weight and height; the colour code indicates appropriate therapeutic pathways. In a simulated environment, student nurses were required to administer medication in a paediatric rapid response scenario.

The primary outcome was an 11-item medication administration accuracy checklist (MEDCHECK); hand-off communication (measured by the SBAR tool[7]) and workflow turn-around time were also measured.

Study quality: This RCT study was assessed to be sound. The study has a low risk of bias.

Findings: This study found a statistically significant difference in administration accuracy for simulated situations in favour of the intervention group compared to the control (*d* = 0.87, 95% CI 0.37-1.37). No significant difference between the groups on turn-around time or communication was found.

Author conclusions: 'the treatment condition with the CCK system had a highly significant effect on the safe administration of medication in a simulated pediatric rapid response scenario compared to the traditional method of medication administration' (p. 82).

Frush et al. (2004)

Aims and setting: This study aimed to compare caregivers' dosing determination and measuring when using a colour-coded measuring device for paracetamol, with conventional methods. It was conducted in a tertiary care paediatric emergency centre in the US.

Methods: One hundred caregivers were randomly assigned to a control ('conventional dosage measurement methods') or colour-coded measuring device condition. Researchers then asked caregivers to determine and measure a dose of paracetamol for their child. The main outcome measures were accuracy in dose determination (stated) and dose measuring (demonstrated) as indicated by percentage of deviation from recommended paracetamol dosage.

Study quality: This RCT study was assessed to be sound. The study has a low risk of bias.

Findings: This study found a statistically significant difference in accuracy of dose determination in favour of the intervention group compared to the control (*RR* = 0.16, 95% CI 0.06-0.426). A significant difference between the groups favouring the colour-coded condition for dose measurement was also found.

Author conclusions: 'This study suggests a marked improvement in caregivers' ability to correctly determine and measure an over-the-counter medication for their child using a color-coded method compared with conventional methods' (p. 620).

Hixson et al. (2009)

Aims and setting: This study aimed to compare the accuracy of prescribing analgesic and anti-emetic drugs to children when using either the 2006 British National Formulary for

[7] Situation-Background-Assessment-Recommendation

children (BNFC) or a new device, the Paediatric Analgesia Wheel. It was conducted in an acute hospital in the UK.

Methods: 52 practising hospital doctors (anaesthetists and physicians) were randomly assigned to a control (BNFC) or intervention (Paediatric Analgesia Wheel) condition. A simulated prescription chart was created, which required doctors to prescribe seven drugs to each of two fictitious children. The primary outcome was correct prescribing; time taken to complete the chart was also measured.

Study quality: This RCT study was assessed to be sound. The study has a low risk of bias.

Findings: This study found a statistically significant difference in simulated total prescribing error in favour of the intervention group compared to the control (d = 2.90, 95% CI 2.10-3.69). The mean turn-around time was significantly shorter for the Paediatric Analgesia Wheel condition (5.8 minutes) compared with the BNFC (12.4 minutes).

Author conclusions: 'The Paediatric Analgesia Wheel provides a time-efficient method of prescribing commonly used analgesic and anti-emetic drugs to children and results in improved accuracy when compared with using the BNFC' (p. 268).

Hixson et al. (2010)

Aims and setting: This study aimed to examine the effectiveness of using the Parental Analgesia Slide by parents to calculate and demonstrate the correct paracetamol dose, interval, and frequency for their child, compared to using standard product information leaflets. It was conducted in a hospital setting in the UK.

Methods: 160 caregivers were randomly assigned to a control (product information leaflets) or intervention (Parental Analgesia Slide) condition. The slide provides parents with pre-calculated drug administration information. Caregivers in both groups were asked to record the formulation and volume of paracetamol, state the frequency and interval of the dose, and measure their recorded paracetamol volume.

Study quality: This RCT study was assessed to be not sound because the characteristics of the two groups were not reported so we cannot be sure that they were equivalent at baseline. The study has a high risk of bias.

Findings: This study found a statistically significant lower administration error rate for caregivers using the slide compared to the product information (effect size not calculable; the authors reported an absolute percentage dose error median of 33.3% in the control compared to 0% in the intervention, p <0.001).

Author conclusions: 'The Parental Analgesia Slide resulted in improved parental ability to calculate paracetamol dose, interval, and frequency while preserving their ability to demonstrate an accurate drug volume' (p. 612).

Skouroliakou et al. (2005)

Aims and setting: This study aimed to assess the reduction in error using a new computerised procedure for total parenteral nutrition (TPN) formulation, compared to the existing manual process. It was conducted in a gynaecology hospital in Greece.

Methods: Over a 6-month period, 941 pre-term and sick term neonates receiving TPN were included in the study. For these infants, calculations for the composition of the TPN solution were done simultaneously by a computer (the intervention condition) and a physician or pharmacist (the control condition). The calculations were compared for accuracy by a third individual. The primary outcomes for the prescribing part of the evaluation were errors and time taken to calculate. In addition, an automated mixing device (the 'compounder') was used in the computer-driven process of TPN solution

formulation, which was compared with manually prepared solutions; only turn-around time was reported as an outcome for this aspect of the study.

Study quality: This non-RCT study was assessed to be not sound. The study has a high risk of bias. This is because it did not report separately the results that address the objective: 'the usefulness of the automated compounder in the computer driven process of TPN solution formulation was also assessed' (only turn-around time but not error rates in formulation were reported), and was therefore deemed to be at risk of selective reporting bias. Also, it did not report how many physicians/pharmacists were involved in the manual calculations.

Findings: This study found statistically significant lower prescribing error rates in favour of the intervention group compared to the control (*RR* = 0.02, 95% CI 0.00-0.29). The time taken to calculate the prescription of the TPN formula and the time spent on preparation of the TPN solution were also significantly lower in the computerised condition compared to the control.

Author conclusions: 'Use of this system can optimize pharmacists' and physicians' work and help prevent prescription and preparation errors' (p. 305).

Appendix 8: Effectiveness synthesis: miscellaneous interventions table of studies and structured summaries

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
Allegaert et al. (2006)	**Error:** With the paediatric vial there were more concentrations in the target zone compared to the adult vial (72% and 58% respectively).	**Design:** nRCT **Sound:** Yes **RoB:** Low	**Setting:** NICU **Country:** Belgium	**Intervention type:** Paediatric concentrations/doses – 'paediatric' vial **Comparison:** 'adult' vial **Who received the intervention?** Health professional **Drug types targeted:** Antibiotics	**PP:** Administering **ET:** Wrong dose	IV= 56 CT=75
Cunningham et al. (2008)	**Error:** ICP resulted in significant reduction in mean prescribing errors (ICP= 10.4, Control=14.8, P=0.002).	**Design:** RCT **Sound:** Yes **RoB:** Low	**Setting:** Emergency department **Country:** UK	**Intervention type:** Integrated care pathway (ICP) – a single document combining all nursing, medical, clinical observation and prescribing charts **Comparison:** Separate charts. **Who received the intervention?** Nurses Physicians Pharmacists **Drug types targeted:** Bronchodilators (Salbutamol) Prednisolone	**PP:** Prescribing **ET:** Total error	IV= 163 CT= 135

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
Kaushal et al. (2008)	**Error:** Significantly fewer serious medication errors with full time pharmacist (30 fewer serious medication errors per 1,000 patient days in IV group compared to CT, p = 0.01) No evidence of effect with part time pharmacist (PMEs per 1,000 patient days - surgical unit, IV = 9, CT = 10, p = 0.89; medical unit, IV = 9, CT = 8, p = 0.78)	**Design:** RCT **Sound:** No **RoB:** High	**Setting:** PICU and paediatric wards (surgical, medical) **Country:** USA	**Intervention type:** Ward-based pharmacist support **Comparison:** Usual practice Who received the intervention? Nurses Physicians **Drug types targeted:** No focus on specific drug types	**PP:** Prescribing, transcribing, administering, dispensing, monitoring. **ET:** Total errors	IV= 401 CT= 359 (PICU data only)
Kozer et al. (2005)	**Error:** Using the pre-printed form was associated with a significant reduction in the risk for an error (OR 0.55; 95% CI 0.34-0.90)	**Design:** RCT **Sound:** Yes **RoB:** Low	**Setting:** Paediatric emergency department **Country:** Canada	**Intervention type:** Pre-printed prescription order form **Comparison:** Blank order sheets **Who received the intervention?** Emergency department staff ordering medications **Drug types targeted:** No focus on specific drug types	**PP:** Prescribing **ET:** Total error	IV= 376 CT= 411
Porter et al. (2008)	**Error:** Non-significant reduction on rate of error per 100 patients	**Design:** nRCT (cross-over	**Setting:** Emergency department	**Intervention type:** ParentLink health information technology intervention to improve the quality of patient histories by	**PP:** History taking **ET:** Total error	IV= 267 CT= 387

Short Title	Outcomes	Risk of bias (RoB)	Setting	Intervention details	Pathway point (PP) and error type (ET)	Sample size
	with use of ParentLink (IV = 134, CT =173, p = 0.35).	trial) **Sound:** Yes **RoB:** Low	**Country:** USA	enabling parents to input information **Comparison:** Usual practice **Who received the intervention?** Nurse Physician Parent **Drug types targeted:** No focus on specific drug types		
Wheeler et al. (2008)	**Error:** Significantly fewer medication errors in IV group than control (IV = 79% doses within 10% of recommended dose CT = 14%, p = 0.009, chi-square test). **Turn-around times:** Median time to administer drugs significantly shorter for IV group (IV = 35.5 seconds, IQR 27-65 seconds; CT = 130 seconds, IQR 112-171 seconds, p≤0.001).	**Design:** RCT **Sound:** Yes **RoB:** Low (Note: small sample size)	**Setting:** Emergency department **Country:** UK	**Intervention type:** Labelling drugs using mass concentration **Comparison:** Ratio concentration labels **Who received the intervention?** Physician **Drug types targeted:** Epinephrine	**PP:** Administration **ET:** Wrong dose	IV= 14 CT= 14

Notes: nRCT = non-randomised controlled trial; RCT = randomised controlled trial; IV = intervention group; CT = control group; IQR = interquartile range.

Allegaert et al. (2006)

Aims and setting: The study investigated whether the introduction of a paediatric vial with a standardised concentration (50 mg/ml, Amukin ready to use 100 mg) improved antibiotic dose precision when compared to an adult vial (250 mg/ml, Amukin ready to use 500 mg). It was conducted in a hospital neonatal intensive care unit in Belgium.

Methods: The study compared findings from before the paediatric vial was introduced (2002–2004 - 75 neonates) to after the implementation of the paediatric vial (2004–2005 - 56 neonates). Amikacin serum concentration was assessed from assays of blood samples taken just before administration (trough) and 1 hour after initiation of administration (peak) of the second administration. They measured clearance (CL) and volume of distribution (V) changes as markers of dose accuracy.

Study quality: This nRCT was found to be sound; it has a low risk of bias.

Findings: With the paediatric vial, there were more amikacin plasma concentrations in the target zone (amikacin peak level > 20 mg/l and trough level of ≤ 5 mg/l) compared to the adult vial (72% and 58% respectively).

Author conclusions: 'We have demonstrated improved drug precision in neonates when a pediatric vial was used in preference to an adult vial.'

Cunningham et al. (2008)

Aims and setting: This UK study aimed to determine whether the introduction of an integrated care pathway (ICP) for acute asthma could improve care delivered to patients visiting an emergency department alone or to patients who were subsequently admitted to a ward. Length of stay and rate of recovery were measured; rates of prescribing error were examined as a secondary outcome.

Methods: Over a 26 week period, children aged 2-16 (n=298) visiting the emergency department with acute asthma/wheeze were randomised using a block cluster randomisation design (seven-day periods in eight-week blocks) to receive either standard care (separate documentation for nursing, medical, clinical observation and prescribing charts) or care provided by an ICP (combining all charts for all disciplines chronologically within a single document). Staff received training on the use of ICP in the month prior to its introduction. Prescribing records were assessed to identify errors.

Study quality: This RCT study was assessed to be sound. The study has a low risk of bias.

Findings: The authors found that there were 30% fewer prescribing errors when the ICP was used (standard care=14.8, ICP=10.4, p=0.002). Other outcomes examined by the authors showed that use of the ICP was associated with shorter lengths of stay (ICP=37.6 hours; standard care=40.7 hours); fewer additional visits for first attenders (ICP=16/136, 12.6%; standard care=19/115,17.0%); more clinical contacts (total clinical contacts ICP=22; standard care 19.2, p =.0004) and a greater number of parents receiving advice on acute post discharge care and primary care follow-up.

Author conclusions: 'Use of an integrated care pathway for the children with acute asthma/wheeze who were admitted to the hospital was associated with a modest reduction in length of stay, fewer prescribing errors, provision of more education, and improved advice to attend primary care, although more clinical contacts were required during the patient stay.'

Kaushal et al. (2008)

Aims and setting: This US study evaluated whether the introduction of a clinical pharmacist to ward-based clinical teams reduced serious medical errors among children.

The study examined the impact of a full-time pharmacist on the PICU, and part-time (mornings only) pharmacists on general and surgical wards.

Methods: The pharmacists' role involved: the provision of information and advice to physicians; the facilitation of communication between the medical care team and the pharmacy; the provision of information on administration and monitoring to nurses; and monitoring of medication transcription, preparation, storage and distribution. Medication orders, administration records and patients' charts were examined to determine error rates. Baseline data were collected for six to eight weeks (March to August 2000), and post-intervention data for three months (June to November 2000). Data were collected from a total of 760 children in the PICU, 1251 children on general medical units and 1276 children on general surgical units. Serious medical errors were defined as preventable ADEs and non-intercepted near misses.

Study quality: This randomised controlled trial was found to be unsound because the patients in the two groups were not equivalent (the age profile of the control and intervention groups differed), and because the paper did not fully report results for all outcomes measured. Thus the study has a high risk of bias.

Findings: Compared to the control group, the introduction of a *full-time* clinical pharmacist in a PICU was associated with significantly fewer serious medication errors per 1,000 patient days (6 versus 30, $p<0.01$). These findings were adjusted, as an increase in errors in the control PICU was identified as being due to an incorrect pre-printed order template. After excluding these errors from their data analysis, the authors identified that there was still a net of 30 fewer serious medication errors per 1,000 patient days in the intervention PICU than in the control PICU ($p = 0.01$). When compared to controls, the introduction of a *part-time* pharmacist on the general wards did not result in statistically significant findings: on the surgical unit, lower levels of PME per 1,000 patient days were found for the intervention group, though the finding was non-significant (9 versus 10, $p = 0.89$) and on the general medical unit, rates of PME per 1,000 patient days were *higher* in the intervention group than in the control group though again the findings were non-significant (9 versus 8, $p = 0.78$).

Author conclusions: 'A full-time unit-based clinical pharmacist substantially decreased the serious medication error rate in the pediatric intensive care setting, but a part-time pharmacist was not as effective in general pediatric wards.'

Kozer et al. (2005)

Aims and setting: This study sought to assess the impact of structured pre-printed order sheets on the incidence of medication errors. It was conducted in a tertiary care paediatric emergency department in Canada.

Methods: The pre-printed sheet required staff to specify the dose, weight-adjusted dose, total daily dose, route of administration and frequency for each medication ordered. Eighteen days were selected randomly by a computer-generated random numbers system (block randomisation) into two arms: day when the regular blank order sheets were used (regular form) and days when the pre-printed order sheets were used (experimental form). Patient charts were reviewed to determine rates of PME; 411 control group charts and 376 intervention group charts were reviewed.

Study quality: This RCT was found to be sound. The study has a low risk of bias.

Findings: Drug errors identified were significantly greater when the blank form was used (n=68; 16.6%) compared to pre-printed structured form (n=37; 9.8%). Using the pre-printed structured form was associated with a significant reduction in the risk of an error (OR 0.55; 95% CI 0.34-0.90). There was an even greater reduction in the risk of a severe or significant error (IV = 14, CT = 36, OR 0.39; 95% CI 0.21–0.77).

Author conclusions: 'The use of a pre-printed structured order form significantly reduces medication errors among pediatric patients in the ED.'

Porter et al. (2008)

Aims and setting: This US study evaluated the impact of ParentLink, a computer programme designed to collect patient histories from parents, on the error rate for ordering and prescribing medications during emergency paediatric care. The aim was to improve the quality of information available to physicians before they prescribed.

Methods: This cross-over study gathered data from two sites, each site acting as both intervention and control; 1,097 patient records of 654 patients targeted by ParentLink were reviewed. During the intervention, parents entered data on their child's symptoms, current medications and allergies as they waited to be seen. Parents in the control condition received usual care. Medication error rates were determined from parent reports and patient charts.

Study quality: Despite some differences between groups, this study was found to be sound, as differences were small and deemed to be unimportant. The study has a low risk of bias.

Findings: Although the rate of error per 100 patients was lower during the intervention than during the control periods, the findings were not significant (134 vs. 173 respectively, $p = 0.35$).

Author conclusions: 'The implementation of ParentLink did not change the rate of medication error. Further efforts in developing these technologies should focus on mechanisms to more tightly integrate patient-produced information with existing data systems and solutions.'

Wheeler et al. (2008)

Aims and setting: This UK study investigated whether labelling drugs using mass concentration (1 mg in 1 ml) rather than ratio concentration (1 ml of a 1:1000 solution) would improve physicians' accuracy of drug dosing during a simulated emergency scenario. The simulated setting was an emergency department in a rural hospital.

Methods: Physicians received either an ampoule of epinephrine labelled as 1mg in 1 mL or as 1 mL of 1:1000 and were asked to calculate the correct volume of epinephrine for the acute management of a child with anaphylaxis. Twenty-eight doctors agreed to participate and they were randomly allocated to each condition. The researchers assessed the accuracy of the dose and the time taken to do the calculation.

Study quality: This RCT was considered to be sound and therefore it has a low risk of bias. It should be noted however, that the number of subjects in the intervention and control groups was relatively small.

Findings: Eleven of 14 (79%) providers in the mass concentration group calculated a dose within 10% of that recommended by the protocol, compared with 2 (14%) in the ratio group ($p = 0.009$, chi-square test). The median time taken to administer epinephrine for the mass concentration group was 35.5 seconds (IQR, 27.0 to 65.0 seconds) compared with 130.0 seconds (IQR, 112.0 to 171.0 seconds) for the ratio group ($P \leq 0.001$). Physicians were more likely to give the wrong dose of epinephrine and take longer to do so when the strength of the epinephrine was expressed as a ratio (OR for dose error 13.4, 95% CI 2.2 – 81.7, $p = 0.005$).

Author conclusions: 'The differences seem not only statistically but also clinically significant, given that the consequences of a delay in treatment or an overdose of epinephrine in an emergency are potentially catastrophic.'

Appendix 9: Intervention features synthesis: EP table details of intervention packages

Study	Setting	Package type	Paediatric-specific	Decision support tools			Safeguarding features			
				Dose calculation	Structured order sets	Information access	Alerts	Mandatory fields	Access security	Other
Barnes (2009)	PICU	Unidentified	Unclear	No	No	Patient history	Dose Route Other	No	No	Additional signature required Standard dosing unit
Cordero et al. (2004)	NICU	Customised	Yes	Yes	Yes	Lab results Radiology results Dietary results	Allergy Dose Drug interaction Duplication Route Other	Yes	No	Not stated
Del Beccaro et al. (2006)	PICU	Customised	Yes	No	Yes	Lab results Patient history	Allergy Dose	No	Yes	Not stated
Han et al. (2005)	Children's hospital	Off the peg	No	No	No	No	Allergy Drug interaction Food	Yes	No	Additional signature required Possible to override

Study	Setting	Package type	Paediatric-specific	Decision support tools			Safeguarding features			
				Dose calculation	Structured order sets	Information access	Alerts	Mandatory fields	Access security	Other
Holdsworth et al. (2007)	PICU and general paediatric units	Customised	Yes	Yes	Yes	Patient history Pharmacy interface	Dose	Yes	No	Not stated
Jani et al. (2010)	Acute tertiary care paediatric hospital	Off the peg	No	No	Yes	Online formulary/ best practice Pharmacy interface	Age/weight ratio Allergy Drug interaction Duplication	Yes	No	Not stated
Kadmon et al. (2009)	PICU	Customised	Yes	No	Yes	Online formulary/ best practice	Dose	No	Yes	Possible to override Access security features Maximum doses
Kazemi et al. (2011)	Neonatal ward	Customised	Yes	Yes	Yes	Online formulary/best practice Lab results Patient history	Dose	Yes	No	Additional signing required Possible to override

Study	Setting	Package type	Paediatric-specific	Decision support tools			Safeguarding features			
				Dose calculation	Structured order sets	Information access	Alerts	Mandatory fields	Access security	Other
Keene et al. (2007)	PICU and NICU	Customised	Yes	No	Yes		No	No	Yes	Not stated
King et al. (2003)	Tertiary care paediatric hospital	Off the peg	No	No	No	Lab results Pharmacy interface Patient history	No	No	No	Not stated
Lehmann et al. (2004)	NICU	Home grown	Yes	Yes	Yes	Online formulary/best practice Pharmacy interface Other departments interface	Age/weight ratio Dose Other	Yes	Yes	Reminders
Lehmann et al. (2006)	Children's hospital/ academic setting	Home grown	Yes	Yes	Yes	Online formulary/ best practice	Dose Other	No	No	Maximum doses
Maat et al. (2013)	Academic setting	Home grown	Yes	Yes	Yes	Lab results Hospital-wide interface	No	No	No	Not stated

Study	Setting	Package type	Paediatric-specific	Decision support tools			Safeguarding features			
				Dose calculation	Structured order sets	Information access	Alerts	Mandatory fields	Access security	Other
Potts et al. (2004)	PICU	Home grown	No	Yes	No	Online formulary/ best practice Lab results Patient history	Allergy Dose Drug interaction Lab test interaction Food	No	No	Not stated
Sowan et al. (2010)	PICU	Home grown	Yes	Yes	No	Online formulary/ best practice	No	No	No	Not stated
Sullins et al. (2012)	Children's hospital	Unidentified	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Upperman et al. (2005)	Children's hospital	Customised	Yes	Yes	Yes	Online formulary/ best practice Lab results Pharmacy interface Patient history	Allergy Lab test interaction	Yes	No	Reminders

Study	Setting	Package type	Paediatric-specific	Decision support tools			Safeguarding features			
				Dose calculation	Structured order sets	Information access	Alerts	Mandatory fields	Access security	Other
Vardi et al. (2007)	PICU	Home grown	Yes	Yes	No	Online formulary/ best practice Lab results Pharmacy interface	Age/weight ratio Lab test interaction	No	Yes	Not stated
Walsh et al. (2008)	NICU, PICU and inpatient paediatric wards	Off the peg	Yes	Yes	Yes	No	Allergy Dose Drug interaction	No	Yes	Not stated
Warrick et al. (2011)	PICU	Customised	Yes	Yes	Yes	Online formulary/best practice Patient history	No	Yes	No	Reminders

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