Adverse Drug Reactions in Children

The Contribution of Off-label & Unlicensed Prescribing

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

by

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Abstract

Adverse drug reactions (ADRs) in children are common but their predictors are not fully characterised. It is known that both increasing age and number of concomitant medicines increase ADR risk in children, and there is also some evidence that off-label and unlicensed medicine use may contribute. The purpose of the thesis was to characterise ADRs in children, focusing on known risk factors, which have not been adequately evaluated in the literature.

The contribution of off-label and unlicensed prescribing to ADR risk in children was assessed in two large prospective studies. In the first study, which evaluated ADR-related hospital admissions, off-label or unlicensed medicines were more likely to be implicated in an ADR than authorised medicines (relative risk 1.67, 95% CI 1.38, 2.02, $p < 0.001$). In a multivariate analysis, patients admitted under the care of oncology were more likely to have experienced an ADR (odds ratio (OR) 25.70, 95% CI 14.56, 45.38, $p < 0.001$). The following risk factors were also associated with increased ADR risk: increasing age (OR 1.04, 95% CI 1.00, 1.08, $p = 0.045$), number of authorised medicines (OR 1.25, 95% CI 1.16, 1.35, $p < 0.001$) and number of off-label or unlicensed medicines (OR 1.23, 95% CI 1.10, 1.36, $p < 0.001$). In a sub-group analysis which excluded oncology patients, age and number of authorised medicines predicted ADR risk (OR 1.05, 95% CI 1.01, 1.09, $p = 0.023$ and OR 1.33, 95% CI 1.23, 1.44, $p < 0.001$ respectively) but the number of off-label and unlicensed medicines did not (OR 1.04, 95% CI 0.89, 1.12, $p = 0.627$). The second prospective study examined ADRs occurring in paediatric inpatients. Again, off-label or unlicensed medicines were more likely to be implicated in an ADR than authorised medicines (OR 2.25, 95% CI 1.95, 2.59, $p < 0.001$). Medicines licensed in children but given to a child below the minimum age or weight recommended had the greatest risk of being implicated in an ADR. Multivariate analysis showed that increasing age (HR 1.04, 95% CI 1.02, 1.05, $p < 0.001$) and receipt of a general anaesthetic (HR 5.30, 95% CI 4.42, 6.35, $p < 0.001$) were positive predictors of ADR risk. Both the number of authorised (HR 1.22, 95% CI 1.17, 1.26, $p < 0.001$) and the number of off-label or unlicensed (HR 1.27, 95% CI 1.20, 1.34, $p < 0.001$) medicines were predictors of ADR risk.

ADR detection in the above studies was based on intensive surveillance. One possible method of detecting ADRs may be through the ICD-10 clinical coding system but this has not been investigated for paediatrics. Only 31.5% of the 241 ADRs evaluated from the prospective admissions study were coded correctly using at least one ICD-10 code. The clinical coding system could contribute to pharmacovigilance if deficiencies in how ADRs are recorded in the case notes and the clinical coding system can be addressed.

An important ADR detected in the admissions study was the occurrence of haemorrhage post-tonsillectomy which has been attributed to the use of dexamethasone. In order to analyse this further, a systematic review and meta-analysis of dexamethasone and non-steroidal anti-inflammatory drug (NSAID) use in paediatric tonsillectomy was undertaken. Although there were a large number of randomised controlled trials and observational studies in this area, analysis of all of these led to the conclusion that there was insufficient evidence to rule out an increased risk of haemorrhage with dexamethasone use whether in combination with NSAID or not (Peto odds ratio for dexamethasone versus another intervention 1.41, 95% CI 0.89, 2.25, $p = 0.15$). Further, well powered, well designed studies are needed in this area.

An important ADR detected in the in-patient study was post-operative nausea and vomiting. More detailed analysis was therefore undertaken to identify the risk factors for post-operative vomiting (POV), with a view to developing a risk score. The following were all identified as predictors of POV risk: age (OR 1.06, 95% CI 1.03, 1.10, $p<0.001$), duration of anaesthesia (OR 1.00, 95% CI 1.00, 1.01, $p <0.001$) and the use of intra-operative analgesics (OR 2.22, 95% CI 1.58, 3.12, $p < 0.001$). However, it was not possible to develop a robust model to predict the risk of POV because of the heterogeneity of the patient groups, the types of surgery, and the different clinical practices between different anaesthetists in terms of anti-emetic (choice, timing and doses).

The use of off-label and unlicensed medicines in children is common but necessary and these medicines are frequently associated with ADRs. The rational prescribing of medicines is an important measure in the reduction of ADR risk and a solid evidence-base is a pre-requisite. The aim should be that the minimum number of medicines is used safely and effectively, at the lowest dose possible, for the minimum duration necessary.

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Table of contents

List of tables

Table of figures

Abbreviations used in this thesis

ABPI	Association of the British Pharmaceutical Industry
ADE	adverse drug event
ADR	adverse drug reaction
ADRIC	Adverse Drug Reactions in Children
AED	accident and emergency department
APAGBI	Association of Paediatric Anaesthetists of Great Britain & Ireland
API	active pharmaceutical ingredient
AUC	area under the curve
BNF	British National Formulary
BNF-C	British National Formulary for Children
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CIVAS	Central Intravenous Additive Service
DH	Department of Health
DoTS	Dose relatedness, Timing and Susceptibility
DTP	diphtheria, tetanus, pertussis
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium
FDA	Food and Drug Administration
GA	general anaesthetic
GFR	glomerular filtration rate
GMP	good manufacturing practice
GOR	gastro-oesophageal reflux
GP	general practitioner
HES	hospital episode statistics
HR	hazard ratio
ICD	International Classification of Disease
IQR	inter-quartile range
JIA	juvenile idiopathic arthritis
LCAT	Liverpool Causality Assessment Tool
MA	marketing authorisation
MHRA	Medicines and Healthcare products Regulatory Agency

NCA	nurse controlled analgesia
NGT	nasogastric tube
NHS	National Health Service
NICU	neonatal intensive care unit
NIHR	National Institute of Health Research
NRS	non-randomised studies
NSAID	non-steroidal anti-inflammatory drug
OLUL	off-label or unlicensed
OPCS	Office of Population Census and Surveys
OR	odds ratio
PALS	Pediatric Advanced Life Support
PCA	patient-controlled analgesia
PD ADR	possible or definite ADR
PI	Product Information
PICU	paediatric intensive care unit
PIP	paediatric investigation plan
PKPD	pharmacokinetic and pharmacodynamic
POD	post-operative day
PONV	post-operative nausea and vomiting
POV	post-operative vomiting
POVOC	POst-operative VOmiting in Children
PUMA	Paediatric Use Marketing Authorisation
q-RCT	quasi-randomised controlled trial
RCT	randomised controlled trial
RMP	risk management plan
ROC	receiver operating characteristic
RR	relative risk
SD	standard deviation
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics
TEDDY	Task-force in Europe for Drug Development for the Young
WHO	World Health Organisation

Publications and presentations arising from work in this thesis

Some of the work contained in Chapter 1 had been published in the European Journal of Clinical Pharmacology (Mason, Pirmohamed and Nunn, 2012).

The work contained in Chapter 2 has been published in the British Journal of Clinical Pharmacology (Bellis et al., 2013). It was presented at the British Pharmacological Society Winter Meeting (London 2012).

The work contained in Chapter 3 has been published in BMC-Medicine (Bellis et al., 2013a) and was presented at the British Pharmacological Society Winter Meeting (London 2012) and the Neonatal and Paediatric Pharmacists Group Annual Conference (Liverpool 2012).

The work contained in Chapter 5 has been accepted for publication in the British Journal of Anaesthesia (Bellis et al., 2014).

1 Introduction

1.1 Background

When making decisions about prescribing medicines, clinicians are required to consider both the potential benefits and the potential risks of the treatments available. Potential risks relate to the likelihood of the patient developing an adverse drug reaction (ADR). The risk of an ADR may be intrinsic to the medicine or it may be related to the susceptibility of the patient to the adverse effects of the medicine (Aronson and Ferner, 2003).

Clinicians are guided by the available evidence. Information about medicine use in children and its potential risks is of varying quality; this may be particularly true for off-label and unlicensed medicines. Where there is a lack of good quality information, this is a result of how the development of medicines has traditionally focussed on the adult population with few clinical trial data being generated in children (Choonara and Dunne, 1998). When prescribing for children, evidence about ADR risk may be derived from various sources: extrapolation of adult data, consideration of any clinical trial data which does exist, other studies of the medicine in use, or the experience of clinicians. Epidemiological studies which present data on ADR risk factors in children also provide insight. In practice, this information is collated into an accessible format such as, in the UK, the British National Formulary for Children. This reference is evidence-based and is regularly updated as new evidence emerges. Updates are the responsibility of a team of writers who assess that the new data are relevant and reliable. Draft amendments are made and then reviewed by expert advisers. Subsequently, the amendments are discussed and ratified by the Paediatric Formulary Committee (PFC). The PFC includes a neonatologist, paediatricians, paediatric pharmacists, doctors appointed by the BMJ Group, a GP and representatives from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Department of Health for England (Paediatric Formulary Committee, 2009/2010).

In 2007, The National Institute of Health Research (NIHR) awarded a grant to the University of Liverpool and Alder Hey Children's Hospital in Liverpool to fund a series of studies into ADRs in children – the Adverse Drug Reactions in Children (ADRIC) programme. The work included two large observational studies; the first investigated the prevalence of ADRs detected at the point of admission and the second investigated the prevalence of ADRs in inpatients. A series of qualitative studies described the experiences of children who had experienced an ADR and their families.

Both observational studies of ADR prevalence were undertaken by a multidisciplinary study team made up of a paediatrician, a paediatric nurse and at least one clinical pharmacist. Having joined the ADRIC programme in March 2008, the author of this thesis (JRB) was a full time member of the study team for the duration of both observational studies and contributed to design, planning and data collection. Subsequently JRB contributed to the clinical evaluation of suspected ADRs, inclusive of the development of a novel causality assessment tool (Gallagher et al., 2011). Finally, in co-operation with experts in statistical analysis, JRB assisted in the analysis and interpretation of the study findings. The aims of these studies were to quantify the burden of ADRs in a paediatric population and to characterise those ADRs. The author's unique contribution to this work was to describe, in detail, the medicines involved inclusive of whether they were off-label or unlicensed. Having done this, JRB undertook and investigation ofthe relationship between the use of such medicines and ADR risk.

This chapter will discuss how ADRs are defined and detected, their prevalence in children, risk factors, mechanisms and characterisation. It will go on to define off-label and unlicensed medicine use, explain why it is necessary in paediatric practice and describe its prevalence. Finally, it will review previous studies which have examined off-label and unlicensed medicines use as an ADR risk factor.

1.2 Adverse drug reactions in children

1.2.1 Definition of adverse drug reaction

A clear definition of adverse drug reaction is needed so that data on ADRs can be consistently reported and reliably interpreted. A definition commonly used in the existing pharmacovigilance literature is the World Health Organisation (WHO) definition (1972):

'*A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function*'.

Edwards and Aronson (2000) proposed a definition which has also been widely used:

'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.'

Although both of these commonly used definitions do not include responses or reactions which result from drug errors or deliberate or accidental poisoning, some studies have included ADRs alongside drug errors under the term 'adverse drug events' (Bates et al., 1999). The definition utilised in European Parliament Directive on the Community code relating to medicinal products for human use corresponds to the WHO definition (World Health Organisation, 1972) but also includes noxious and unintended effects resulting from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product (The European Parliament and the Council of the European Union, 2010).

1.2.2 Detection of adverse drug reactions

Although the adverse reaction profile of a medicine may be predictable from its known pharmacology, much of the information about ADRs is derived from ADR reports for medicines in use. ADRs may be detected during the development of the medicine when its effects, both beneficial and adverse are intensively monitored. Any ADRs detected during the development process will, in the UK, appear in the summary of product characteristics (SmPC) when the medicine is granted a marketing authorisation (MA). Once a medicine is in use in clinical practice, the detection of ADRs is undertaken by clinicians and patients in co-operation with the MA holder and their regulator. ADRs detected may be those which appear in the SmPC or may be previously unrecognised reactions. The reason why additional ADRs are likely to be detected once the medicine is in clinical use is that a greater number of patients, including those originally excluded from the drug development process, will be exposed to the medicine; these include patients with multiple co-morbidities and those who are taking other medicines (including non-prescription and alternative therapies) which have the potential to interact with the new medicine, previously unrecognised food-drug interactions may also emerge. Children are one patient group which, until recently, has frequently been excluded from the drug development process. Clinicians may observe previously unrecognised ADRs or patterns of ADR occurrence and disseminate their observations by publishing a case report or case series. Clinicians, patients and carers may also report ADRs using a voluntary, spontaneous reporting system which in the UK is known as the Yellow Card Scheme and is administered by the Medicines and Healthcare products Regulatory Agency (MHRA, 2012). An advantage of this system is that it has the potential to pick up ADR signals from across the UK; submitted reports are monitored and previously unrecognised reactions have been highlighted in this way. When an important new ADR is identified, the regulator will issue

advice which may include amendments to, or the withdrawal of the medicine's MA. However, the spontaneous reporting system is hindered by under-reporting. A systematic review of 37 studies of under-reporting estimated its incidence to be between 6 and 100% (Figure 1.1) (Hazell and Shakir, 2006).

Figure 1.1 Distribution of under-reporting rates across 37 studies (taken from Hazell, Shakir 2006)

Another method for the detection of ADRs is intensive surveillance which can be undertaken by manufacturers, clinicians and/or researchers. Examples include post-marketing studies and epidemiological work such as cohort and case-control studies.

There is considerable interest in linking existing prescription data to patient medical records in order to conduct large pharmacovigilance studies. The benefit of this approach is that it links together large amounts routinely collected data making it far more cost-effective than, for example, a prospective cohort study. This approach assumes the suitability of routinely collected data for research, however it must be remembered that this is not the primary purpose for which they are collected. There are concerns about sharing confidential patient information for research and undoubtedly it needs to be done with attention to the security of the data. Therefore, work is underway in the UK to explore this strategy, inclusive of whether such an approach to pharmacovigilance in children is acceptable to stakeholders, inclusive of patients, their families and healthcare professionals (Hopf et al., 2012).

Since July 2012, MA holders in the European Union have been required to have a risk management plan (RMP) for new medicinal products (European Medicines Agency, 2012). This document details important identified risks, important potential risks, important missing information (patients or conditions where a product has not been used and where there is no clinical experience), efficacy, how safety is being monitored and measures being taken to minimise risk. This requirement for new medicinal products to have a RMP is an attempt to address the deficit of safety information that is available at the time that a medicine is authorised.

Systematic reviews, which may include a meta-analysis of the adverse effects of medicines, can be used to synthesise data from a number of small clinical studies in order to increase the precision of the results (Loke et al., 2007).

The trade-off between the benefits and harms of a drug intervention is of utmost importance in clinical decision making.

1.2.3 Incidence of adverse drug reactions in children

A meta-analysis published in 2001 included 17 studies and described the incidence of ADRs in children as follows: 4.37% to 16.78% in hospitalised children, 0.59% to 4.1% in children being admitted to hospital and 0.7% to 2.7% in outpatients (Impicciatore et al., 2001). A more recent meta-analysis included fewer studies (eight) and found the incidence to be 1.5% to 19.9% in hospitalised children, 0.6% to 6% in children being admitted to hospital and 0.7 to 11% in outpatients (Clavenna and Bonati, 2009). Finally, a systematic review published in 2012 included 102 studies but not all had reported ADR incidence (Smyth et al., 2012). There were 31 studies of hospital admissions and for those which reported results for single admissions (n=11), the ADR incidence ranged from 0.4% to 10.3% (Figure 1.2). Of the inpatient studies included, 32 provided an estimate of ADR incidence. Amongst the studies which reported it for single admissions (n=11), the incidence ranged from 0.6% to 16.8% (Figure 1.3). 16 outpatient studies reported an ADR incidence which ranged from 0.3% to 11.0%. These reviews established that ADRs in children are a significant problem but their aim was to estimate incidence rather than to explore in any detail the factors which contribute to ADR risk in children.

Figure 1.2 Adverse drug reaction incidence in admissions studies (taken from Smyth et al. 2012)

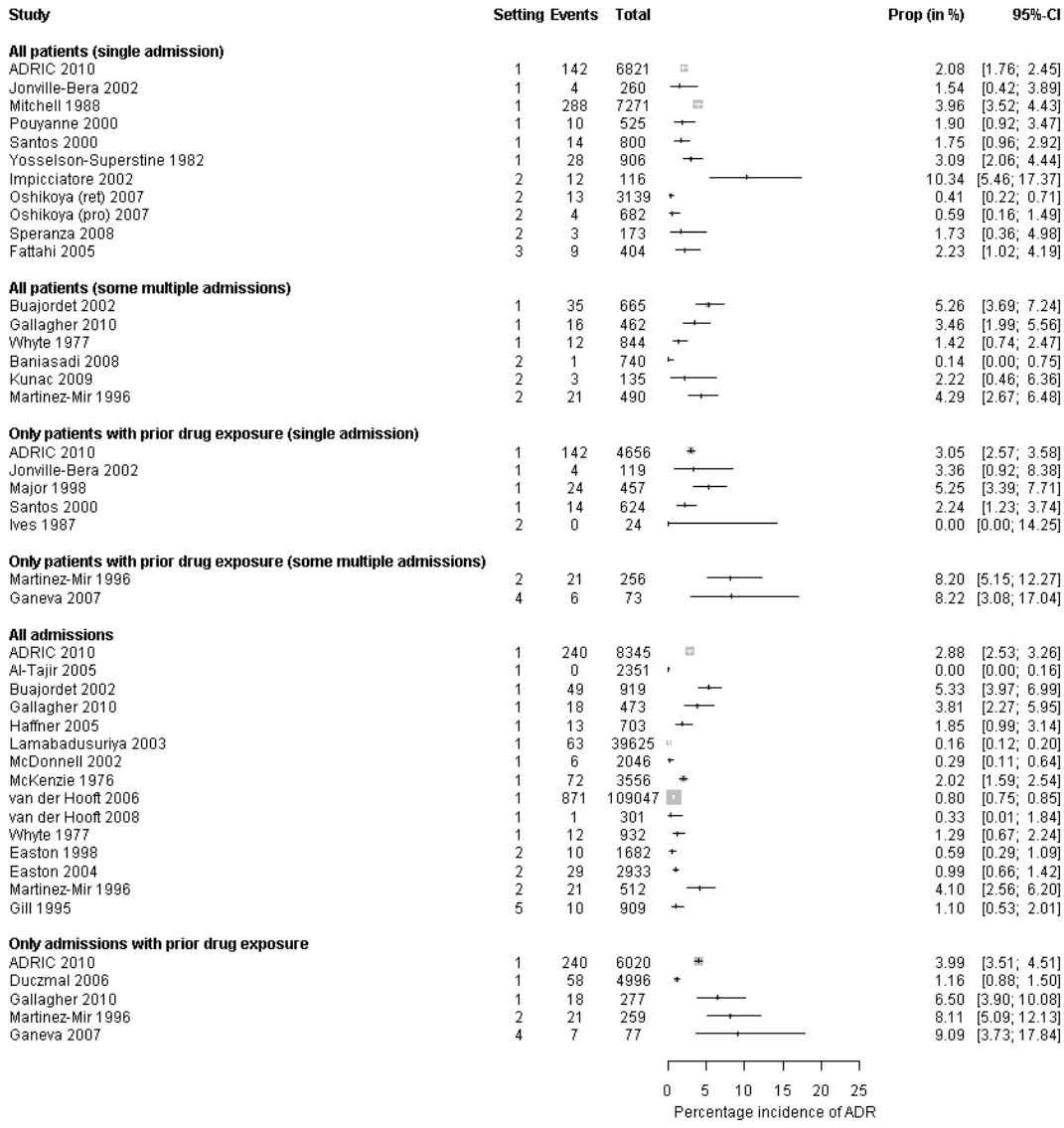
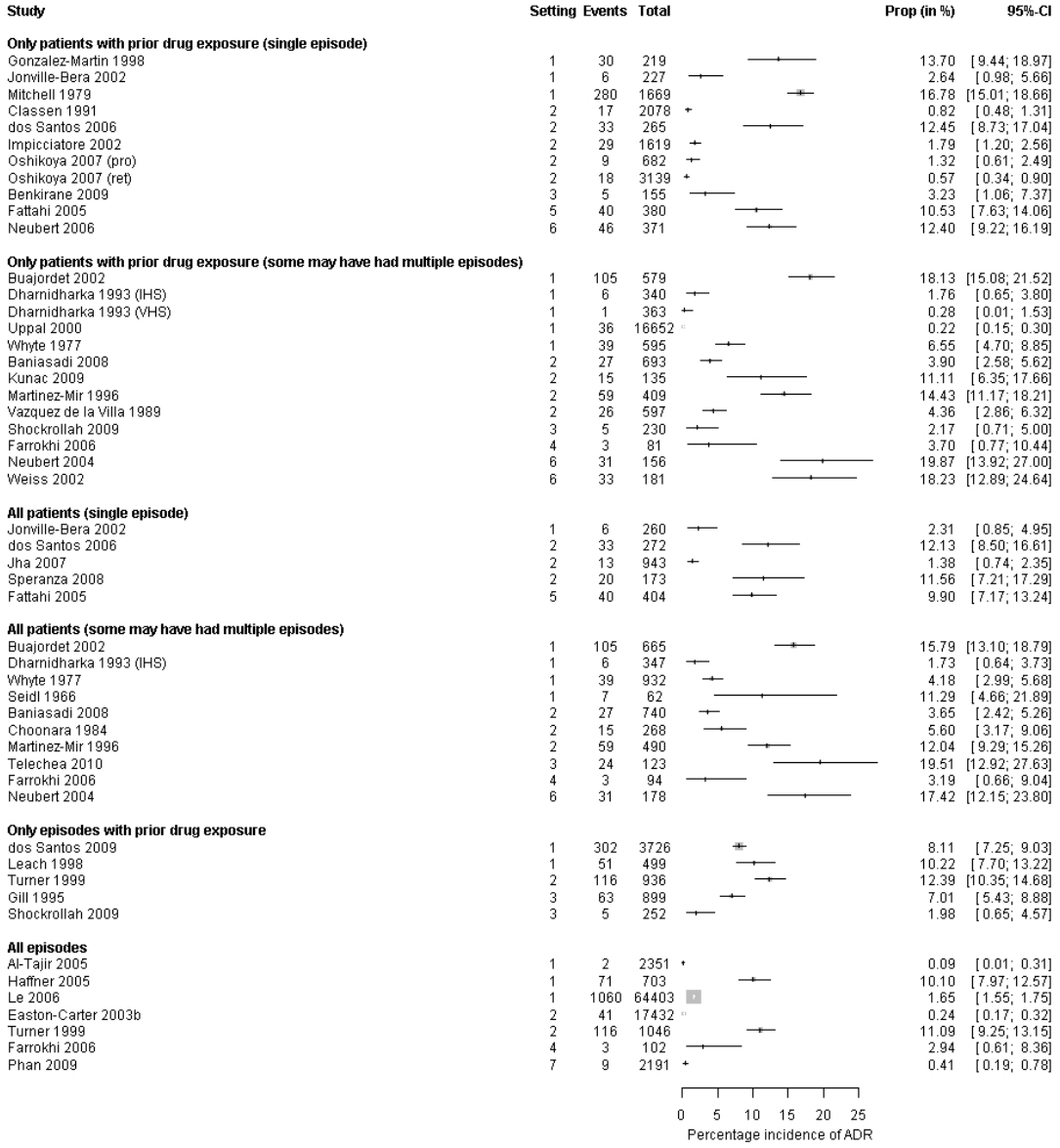


Figure 1.3 Adverse drug reaction incidence in inpatient studies (taken from Smyth et al. 2012)



1.2.4 Risk factors for adverse drug reactions in children

Several ADR risk factors in children have been identified in previous studies. These have also described the types of drug or drug classes most frequently implicated in ADRs.

In a study of paediatric inpatients in the UK (Whyte and Greenan, 1977), an ADR was defined as any undesired or unintended response to the patients' own current medication (excluding accidental poisoning). Of 595 patients who received at least one medicine in hospital, 39 (6.6%) experienced at least one ADR. An evaluation of ADR risk factors determined that ADRs were more common in serious disease, 64.7% of ADRs occurred in children being treated for malignant disease. The number of medicines administered was a predictor of ADR risk, with patients who received more than four medicines at greater risk than those who received fewer than four. The types of medicine which most frequently caused ADRs were anti-neoplastic agents and antimicrobials. No association of ADR risk with either age or gender was demonstrated.

A study of drug-related admissions undertaken on a paediatric ward in Israel reported an ADR incidence of 3.2% amongst 906 admissions (Yosselson-Superstine and Weiss, 1982). ADRs were more common amongst females and children aged between 6 and 10 years old and the most frequently implicated drugs were anti-neoplastic agents, corticosteroids, anticonvulsants and antimicrobials.

A large US study prospectively monitored 3026 neonatal intensive care unit (NICU) admissions, 725 oncology admissions and 6546 general and specialty paediatric admissions (Mitchell et al., 1988). A small proportion of NICU admissions were ADR related (0.2%) and the ADRs recorded were not consistently associated with a particular drug or drug class. In contrast, 22% of oncology ward admissions were due to an ADR with the most common cause being anti-neoplastic drugs. Finally, 2.0% of general and specialty paediatric admissions were due to an ADR and the likelihood increased from birth until 5 years after which it did not increase significantly. In the latter group, anticonvulsants, antimicrobials and aspirin were the most frequently implicated drugs.

A study of 219 paediatric inpatients in Chile reported an ADR incidence of 13.7% (Gonzalez-Martin, Caroca and Paris, 1998). The most commonly implicated medicines were antineoplastic agents, anticonvulsants, antimicrobials and salbutamol. ADR risk factors were length of stay and number of medicines.

A UK study of 1046 inpatients reported that the number of medicines was a predictor of ADR risk and the drugs commonly implicated in ADRs were antimicrobials, opioids and diuretics (Turner et al., 1999). This study aimed to determine the impact of off-label and unlicensed medicine use and it, along with other studies of this particular risk factor, is described in more detail in section 1.4.1 below.

The ADR incidence in a Brazilian study of 265 paediatric inpatients was 12.5% (dos Santos and Coelho, 2006). The most frequently implicated drug classes were antimicrobials, systemic hormones and central nervous system drugs including analgesics. ADR risk factors were decreasing age, increased length of stay and number of drugs.

In a study of 1253 paediatric inpatients across five countries (Rashed et al., 2012), the WHO (1979) definition of ADR was adopted and ADR incidence of 16.7% was reported (The ADVISE Study). Five categories of high risk drugs were defined: analgesics, antiepileptics, antibacterials and antimycotics for systemic use, corticosteroids for systemic use and immunosuppressant agents. The administration of three of more high risk drugs was a predictor of ADR risk. All other drugs were defined as low risk and the administration of five or more of these predicted ADR risk, increasing age was also a risk factor.

A large prospective study of 8345 paediatric admissions was undertaken as part of the ADRIC programme. It reported an ADR incidence of 2.9% and the most frequently implicated medicine types were antineoplastic agents, corticosteroids, non-steroidal anti-inflammatory drugs, vaccines and immunosuppressants (Gallagher R.M. et al., 2012). Risk factors identified in this study were increasing age, number of medicines and being an oncology patient. A prospective study of 6,601 paediatric inpatients was also undertaken within the ADRIC programme and the ADR incidence was 17.7% (Thiesen et al., 2013). The most frequently implicated medicine types were opioid analgesics and anaesthetic agents. The ADR predictors were increasing age, number of medicines, receipt of a general anaesthetic and being an oncology patient.

1.2.5 Adverse drug reaction mechanisms

1.2.5.1 Classification of adverse drug reactions

The definition of ADR may be supplemented by a description of ADR type. A simple categorisation is type A or type B, the former being dose-related and predictable from the known pharmacology of the medicine and the latter being non-dose-related and unpredictable. This categorisation has been extended further to include type C (dose and time related) and type D (delayed reactions) (Edwards and Aronson, 2000).

A 'three dimensional' classification has also been proposed which takes into account not only the properties of the medicine implicated in the ADR but also the characteristics of the reaction and of the individual who experienced the reaction i.e. Dose relatedness, Timing and Susceptibility (DoTS classification). The proposers of this classification describe how, although dose-relatedness is traditionally thought of in the context of non-immunological reactions, it is actually relevant to all reactions inclusive of immunological reactions. ADRs can be classified as either those that occur at supratherapeutic doses (toxic effects), at standard therapeutic doses (collateral effects) or at subtherapeutic doses in susceptible patients (hypersusceptibility reactions). The concept of timing takes into consideration when the reaction becomes apparent in relation to when the dose was given and a reaction can be classified as either rapid, first dose, early, intermediate, late or delayed. Susceptibility specifically relates to the patient and is made up of the interactions between genetic variation, age, sex, physiological variation, exogenous factors, and disease (Aronson and Ferner, 2003).

1.2.5.2 Overview of adverse drug reaction mechanisms

As described by the simple Type A/Type B classification, the mechanism of an ADR may be either related or unrelated to its known pharmacology.

Examples of ADRs which result from an extension of the intended therapeutic effect of a drug are hypoglycaemia secondary to insulin and haemorrhage secondary to anticoagulant. Both of these reactions have potentially serious consequences but both would be expected to respond to dose reduction.

Acute renal insufficiency secondary to non-steroidal anti-inflammatory drug (NSAID) use in patients with cardiac or hepatic disease is an example of an ADR which results from the known pharmacology of the drug but is distinct from its intended therapeutic effect. The

therapeutic uses of NSAIDs are in the management of fever, pain and inflammation. These effects are achieved via the inhibition of the cyclo-oxygenase enzyme and consequently the synthesis of prostaglandins. Within the renal vasculature, prostaglandins act to maintain adequate perfusion. An inhibition of prostaglandin synthesis results in decreased renal blood flow and a consequent reduction in the glomerular filtration rate. Patients with pre-existing compromised renal function are more susceptible to this ADR (Murray and Brater, 1993).

Paracetamol-associated hepatotoxicity usually results from the administration of a dose above the therapeutic range for example in accidental or deliberate overdose, the mechanism by which it occurs illustrates some of the covalent and non-covalent interactions which facilitate drug toxicity. Paracetamol undergoes hepatic metabolism; at normal therapeutic doses it is deactivated via glucuronidation and sulphation and the resultant metabolites are excreted in the urine. At toxic doses, these metabolic routes become saturated and paracetamol undergoes bioactivation catalysed by cytochrome P450 isoforms CYP2E1 and CYP3A4. It is converted to the reactive metabolite (n-acetyl-p-benzoquinone imine - NAPQI). NAPQI is ordinarily inactivated by hepatic glutathione but in the case of paracetamol overdose, this becomes rapidly depleted. Glutathione plays a role in protecting cells from oxidative stress and so its depletion contributes to hepatotoxicity. The reactive metabolite NAPQI contributes to oxidative reactions and the covalent modification of proteins (inclusive of glutathione) within the hepatocytes (Rang and Dale, 2012, Park et al., 2005).

Hypersensitivity reactions are not related to the principle pharmacology of the drug. These types of reaction are often caused by a chemically reactive metabolite rather than the drug molecule itself and are thought to have an immunological mechanism, mediated either by B- or T-cell activation (although there are interactions between these pathways). An example of B-cell mediated hypersensitivity reaction is anaphylaxis secondary to beta-lactam antibiotics. The drug or its active metabolite acts as antigen leading to the formation of specific IgE antibodies. When bound to the surface of mast cells and basophils, these antibodies cause the release of vasoactive mediators (e.g. histamine, bradykinin and platelet-activating factor) and these produce the clinical manifestations of facial and tongue oedema together with vascular collapse (Rieder, 2009). Other immune-mediated reactions include hepatotoxicity, toxic epidermal necrolysis and nephritis. These are mediated by T cells rather than immunoglobulins. There is evidence that an individual's propensity to

developing a drug hypersensitivity reaction is genetically determined although there may also be other important contributors (environmental factors) which interact with the genome to increase susceptibility (Pirmohamed, 2006).

To complement the DoTS classification, Ferner and Aronson (2010a) proposed a mechanistic adverse drug effect classification system (EIDOS) which takes into account various factors. These can be illustrated using non-steroidal anti-inflammatory drug (NSAID) induced renal impairment as an exemplar:

- the extrinsic chemical species (E) that initiates the effect, e.g. the non-steroidal anti-inflammatory drug (NSAID)
- the intrinsic chemical species (I) that it affects, e.g. the inhibition of cyclo-oxygenase and a reduction in prostaglandin synthesis
- the distribution (D) of these species in the body, e.g. renal prostaglandins
- the (physiological or pathological) outcome (O), e.g. reduced renal blood flow
- and the sequela (S), which is the adverse effect e.g. renal impairment

1.2.5.3 Developmental pharmacology and adverse drug reactions in children

The paediatric population is diverse, ranging from pre-term neonates through to adolescents; this diversity brings with it challenges for those who develop and use medicines in children. These challenges include the production of appropriate formulations and the determination of appropriate dosing regimens. It is not always possible to translate what is known about medicine use in adults into recommendations for medicine use in children. As a child grows and develops, changes affecting drug pharmacokinetics (PK) and pharmacodynamics (PD) determine not only the likelihood of drug efficacy but also the likelihood of toxicity. Both the direction and the magnitude of these changes will differ depending on the drug involved as exemplified for the dose-response relationship in Figure 1.4.

Figure 1.4 The sigmoid Emax model of exposure-response and hypothetical examples of developmental changes in this relationship (taken from Mulla 2010)

Developmental changes in children affect drug disposition; examples of this include differences in gastric pH and gastric emptying, differences in body composition, increased or decreased expression of circulating plasma proteins and drug targets, increased or decreased expression of the enzymes involved in drug metabolism and differences in glomerular filtration rate (GFR). These differences are governed by developmental variations in gene expression (Kearns et al., 2003, Hines, 2008, Becker and Leeder, 2010, Mulla, 2010). The potential toxicity of excipients used to formulate drugs is also significant in children (Choonara and Rieder, 2002).

The effect of changes in gastric pH on drug absorption are illustrated by a study of serum penicillin levels in premature and term neonates, older infants and children (Huang and High, 1953). At 30 minutes, 2, 4 and 6 hours after the oral administration of penicillin, premature and term neonates had significantly higher serum levels of the drug than older

infants and children. The gastric pH gradually declines after birth and hence the rate of penicillin degradation in the stomach increases, leading to a reduction in drug absorption.

The higher body water to fat ratio in infants may affect the apparent volume of distribution and hence the serum concentration of some drugs. For example, the apparent volume of distribution of the hydrophilic drug linezolid is higher in young infants and this must be taken into account in the extrapolation of adult linezolid doses and dose intervals to children in this age group (Kearns et al., 2000).

Developmental changes in the expression and activity of enzymes responsible for drug metabolism influence the rate of drug clearance. For example, metabolism of the phospodiesterase-5 inhibitor sildenafil is catalysed by the cytochrome P450 enzymes CYP3A4 and CYP2C9 and potentially by the foetal isoform of CYP3A, CYP3A7. In vitro data demonstrated that CYP3A4 and CYP2C9 activity levels are low at birth but increase rapidly to adult levels by one month of age whereas CYP3A7 activity is greatest in the first week of life but subsequently declines. These developmental changes in enzyme expression and activity are the proposed mechanism by which sildenafil clearance is significantly correlated with postnatal age, observed in term neonates in the first 1-2 weeks of life (Mukherjee et al., 2009).

The GFR in a term neonate increases rapidly in the first week of life and reaches that of a healthy adult by the age of one year. After the first year of life, GFR continues to rise reaching a peak at around three years old and gradually declining towards adulthood. These changes have implications for the clearance of drugs excreted by the kidneys. The milligram per kilogram dose of digoxin in young children is three times that required in adults. This can be partly explained by an increased rate of renal clearance but it is also thought that age-related changes in the secretory function of P-glycoprotein in the renal tubules may contribute (Chen et al., 2006).

In children, an understanding of developmental changes in drug disposition informs appropriate dosing to avoid toxicity but also contributes to an appreciation of why their susceptibility to ADRs might vary. Sodium valproate-associated hepatotoxicity, inclusive of fatal cases, is more common in children. In young children, the hepatic clearance of valproic acid is increased. It is hypothesised that alongside this there is increased production of a hepatotoxic metabolite catalysed by CYP2C9 and CYP2A6. Conversely, children have a

decreased susceptibility to paracetamol overdose-induced hepatotoxicity which is thought to reflect differences in hepatic metabolism, for example an increased rate of sulphation and/or an increased rate of glutathione synthesis (Johnson, 2003).

1.2.6 Evaluation of adverse drug reactions

In the same way that the definition of ADR varies between authors, disparities exist in the way ADRs, once defined and detected, are evaluated. Three key aspects which are commonly considered are causality, severity and preventability (also called avoidability).

1.2.6.1 Causality assessment methods

The assessment of ADR causality is a process which aims to determine the likelihood that an ADR has occurred. To evaluate causality, there are six key questions about a suspected ADR which need to be considered:

1. Does it have a temporal relationship with the administration of the medicine?
2. Could there be another explanation for it? (e.g. underlying disease)
3. Did it resolve when the medicine was withdrawn? (dechallenge)
4. Has it happened before in the same patient when they received the same medicine?
5. If the medicine was administered again, did it recur? (rechallenge)
6. Is there any objective evidence for its occurrence?

The causality assessment should also take into account whether the suspected reaction has previously been recognised.

A recent systematic review of the available methods for causality assessment acknowledged that there is currently no 'gold standard' method; all the algorithms available have shortcomings and these relate in particular to the knowledge and experience of the person using the algorithm and the type of ADR being evaluated (Agbabiaka, Savović and Ernst, 2008). The review identified three types of method:

1. Global introspection
2. Probabilistic or Bayesian techniques
3. Algorithms or standardised assessments

The third of these was the most commonly used method. The authors of the review commented that those methods which relied on expert judgement did not guarantee a

consistent approach and better inter-rater reliability was found in studies which used algorithms composed of questions of a factual nature.

Karch & Lasagna (1977) developed a methodology for assessing the causality of ADRs which comprises a series of three decision tables. The first table facilitates the identification of potential drug-related events – the investigator must consider the temporal relationship between drug administration and the event, and whether the event was secondary to one of the following circumstances: accidental poisoning, a suicide attempt or non-compliance. Only when the investigator has established a temporal relationship and determined that the event was not secondary to any of the circumstances listed, can they move on to the second decision table which assesses the link between the agent and the event by asking questions about concurrent disease, dechallenge and rechallenge. Having completed this assessment, a causality outcome can be assigned: definite, probable, possible, conditional or unrelated. Finally, if a drug-related event is classified as definite, probable, possible or conditional, the case is examined using the criteria in a third table which considers its cause, for example due to recreational drug use, poor prescribing or prescribing error.

Kramer et al. (1979) developed an algorithm for the assessment of ADRs which consists of what they term 'six axes of decision strategy'. These axes are used to assess the suspected ADR and are as follows:

1. Previous general experience of the drug
2. Alternative etiologic candidates
3. Timing of events
4. Drug levels and evidence of overdose
5. Dechallenge
6. Rechallenge

As the assessor moves through these axes, they accumulate points depending on which path is taken and they are also directed to a subsequent axis to examine the case further. At the end of the process the score accumulated can be used to describe the probability, based on the weight of evidence, that the event represents an ADR.

A widely used algorithm for the assessment of ADR causality is the Naranjo tool (Naranjo et al., 1981) which uses a scoring system to categorise ADRs as definite, probable, possible or doubtful. ADR cases are scored according to a series of questions (Table 1.1) which can be

answered yes, no or don't know; each answer carries a score and the total of these scores determines which category the ADR will fall into:

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

Table 1.1 The Naranjo tool for the assessment of ADR causality (Naranjo et al. 1981)

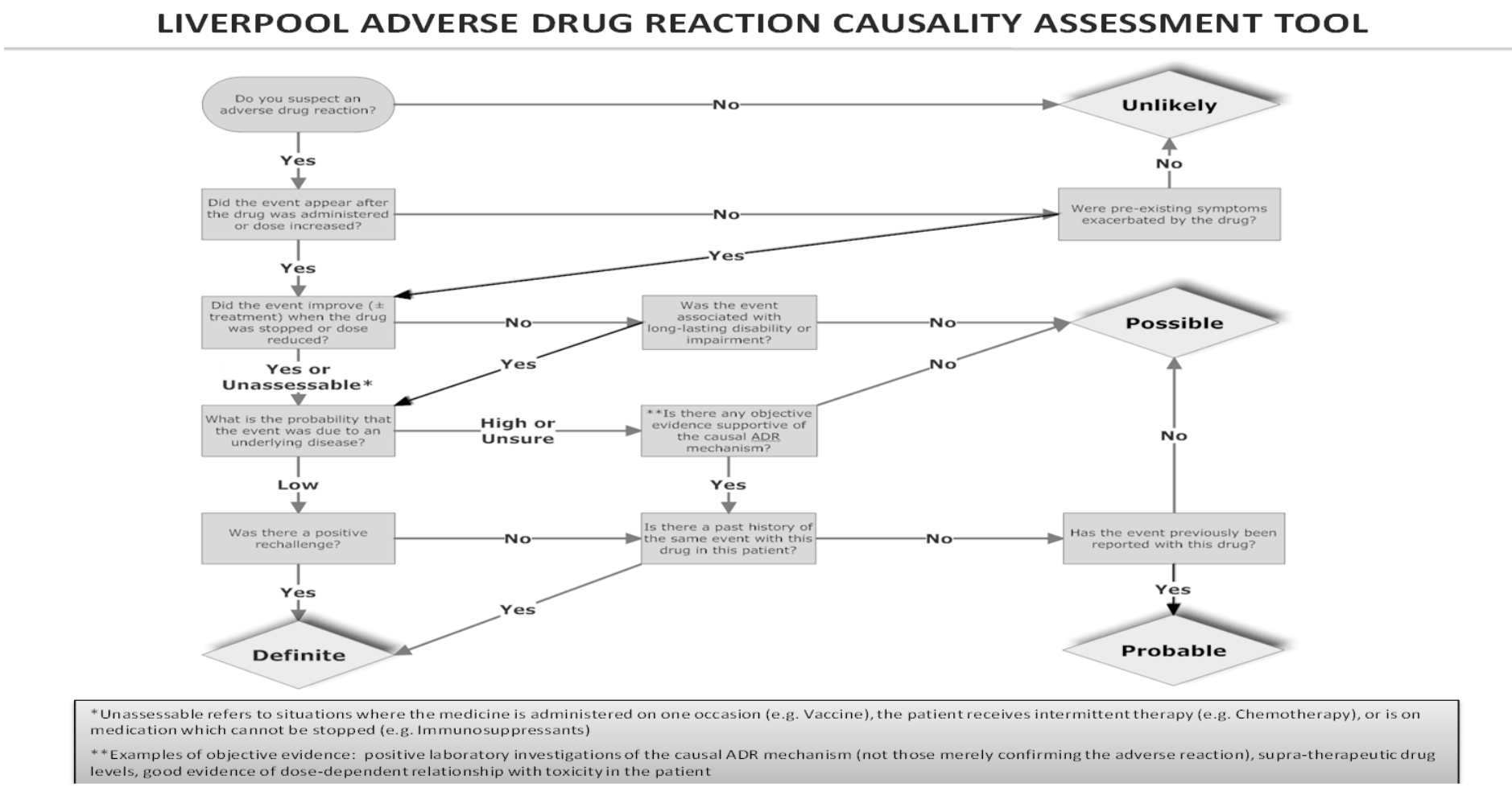
Question No.	Question	Yes	No	Don't know
1	Are there previous conclusive reports of this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3	Did the ADR improve when the drug was discontinued or after a specific antagonist?	+1	0	0
4	Did the ADR reappear after the drug was restarted?	+2	-1	0
5	Are there alternative causes that could have caused the reaction on their own?	-1	+2	0
6	Did the reaction reappear after placebo was administered?	-1	+1	0
7	Were blood levels of the drug in a range known to be toxic?	+1	0	0
8	Was reaction more severe when dose was increased or less severe when dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in a previous exposure?	+1	0	0
10	Was the ADR confirmed by objective evidence?	+1	0	0

Using the concepts of temporal relationship, dechallenge, rechallenge and relationship to disease, Jones (1982) formulated a causality algorithm, which is in the form of a flow diagram – the causal relationship between the drug administered and the event under investigation can be assigned a category of remote, possible or probable.

One group (Koh and Shu, 2005) developed an algorithm on the basis of the information contained in routine ADR reports and combined and modified their questions using Kramer's work as a 'gold standard' (Kramer et al., 1979). Their algorithm takes the form of a list of nine weighted questions to which the user can answer yes, no or don't know to produce a score which allows the reaction to be categorised as definite, probable, possible or unlikely – they conducted a comparative study of various algorithms, including their own, with Kramer's algorithm and found that theirs had the highest congruency with Kramer in terms of the causality outcome for each of 450 cases, 98.44% (95% CI 96.82, 99.37) compared with Naranjo which was the next best with 94.67% (95% CI 92.17, 96.55) congruency.

In the process of assessing causality using the Naranjo tool for the ADRs identified in the ADRIC admissions study, Gallagher et al. (2011) identified several weaknesses in the tool which they felt could be improved upon. The team developed and validated the Liverpool Causality Assessment Tool (LCAT) using the Naranjo score as their comparator (Gallagher et al., 2011). This tool takes the form of a flow diagram (Figure 1.5); the user is able to categorise ADRs as unlikely, possible, probable or definite depending on how they answer the questions in the flow diagram. This tool was subsequently used to assess the causality of all the ADRs identified in both of the ADRIC observational studies of ADR incidence and characteristics.

Figure 1.5 The Liverpool ADR causality assessment tool (taken from Gallagher et al. 2011)



1.2.6.2 Severity assessment methods

The severity of an ADR relates to the effect it has on an individual. This is distinct from the seriousness of an ADR which is a measure of the extent to which it causes harm. The relevance of severity assessment is that it describes the clinical impact of ADRs and enables researchers and clinicians to identify priorities for study and intervention. Severity classification systems have tended to employ terminology such as mild, moderate or severe but this makes the process of severity assessment subjective.

In the context of an existing hospital based ADR reporting system, Hartwig, Siegel & Schneider (1992) used a scale which comprised seven levels to assess the severity of reported ADRs. The focus of the scale was the impact of the ADR on the patient in terms of additional treatment, permanent harm, and admission to hospital or prolonged stay. The severity levels range from level 1: an ADR occurred but required no change in treatment with the suspected drug, to level 7: the adverse reaction either directly or indirectly led to the death of the patient (Table 1.2).

Table 1.2 ADR Severity Assessment (Hartwig, Siegel and Schneider, 1992)

Level	Description
1	ADR occurred but required no change in treatment with the suspected drug
2	ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required, No increase in length of stay
3	ADR required that treatment with suspected drug be held, discontinued, or otherwise changed AND/OR an antidote or other treatment was required. No increase in length of stay
4	Any level 3 ADR which increases length of stay by at least 1 day OR the ADR was the reason for admission
5	Any level 4 ADR which requires intensive medical care
6	The adverse reaction caused permanent harm to the patient
7	The adverse reaction either directly or indirectly led to the death of the patient

Aronson and Ferner (2005) proposed a classification which minimises subjectivity because it asks specific questions about the ADR; it focuses on what needs to be done to manage the ADR. Firstly it asks whether any change in the patient's treatment was required as a result of the ADR and secondly it asks whether the treatment was effective; they term this the 'treatability' of the reaction (Table 1.3).

Table 1.3 Proposed classification of ADR severity (Aronson and Ferner, 2005)

Grade	Change in dosage regimen of the offending drug	Treatability of the reaction
1	No change in dosage regimen required	A. No treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment
2	Altered dosage regimen required or desirable	A. No other treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment
3	Withdrawal required or desirable	A. No other treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment

1.2.6.3 Preventability assessment methods

In order to be able to target interventions aimed at preventing ADRs, it is vital to identify which ADRs are preventable. There is currently no universally accepted standard for the assessment of ADR preventability. Ferner and Aronson (2010) conducted a systematic review of the preventability of drug related harms in which they examined methods proposed to determine the preventability of ADRs. They identified seven proposed methods:

1. analysis without explicit criteria
2. consensus
3. preventability linked to error
4. preventability linked to standards of care
5. preventability related to medication
6. preventability linked to information technology
7. the use of explicit lists

They acknowledged that some authors use a combination of these approaches. They described the limitations of each method. In terms of consensus, it is possible for experts to agree but still be wrong. When considering preventability related to standards of care, if those standards are poorly defined it is difficult to determine preventability. In the final method, the investigator compiles an explicit list of potentially inappropriate medicines and then determines whether they were implicated in any adverse events. This approach considers only the medicine rather than the circumstances and the patient themselves and may result in an underestimate of how many ADRs are preventable.

There are some methods described which appear to be suitable for preventability assessment but their remit could be interpreted as being inclusive of errors which are not consistently included in the definition of the ADR. One of these is the assessment of preventability linked to error; an example given is the widely used Hallas scale, which describes definitely avoidable ADRs as those in which '*the drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account*' (Hallas et al., 1990). This may in some circumstances be considered a prescribing error depending on the details of the case.

Another of these methods is preventability related to medication which is exemplified by two commonly used tools, the Hartwig scale (Hartwig, Siegel and Schneider, 1992) and a tool devised by Schumock and Thornton (1992)(1992). Both tools describe the development of a drug allergy in a patient with documented drug allergy as a preventable ADR whereas some may consider this to be a drug error.

The systematic review conducted by Ferner and Aronson (2010) was followed up with a proposed new method for the assessment of ADR preventability (Aronson and Ferner, 2010). The proposed method takes into consideration both the mechanism of the ADR and its clinical manifestation and draws on both the DoTS and EIDOS classifications. It emphasises that in order to determine ADR preventability, we need to use the knowledge we have about how the implicated medicine acts and interacts as well as any information we have about the susceptibility of individual patients or populations (Figure 1.6). For example, it is known that patients develop a tolerance to carbamazepine-induced dizziness; therefore dizziness associated with the introduction of carbamazepine may be prevented by commencing the patient on a low dose which can be slowly titrated upwards.

Figure 1.6 Flowchart: how preventive strategies can be determined by considering the PKPD mechanisms of the adverse effect and the susceptibility of the patient, the time-course and the dose-responsiveness of the reaction (Aronson and Ferner, 2010)

A recently published systematic review of ADRs in children highlighted that, amongst the 120 studies included, only 21 performed a preventability assessment on the ADRs they had identified and only 13 of these presented preventability data (Smyth et al., 2012). The reasons why preventability has not been widely reported in paediatric ADR studies may include perceived problems with applying the tool criteria in the context of paediatric practice; for example, in cases which involve the management of a rare disease for which there is unlikely to be a well-defined standard of care.

In cases where off-label or unlicensed medicines are implicated, questions about the appropriateness of dose, route and frequency may be difficult to answer. Indeed, although it did not focus on children, a study of the preventability of spontaneously reported ADRs focussed on the use of medicines outside the terms of the SmPC as a key factor in the process of preventability assessment. For any given ADR, if the suspected medicine was not prescribed in accordance with the SmPC and the non-conformity of the prescription to the SmPC was a known and validated ADR risk factor, the ADR was deemed to be either partly or entirely avoidable. The most frequently identified reasons for entirely avoidable ADRs were: not taking into account a history of allergy (could be considered an error), not taking into account altered renal function and not respecting the recommended dose (Jonville-Béra et al., 2009).

1.3 Off-label and unlicensed medicine use

1.3.1 The regulation of medicines

After a new medicine has been developed and before it can be marketed, it must receive approval from the regulatory authority of the country in which it is to be marketed. In the UK this regulatory body is the Medicines and Healthcare Devices Regulatory Authority (MHRA) and in the USA it is the Food and Drug Administration (FDA). Some medicine types in the UK are licensed by the European Medicines Agency (EMA) via the centralised procedure. This is a requirement for certain medicine types; high tech' biotechnology treatments such as gene therapies, medicines to treat HIV/AIDS, cancer, diabetes, and neurodegenerative diseases and orphan drugs (medicines developed for rare diseases, occurring in fewer than five in 10,000 people) (The European Parliament and the Council of the European Union, 2004).

Pharmaceutical manufacturers are required to submit specified information to the relevant regulatory body; this information is derived from data obtained during the development of

the medicine and/or in the post-marketing period. It includes the precise indication and dosage of the product, instructions for administration, contraindications, interactions and possible adverse effects. If, after rigorous evaluation of the data and information submitted, the medicine is authorised it will be issued, in the UK or Europe with a Marketing Authorisation (MA) or, in the USA with an FDA approval (known as the 'label'). One of the conditions of an approval is that the medicine is only marketed for use under the terms outlined in the MA; these terms reflect the content of the original information submitted by the manufacturer. This does not preclude the use of the medicine outside the terms of the MA by individual clinicians (Choonara and Dunne, 1998).

In both Europe and the USA there is additional legislation pertaining to the development and approval of medicines for children namely the Regulation on Medicines for Paediatric Use (The European Parliament and the Council of the European Union, 2006) and the Best Pharmaceuticals for Children Act (Anon, 2007a) and the Pediatric Research Equity Act (Anon, 2007b).

1.3.2 Definitions of off-label and unlicensed medicine use

Broadly, the term 'off-label medicine use' is used to describe the use of a medicine outside the terms of its MA. The term 'label' in the USA is synonymous with MA. Other terms for off-label medicine use are 'off-licence' (Michael Tettenborn, 2003), 'incorrect' (Jonville-Bera, Bera and Autret-Leca, 2005) and 'not appropriate' (Carvalho et al., 2003).

The detailed definitions of off-label use proposed by Turner and Choonara (1997) have been widely used in subsequent studies of off-label prescribing albeit not always in their entirety and sometimes with modifications (Table 1.4). The use of a medicine may be defined as off-label if it matches at least one of the definitions. The detail of the definition varies between authors and is influenced by personal opinion, what information is available to them about the use of the medicine and also the setting of their study.

In the case of surveys of prescription data, there is often no information recorded about indication so this aspect of off-label use cannot be examined (McIntyre et al., 2000, Bücheler et al., 2002, Schirm, Tobi and De Jong-van den Berg, 2002, Ekins-Daukes et al., 2004, Neubert et al., 2004). This means that the prevalence of off-label use may be underestimated. The use of linked datasets would provide an advantage in such studies by linking the prescription data to the medical record, through the indication for the prescription could be determined. Some authors add detail, for example by defining off-

label doses as only those 20% smaller or greater than that recommended (Chalumeau et al., 2000). This approach takes into account the rounding up or rounding down of doses which may occur in practice to permit ease of preparation and administration. Another example is the inclusion of drug-drug interactions as a type of off-label use; a criticism of this is that the prescription of two interacting medicines is not always absolutely contra-indicated and so such a prescription would not necessarily contravene the terms of the MA (Jonville-Bera, Bera and Autret-Leca, 2005).

Table 1.4 Definitions of off-label medicine use (Turner and Choonara, 1997)

1. Medicine administered at a greater dose than recommended in the MA.
2. Medicine administered for an indication not described in the MA.
3. Medicine administered at a greater frequency than recommended in the MA.
4. Medicine administered to children outside the age range specified in the MA.
5. Medicine administered via a route not described in the MA.
6. Medicine administered when a contra-indication is described in the MA.

An unlicensed medicine is one which does not have a MA in the country in which it is being used. The term was coined at a time when MAs were referred to as product licences and a medicine which had received approval was referred to as being 'licensed'.

The definitions of unlicensed medicine outlined by Turner and Choonara (1997) have been adopted by most subsequent studies (Table 1.5). A medicine may have a MA in one country but it is still an unlicensed medicine if used in other countries even when used within the terms of that MA. Some studies define unlicensed medicines as those which are a modification of medicines which hold a MA, for example, the crushing of tablets to make an extemporaneous suspension in a pharmacy (Gavrilov et al., 2000, Bajcetic et al., 2005). Modification of medicines in this way has also been defined by some as off-label (Pandolfini et al., 2002). Further discrepancies arise when authors include some of the uses commonly classified as off-label in their definition of unlicensed medicines, for example the use of a

contraindicated medicine or the use of a medicine with no dosing guidelines for children ('t Jong et al., 2002b).

Table 1.5 Definitions of unlicensed medicines (Turner and Choonara, 1997)

1. Modification to licensed medicines (e.g. extemporaneous pharmacy preparations)
2. Licensed medicines in a modified formulation manufactured under a specials manufacturing licence[i] (e.g. a liquid form for ease of administration)
3. New medicines available under a specials manufacturing licence (NB this assures the quality of the manufacturing process but not the safety or efficacy of the product)
4. Use of chemicals as medicines
5. Medicines used before a licence has been granted
6. Imported medicines (licensed in another country)

In view of these difficulties, the Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence conducted a Delphi round survey. Their intention was to reach a consensus on the definitions of both unlicensed and off-label medicine use in children (Neubert et al., 2008).

There was disagreement about some aspects of the definition amongst the 34 respondents in the first round of the survey which persisted amongst the 23 respondents in the second round. For example, the use of authorised drugs in an unapproved formulation prepared under good manufacturing practice (GMP) conditions e.g. by a pharmacist – was regarded as unlicensed by 42% of respondents while another 42% thought it was off-label. Similarly there was disagreement about use of authorised drugs in an unapproved formulation not prepared under GMP conditions e.g. by a parent – 50% thought it was unlicensed, 25% thought it was off-label and the remainder thought it was neither. The use of an authorised

[i] In the UK these are medicines made to satisfy an individual patient's needs by a commercial or hospital MHRA licensed manufacturing unit (MHRA, 2013)

drug in a condition labelled as 'contraindicated' was thought to be off-label by 21% of respondents, unlicensed by 33% and neither by 46%.

Definitions of off-label and unlicensed use were agreed in the third round of the survey (20 respondents). Off-label use was defined as:

'all uses of a marketed drug not detailed in the SPC including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration'

Unlicensed use was defined as:

'all uses of a drug which has never received a European Marketing Authorisation as medicinal for human use in either adults or children'

1.3.3 Reasons for, and prevalence of, off-label and unlicensed medicine use in children

Typically children have been excluded from the drug development process. There have been ethical concerns raised about testing new medicines on children. Investment in paediatric studies may also not give a good financial return because the number of patients for whom the product can be marketed is likely to be small. The result is that, although medicines which are authorised for use in children exist, there are many medicines which are not authorised for use in children and these have to be used off-label.

Medicines to treat rare conditions may not be available at all and may have to be imported or made to satisfy an individual patient's needs by a commercial or hospital MHRA licensed manufacturing unit or by a health care professional, for example a pharmacist. The available dosage forms of authorised medicines may not be appropriate for children to take so they may need to be altered before administration. This is done by pharmacists (extemporaneous preparation or compounding) and at the point of administration by a health-care professional, carer or patient (manipulation). These processes may or may not be supported by industry-generated data, pharmacopoeia information or peer-reviewed guidelines and some may also be outlined in the SmPC for the authorised medicine (Ernest et al., 2012).

Out of necessity, clinicians prescribing for children commonly prescribe off-label and unlicensed medicines which have not been rigorously tested in children. The proportion of paediatric prescriptions which are off-label or unlicensed in the community setting is 11-

40% and in hospital it is 22-87% (Kimland and Odlind, 2012). For many off-label and unlicensed medicines used routinely in paediatrics, there is good information available about how they should be used which is derived from clinical experience and clinical studies. However for others, information is sparse and the data have not been subjected to regulatory scrutiny. Where the latter is true, children are being exposed to medicines for which the prescriber cannot make a detailed benefit-risk evaluation. In an attempt to address this problem, all new medicines under development in Europe now must have a paediatric investigation plan (PIP) and all applications submitted for a MA must contain the results of any studies included in that plan. The pharmaceutical industry is now also offered incentives to develop medicines for use in children and to investigate and develop older off-patent medicines for paediatric use (The European Parliament and the Council of the European Union, 2006).

1.4 Off-label and unlicensed medicine use and adverse drug reactions in children – an overview of the existing literature

1.4.1 Search strategy and study selection

A Medline search of titles and abstracts from 1950 to December 2009 was performed using the search terms unlicensed/ off-label/ license/ licensed/ licensing/ label/ labelled/ labelling/ approved/ approval/ unapproved/ prescription/ prescribed/ prescribing/ prescribe/ prescriber(s)/ incorrect AND adverse effects/ adverse drug reaction reporting systems / drug therapy / pharmaceutical preparations AND child/ child, preschool. An EMBASE search of titles and abstracts from 1980 to December 2009 was also performed using the search terms unlicensed and off-label use AND child AND adverse drug reaction/ drug surveillance program. The limits Human and English Language were applied to both searches.

The method used to select papers for inclusion is summarised in Appendix 1. The titles were screened for reference to off-label and unlicensed medicine use or adverse drug reactions. Papers relating to specific treatments, conditions or reactions were excluded as well as those relating to prescribing and medication errors. Editorials, notes and letters were also excluded. The remaining abstracts (or papers when no abstract was available) were read and excluded if they made no reference to ADRs in the context of off-label or unlicensed medicine use.

The search was originally undertaken in December 2009 and 12 studies were identified. One additional study was identified by reviewing the reference lists of the original 12 and another was highlighted in a national update (Appendix 1). The search was updated in 2013 during the preparation of this thesis, three additional studies were idenitified (Posthummus et al., 2012, Bissuel et al., 2013, Ballard et al., 2013).

1.4.2 Prospective studies

A prospective study of 5 months duration employed active patient follow up to monitor for adverse drug reactions in a community setting (Kramer et al., 1985). No definition of ADR was provided. The percentage of patients who received off-label medicines was not recorded. The ADR incidence was 11.1% in the study population. This study considered only a single aspect of off-label medicine use: the receipt of a total daily dose above that recommended by the manufacturer. There was an increased relative risk of probable or definite ADRs in patients receiving medicines which were off-label for this reason (7% compared to 4.3%; relative risk 1.63; 95% CI 1.23, 2.16; $p<0.001$). The interpretation of these findings and their comparison with those of others is hindered by a lack of data on the prevalence of off-label medicine use and the inclusion of only one type of off-label use. Furthermore, since no definition of ADR was provided there is a possibility that reactions which were a result of medication errors were included.

A prospective study carried out in the UK over 28 months (Gill et al., 1995) included all patients on a regional paediatric intensive care unit (PICU). No definitions of ADR or unlicensed medicine were provided. A medicine was described as off-label if it was prescribed at a different dose, for a different indication or for a child outside the age range specified in the MA. ADRs were detected by means of spontaneous reports from health professionals and daily chart review by a research pharmacist. There were 909 patients admitted to the PICU during the study and ten of these were admitted because of an ADR. 76 ADRs were detected in 63 inpatients (7%), 25 (33%) of the medicines implicated in the 76 ADRs were off label and one was unlicensed. In a subsequent study on the same PICU over a four month period 136 of the 166 patients admitted (70%) received at least one off-label or unlicensed medicine during their stay (Turner et al., 1996). This demonstrates that although an association between ADR risk and off-label and unlicensed medicine use is implied by the initial study, it is important to take into account the prevalence of such use.

Turner et al. (1999) conducted a prospective study in a children's hospital in the UK over 13 weeks. It included the following specialities: medicine, surgery, neonatal surgery, cardiac PICU and general PICU. They did not record an ADR definition and their definitions of off-label use and unlicensed medicines are shown in Tables 1.4 and 1.5. The primary reference source for details of the product licence (MA) was the Association of the British Pharmaceutical Industry's (ABPI) data sheet compendium (1995-1996), while secondary reference sources were the package insert and the British National Formulary (BNF) 1996 Edition. ADRs were detected by means of spontaneous reports from health professionals and daily chart review by a research pharmacist. 936 of 1046 admissions reviewed received medicines during their hospital stay. The total number of prescriptions was 4455, of which 1574 (35%) were off-label or unlicensed. 507 (48%) of these admissions received at least one unlicensed or off-label medicine and 116 (11%) of 1046 admissions experienced an ADR. 112 (3.9%) of 2881 authorised prescriptions were associated with an ADR and 95 (6%) of the 1574 off-label or unlicensed prescriptions were associated with an ADR. The number of medicines administered was significantly associated with the risk of an ADR but off-label or unlicensed medicine use did not impact ADR risk. There was a trend towards an increased risk of severe ADRs with off-label and unlicensed medicine use, 19 medicines were implicated in severe ADRs and of these, 14 were off-label or unlicensed. Again, the absence of an ADR definition in this study impacts of the interpretation of the results. The results must also be interpreted in the context of the specialties included. For example, due to differences in the clinical stability of the patients and the types of medicines being used, on PICU we might expect different ADR types and frequencies than on a general medical ward. Furthermore, because of differences in the the level of monitoring required there will be differences in how ADRs are detected and evaluated. For example, electrolyte disturbances may be easier to detect and subsequently monitor on PICU where they are monitored hourly than on a general medical or surgical ward where monitoring is more infrequent.

A prospective pharmacovigilance study was undertaken in France over five months (Horen, Montastruc and Lapeyre-Mestre, 2002). The setting was community paediatric practice and patients <16 years old were included, no ADR definition was provided and the study did not consider unlicensed medicine use. Off-label medicine use was defined by one of seven categories which matched those described by Turner and Choonara (Turner and Choonara, 1997) with the omission of 'medicine administered at a greater frequency; the amendment of 'medicine administered at a greater dose to 'medicine administered at a different dose'

and the addition of ‘medicine used in inadvisable co-prescription’. The source used for details of the MA was Dictionnaire Vidal 2000 (the French medicine formulary). All ADRs were identified by one of 39 participating paediatricians; they recorded the following information on the first patient seen during a medical visit or consultation until they had 40 records: demographic details, age, weight, diagnosis and medicines prescribed (including dose and indication). The record was retained for seven days in order to describe any developing ADRs. 1419 patients were included and of these 20 (1.4%) experienced an ADR, 18.9% of the total prescriptions were off-label and 42% of patients received at least one off-label medicine. The incidence of ADRs in the population receiving at least one off-label medicine was 2%. In a multivariate analysis, the risk of ADR was significantly associated with exposure to off-label medicines (RR 3.44 95% CI 1.26, 9.38). In terms of the subcategories of off-label medicines use, medicines prescribed for an indication different to that recommended had the most significant impact on ADR risk (RR 4.42 95% CI 1.60, 12.25). The mean number of medicines was 3.6 (standard deviation 1.5) in patients receiving off-label medicines and 2.6 (standard deviation 1.2) in patients not receiving off-label medicines. This study did not include all patients within the community paediatric practice but relied on the participating clinicians to recruit the first patient seen, it is unclear whether this approach had the potential to introduce bias. It is also unclear whether data on ADRs were actively collected, for example by telephoning the patient or their family, or whether they were passively collected by waiting for the patient to return to the clinic with a problem. The latter approach would be likely to underestimate ADR incidence.

Impicciatore et al. (2002) undertook a prospective study in Italy over 9 months. The setting was a paediatric ward and the WHO definition of ADR was used (World Health Organisation, 1972), unlicensed medicine use was not considered in this study. Prescriptions were assigned off-label status as described by Turner and Choonara (1997) with the omission of ‘medicine administered when a contra-indication is described’ and ‘medicine administered at a greater frequency than recommended’ and the amendment of ‘medicine administered at a greater dose’ to ‘medicine administered at a different dosage or frequency’. All eligible patients were monitored and demographic information, weight, reason for admission, length of stay and prescription information was recorded. The prescription information recorded was dose, route, indication, duration and changes. Of 1619 patients, 41 (2.53%) experienced an ADR, 29 ADRs were attributed to medicines administered in the hospital (1.8%) and 12 ADRs were attributed to medicines administered before admission (0.74%).

In 16 (39%) of the 41 patients experiencing an ADR, it was caused by a medicine which was being used off-label. This was made up of 11 (38%) of the 29 patients who experienced an ADR due to medicines administered in the hospital and 5 (42%) of the 12 patients who experienced an ADR due to medicines administered before admission. The authors commented that there was an association between off-label medicine use and the occurrence of ADRs but that the small study size limited an evaluation of its significance.

Neubert et al. (2004) conducted a prospective study in Germany over eight months in 2001. The setting was a ten-bed paediatric ward, patients <18 years were included and the WHO definition (World Health Organisation, 1972) of ADR was used. To retrospectively assign off-label or unlicensed status to the use of a medicine, the system described by Turner and Choonara (1997) was used. Some details of the off-label definition were expanded - if use in children was not mentioned, the minimum age for use was assumed to be 18 years, if use in children was mentioned but without a specified age range, the minimum age was assumed to be 0 years. If the medicine was being used in a child of an authorised age via an authorised route and the dose did not exceed the maximum recommended (for any indication) then the use was considered not to be off-label. The primary reference source for details of the MA was Fachinfo (2001) and the secondary source was Rote List 2001 (equivalent of the BNF). ADRs were identified by a weekly review of patient charts; this was conducted by a team comprised of a clinical pharmacologist, a pharmacist and a paediatrician. 178 patients were reviewed and 156 of these had received at least one medicine, the total number of prescriptions was 740, of these three (0.4%) were unlicensed medicines and 195 (26.3%) were off-label, 25 (3.4%) could not be classified. 31(17.4%) of the 178 admissions experienced an ADR and 92 (51.7%) patients received at least one off-label or unlicensed medicine. Of the 517 licensed prescriptions, 29 (5.6%) were associated with an ADR and of the 198 off-label or unlicensed prescriptions, 12 (6.1%) were associated with an ADR. The risk of ADR increased with number of medicines prescribed but there was no significant relationship between off-label or unlicensed medicine use and the risk of an ADR. Patients receiving at least one off-label or unlicensed medicine experienced at least one ADR more frequently (26 out of 92 patients, 28.3%) than those receiving only licensed medicines (5 out of 64 patients, 7.8%). In this study, the retrospective approach to classification meant that the indication for use could not be assessed and it was not always clear from the patient record precisely which formulation had been administered. If a classification could not be made because information was incomplete, the prescription was excluded from further analysis. The exclusion of ‘different indication’ as a type of off-label

use will have resulted in an underestimate of off-label medicine use. If some of these off-label medicine courses contributed to ADRs, the study may have demonstrated a relationship between off-label use and ADR risk.

A Brazilian study carried out over 5 months was undertaken in a 36 bed paediatric ward, no definition of ADR was given (Santos et al., 2008). Unlicensed medicines were those:

- contraindicated for use in children
- extemporaneous preparations that were manufactured (home label medicines) or modified by the hospital or nurse
- drugs for which safety and efficacy in the paediatric population were not established

Off-label medicines were those for which the prescription showed a discrepancy with the licence information for:

- age (or weight)
- dose (or frequency)
- route of administration
- formulation

ADRs were detected on a daily ward visit by a clinical pharmacist who reviewed medical records and attended clinical rounds. 272 patients were reviewed, 265 had received at least one medicine and 47 ADRs were detected in 33 children. 5.5% of prescriptions were unlicensed, 39.6% were off-label. 82.6% of children had received at least one unlicensed or off-label drug. The ADR incidence was 12.5% in whole study population and 16.3% in patients exposed to at least one off-label drug. The definitions of off-label and unlicensed medicines used in this study were different to those used in the majority of others. Medicines contra-indicated for use in children and those for which safety and efficacy in children were not established were defined as unlicensed rather than off-label. In agreement with previous studies, extemporaneous preparations were defined as unlicensed however, unlike in other studies, modifications by nursing staff were also included. These discrepancies in defining off-label and unlicensed medicines complicate the interpretation of the results of this study. This is one of only two non-European studies included in this review of the literature and therefore the results must also be interpreted in the context of differences in the patterns of disease and medicine use. For example,

there were a high number of prescriptions for anthelmintics, this was not seen in other studies.

A prospective study of admissions related to ADRs was carried out in a paediatric hospital in The Netherlands over a period of 18 weeks (Posthumus et al., 2012). ADR was defined as 'an unintended noxious response to a drug' and the medicines implicated in an ADR were categorised as 'licensed', 'unlicensed' or 'off-label used'. 'Licensed' medicines were registered for children at the Dutch Medicine Evaluation Board, and 'unlicensed' medicines were not, 'off-label used medication' referred to medicines used outside the terms of the product licence. 47 of 683 (6.9%) patients were admitted due to an ADR and eight ADRs involved an unlicensed medication, eight involved medicines used off-label and 16 involved a combination of unlicensed, off-label and licensed medications. In contrast to the majority of other studies, this study included medication errors which resulted in an adverse drug reaction in the definition of ADR. Two ADRs which resulted from a medication error were identified. Exposure to cancer chemotherapy had a significant impact on the results of this study. 68.1% of admissions who had been exposed to cancer chemotherapy were admitted due to an ADR, compared to 2.4% of non-oncology admissions. ADRs detected in the oncology sub-group were more likely to be attributed to an off-label or unlicensed medicine (84.6%) than those in the non-oncology sub-group (33.3%) but this finding must be interpreted with caution due to the small size of the study. Since the medicines not involved in an ADR were not categorised, it was not possible to compare ADR risk for off-label or unlicensed medicines and licensed medicines.

A study of off-label and unlicensed prescribing and related ADRs in France included patients aged 0-16 years who consulted their general practitioner (GP), it was undertaken over a period of 5 months (Bissuel et al., 2013). No definition of ADR was provided. Off-label prescribing was defined as prescribing outside the specifications of the SmPC and unlicensed medicines were those without a valid MA. Amongst 1960 patients who received at least one prescription, 37.6% were exposed to at least one off-label medicine and 6.7% to at least one unlicensed drug. The most common type of off-label use was for an unapproved indication. There were 23 ADRs reported; the ADR incidence in the entire population was not significantly different to that in the subpopulation of patients exposed to at least one off-label prescription (1.0% vs. 1.5%). It is unclear whether active surveillance for ADRs was undertaken in this study, or whether ADRs were only identified if patients re-presented. The study relied on the GP, rather than an independent observer, to

detect and record the ADR. If no definition of ADR was provided to the GPs involved in the study, it is possible that they may have overlooked some ADRs or included drug-related problems which were not ADRs. Furthermore, it is possible that they may have been less willing to report an ADR to an off-label or unlicensed medicine because of concerns about their liability for the event.

1.4.3 Retrospective studies

A retrospective study of off-label prescribing for paediatric inpatients (< 12 years old) in Australia examined the medical records and prescription charts of 300 patients admitted over approximately 3 months (Ballard et al., 2013). Prescriptions were classified as off-label, registered (i.e. licensed) or unregistered (i.e. unlicensed) using eMIMS as a reference for the Australian Product Information (PI). A medicine could be classified as off-label for one or more of the following reasons: dose/frequency, age/weight, indication or route. 32% of prescriptions were off-label; the most common category was dose or frequency greater than that sanctioned by the PI. Five ADRs were identified (incidence 1.7%) of which two involved off-label medicines. The retrospective design of this study relied on the accurate recording of both prescription details and suspected ADRs. Although the proportion of off-label prescriptions was similar to that reported in other inpatient studies, the ADR incidence reported was lower, which may reflect poor record-keeping.

1.4.4 Studies of spontaneous ADR reports

Studies of spontaneous ADR reports seek to characterise those ADRs and consider trends in ADR reporting. They are unable to estimate ADR incidence because not every ADR is reported. Guidance varies between countries but, in general, spontaneous reporting schemes request that only serious or unexpected ADRs be reported. Furthermore, they cannot estimate the likelihood of an ADR for a particular medicine because, in addition to incomplete reporting, data on medicine consumption in the general population is not always available. In the context of this review of the literature, their value is limited since they cannot compare the rate of ADRs with authorised medicines to that with off-label or unlicensed medicines.

Ufer, Kimland and Bergman (2004) reviewed a national database of spontaneous ADR reports in Sweden during the year 2000. The system relies on the legal obligation of healthcare professions to report ADRs to new medicines and ADRs which are serious, uncommon or unexpected. The WHO definition of ADR was used (World Health

Organisation, 1972) and they selected reports involving individuals < 16 years old and excluded ADR reports concerning over the counter preparations, vaccines given at vaccine centres, medicines administered during pregnancy and affecting the newborn and medicines administered in hospital. The primary reference sources for details of the MA were the Swedish Physician's Desk Reference (2000) and Pharmacy Prepared Drugs (2000), the secondary source was product information provided by the medicines regulatory authority (Swedish MPA) or the manufacturer. To assign off-label or unlicensed status to the use of a medicine, the authors used a similar system to Turner and Choonara (1997) with some amendments:

- 'Medicine administered when a contra-indication is described' was omitted
- If no information about paediatric use was found, the use was classified as off-label
- If paediatric use was mentioned but no age was specified, the use was not classified as off-label
- If the dose was weight or surface area based, this was estimated according to age.
- 'Medicine administered at a greater dose than recommended' was defined as a dose exceeding that recommended by greater than 20%

The study included 112 reports and these contained 158 ADRs; of these 42.4% were related to off-label medicine use. Of the ADRs reports classified as serious, 51% were related to off-label medicine use and 38.5% of non-serious ADRs were related to off-label medicine use.

Schirm et al. (2004) reviewed a national database of spontaneous ADR reports in the Netherlands from 1995-2001 and aimed to compare these reports with the use of medicines in the general paediatric population. The reports were spontaneous and more likely to concern reactions to new medicines or those considered serious or unexpected. All ADR reports from GPs or pharmacists for children aged 0-16 years were included; reports concerning vaccines were excluded. The use of medicines in the general population was obtained from a regional community pharmacy database. For each medicine, the following details were obtained – demographic data for recipient, route, licensed / unlicensed / off-label, frequency of use in the population, years on the market (>/<10 years) and target organ class. Off-label medicine use was defined as follows: the medicine was not authorised for use in children or if the child was below the minimum age specified. The dose, frequency, route and indication were not considered. Unlicensed medicines were defined as those without a MA; in this study this would only include pharmacy preparations. It was determined that, in the general paediatric population, 23% of medicines were off-label and

14.6% of medicines were unlicensed and in 773 paediatric ADR reports 24% of medicines suspected of causing an ADR were off-label and 1.9% were unlicensed. As well as evaluating data on off-label and unlicensed medicine use in a sample of the national paediatric population represented in spontaneous ADR reports, this study evaluated paediatric medicine use in a regional population. The retrospective approach to medicine categorisation meant that several aspects of off-label use could not be assessed. Therefore the rate of off-label prescribing may have been underestimated. Since the spontaneous reports were more likely to concern reactions to new medicines or those considered serious or unexpected, the sample did not reflect the full range of ADRs in the population and may have over- or under-estimated the relative involvement of off-label and unlicensed medicines.

Spontaneous paediatric ADR reports were reviewed in one region of the UK over three years (1998 - 2000) (Clarkson et al., 2004). The principle aim of the study was to evaluate a regional paediatric ADR monitoring scheme and reports were received from 20 selected hospitals. To assign off-label or unlicensed status to the use of a medicine, the system described by Turner and Choonara (1997) was used. The SmPC for a medicine was used as the reference source when assigning off-label status to medicines and the manufacturer of the medicine was contacted if further clarification was required. Over the period of the study, 456 ADR reports were received and 242 of these were used for the analysis. 84 (35%) involved a medicine that was either used off-label or was unlicensed. The reports were classified in several ways including those considered to be medically significant i.e. fatal, potentially life threatening or disabling. 45 (27%) of the 165 reports considered to be medically significant involved a medicine that was either used off-label or unlicensed. There were ten fatalities associated with a suspected ADR, four were associated with an off-label medicine and two were associated with an unlicensed medicine, this association was not statistically significant.

Jonville – Bera, Bera and Autret-Leca (2005) reviewed all ADR reports (adult and paediatric) sent to a French regional pharmacovigilance centre over a period of five months. The reports were submitted by physicians under a legal obligation to report serious or unexpected ADRs. The information obtained for each report included ADR details and also precise information about the medicine, in particular its indication. A medicine was defined as being used incorrectly (off-label) if it was not being used according to the specifications in the SmPC. The defined categories of incorrect medicine use were:

- administered at a different dose than recommended
- administered for an indication not described
- administered when a contra-indication was described
- used for an improper duration
- involved in a drug-drug interaction

Incorrectly used medicines were more often causally linked to ADRs than correctly used medicines. 182 reports were reviewed: there were 169 'incorrectly' used medicines and 127 (75%) of these were implicated in an ADR, 281 (59%) of 473 'correctly' used medicines were implicated in an ADR.

A study of paediatric ADR-related queries to a drug information centre over a period of 10 years was carried out in Sweden (Kimland et al., 2007). Unlicensed medicines were defined as those not in the Swedish catalogue of medical products (FASS). Off-label medicines were those which fulfilled at least one of the following criteria:

- explicitly not recommended in children
- administered for an indication not described
- administered to children outside the age range specified
- no information about the mode of paediatric use
- no paediatric safety or efficacy studies

The prevalence of off-label and unlicensed medicine use in the general population was not described. The study found that of 91 ADR-related queries, 27% involved off-label medicines and 17% involved unlicensed medicines. Jonville-Bera et al. (2009) undertook a retrospective evaluation of spontaneous ADR reports (for adults and children) received at a French pharmacovigilance centre over a period of 1 year. The study did not consider unlicensed medicine use and they defined off-label use as the use of the medicine outside at least one of the recommendations in the summary of product characteristics, with specific attention to;

- duration of treatment
- dose adaptation
- precautions for use
- monitoring of treatment
- absolute contraindications

- indication
- route

32% of 360 ADR reports were associated with off-label medicine use.

A retrospective study of ADR reports for children 0-17 years which were submitted in Denmark over a ten year period (1998 to 2007) included 4388 reports (Aagaard and Hansen, 2011). The reporting of ADRs in Denmark has been obligatory for doctors and dentists since 1972 and has also been possible for patients since 2003. The authors used the WHO definition of ADR (World Health Organisation, 1972) and the SmPC as their source for details of each MA, off-label medicine use was defined as the use of a medicine in a child below the recommended age group listed in the SmPC. There was also a focus in the study on the seriousness of the ADR and a serious ADR was defined as one that was either fatal or life threatening, required hospitalisation or prolonged hospitalisation, resulted in significant disability or incapacity or another medically important condition. 17% of the reports involved an off-label medicine with two thirds of these involving children between 11 and 17 years old. Of the ADRs reported which did not involve off-label medicines, 35% were classified as serious whereas of those that did involve off-label medicines, 60% were classified as serious.

1.5 Summary

In summary, adverse drug reactions are a significant problem in children but their predictors are not fully established. One risk factor that has been proposed is the use of off-label and unlicensed medicines. In previous studies of the link between off-label and unlicensed medicine and ADR risk there have been discrepancies between how authors have defined ADR, off-label medicine use and unlicensed medicine; this makes the interpretation of their results far from straightforward. However, there seems to be some indication that off-label and unlicensed medicine use is an ADR risk factor and this warrants further detailed investigation.

1.6 Aim of thesis

1.6.1 Aim

The aim of this thesis was to assess, within the ADRIC programme, the characteristics of adverse drug reactions (ADRs) in children in a large children's hospital. The thesis focusses on the contribution of off-label and unlicensed medicines to ADR risk.

1.6.2 Objectives

- Determine the contribution of off-label and unlicensed medicine use to ADR risk when the ADR has led to or contributed to hospital admission.
- Determine the contribution of off-label and unlicensed prescribing to ADR risk when the ADR has occurred during hospital admission.
- Describe in detail off-label and unlicensed medicine use, determine whether some types of off-label or unlicensed medicines are more likely to be implicated in ADRs than others.

2 ADRs detected at the point of admission to a children's hospital – contribution of off-label and unlicensed medicine use to ADR risk

2.1 Introduction

A recent meta-analysis, which included eight studies, reported the incidence of ADRs in children being admitted to hospital as being between 0.6% and 6% (Clavenna and Bonati, 2009). A recent systematic review included 31 studies of paediatric hospital admissions and reported an ADR incidence of between 0.4% and 10.3% (Smyth et al., 2012). A better understanding of the risk factors which predispose children to ADRs will contribute to strategies for their prevention and management.

There are no large paediatric studies which have looked at ADRs leading to hospital admission and then gone on to consider the influence of off-label and unlicensed medicine use. One small pilot study included ADRs to medicines administered before admission and recorded whether the medicines implicated were off-label (Impicciatore et al., 2002). Of the 41 ADRs detected in 41 of 1619 patients, 12 were attributed to medicines administered before admission and 29 were due to medicines administered in hospital. In 16 of the 41 patients experiencing an ADR, an off-label medicine was implicated; five of these were patients who experienced an ADR due to medicines administered before admission. A second admissions study included 683 patients, of whom 47 were admitted due to an ADR. Of 47 ADRs, 20 involved an off-label or unlicensed medicine (Posthumus et al., 2012). Neither study was large enough to prove or disprove a relationship between off-label and unlicensed medicine use and ADR risk.

This present study aims to describe the contribution of off-label and unlicensed medicine use to the risk of ADRs detected at the point of admission to a children's hospital.

2.2 Methods

2.2.1 Setting & participants

A twelve month prospective cohort study of unplanned admissions to a paediatric tertiary referral centre in the UK was carried out from 1st July 2008 to 30th June 2009. The study included children between the ages of 0 and 16 years 11 months. A sample size calculation for this cohort study was not undertaken, since the aim of the study was to determine the incidence of ADRs in unplanned admissions. Unplanned admissions were defined as those via the accident and emergency department (AED) and emergency transfers from other hospitals. Also included in this definition were unplanned admissions direct to wards, for example, acutely unwell patients under the care of the oncology unit. Patients who were electively admitted were excluded. The study also excluded patients who presented with deliberate or accidental overdose and those in whom the misuse of medicines (prescription or illicit) had occurred. This study was part of a larger study which used routinely collected clinical data in an anonymised format. The Chair of Liverpool Paediatric Research Ethics Committee (REC) informed us that this study did not require individual patient consent or review by an Ethics Committee. The planned analysis required routinely collected patient data and was therefore classified as an audit (Appendix 13).

2.2.2 Data collection

Patients were identified on a daily basis by use of a file download of new admissions from the hospital electronic patient record system (Meditech®). The file contained the details required for the patient to be identified and located within the hospital, that is, name and ward and also some of the details that were required for analysis: age, sex and admitting specialty. Each eligible patient was reviewed by one member of a multidisciplinary team which consisted of a trainee paediatrician, a paediatric nurse and a pharmacist (JRB). JRB reviewed 2969 of 8345 unplanned admissions (Gallagher, 2013). The aim of the review was to collect the minimum dataset (Table 2.1) and to determine whether any of the signs or symptoms recorded at the time of admission could be attributable to medicines administered in the preceding two weeks. The data were obtained from one or more of the following sources at the team's discretion: hospital electronic medical records system (Meditech®), patient casenotes, clinical team, the patient themselves or their parents. If an ADR was suspected, the case was taken through further evaluation by the study team. A case report was compiled by one member of the team. The case report described in detail the suspected ADR inclusive of the results of any investigations and any action taken by the

clinical team and its outcome. Each ADR case report was then used to assess the following: causality using the Liverpool Causality Assessment Tool (LCAT), (Gallagher et al., 2011) severity using the Hartwig scale (Hartwig, Siegel and Schneider, 1992) and avoidability using the system described by Hallas et al (1990). JRB identified and evaluated 96 of 240 ADRs (Gallagher, 2013).

Table 2.1 Minimum dataset collected for all eligible patients

- Age
- Sex
- Weight
- Admitting speciality
- Underlying diagnoses
- Presenting complaint, signs and symptoms.
- Details of all medicines administered in the 2 weeks before admission, including over the counter medicines, herbal medicines and prescribed medicines

2.2.3 Classification of Medicines

The details of any medicine taken at any time during the two weeks before admission were recorded by the study team, specifically: drug name, route, dose, frequency, duration, indication (if this required clarification) and whether it was a prescription or non-prescription medicine. The definition of a prescription medicine included those administered under a patient group direction. A medicine course was defined as the administration of one type of medicine at least once in the preceding two weeks; this encompassed regular medicines e.g. daily anti-epileptic treatment, short courses e.g. a five day course of antibiotics and intermittent doses e.g. paracetamol for fever given as required.

The data on prescription medicine use were scrutinised by one member of the study team (JRB) in order to define each medicine course as either authorised, off-label, unlicensed or unknown. Non-prescription medicine courses were not classified because the focus of the study was on off-label and unlicensed prescribing. The use off-label and unlicensed non-

prescription medicines by parents and patients involves a different range of medicines and happens for different reasons.

Authorised use was defined as the use of a medicine with a UK marketing authorisation (MA), within the terms of that MA. The terms of the MA were found in the Summary of Product Characteristics (SmPC) available online from the Electronic Medicines Compendium (eMC) (DataPharm Communications Ltd., 2010). The version of the SmPC which was the most up to date during the study was referred to. The 'date of revision of the text' at the end of the electronic SmPC indicated when the information was last updated, if the document had been updated since the date that the medicine was administered, the contemporaneous SmPC was consulted.

If no SmPC was available, the British National Formulary for Children (BNF-C) (Paediatric Formulary Committee, 2008/2009) was consulted for details of the product MA. If neither reference source provided adequate clarity of information, the manufacturer of the medicine was contacted.

Off-label use was defined as the use of a medicine with a UK MA, outside the terms of that MA. A medicine was defined as off-label in this study if its use fitted one of the definitions in Table 2.2, adapted from Turner and Choonara (1997). The specific type of off-label use was not prospectively recorded. Since the primary purpose of the SmPC is not to inform the classification of medicines in this study, it was necessary to develop and apply some rules for the classification of licensed medicines in various scenarios by reference to the SmPC (Table 2.3). Where there was ambiguity in the classification process, rules for specific medicines and groups of medicines were developed and applied (Table 2.4).

Table 2.2 Definitions of off-label use

1. Medicine administered at a greater dose than recommended in the MA, doses less than those recommended will be considered to be authorised
2. Medicine administered for an indication not described in the MA
3. Medicine administered at a greater frequency than recommended in the MA
4. Medicine administered to children outside the age range specified in the MA
5. Medicine administered via a route not described in the MA
6. Medicine administered when a contra-indication is described in the MA
7. Medicine administered in combination with another medicine when the combination is contraindicated in the MA

Table 2.3 Rules for the classification of licensed medicines by reference to the SmPC

Scenario	Rule
SmPC states 'not suitable for children' or makes no reference to use in children	Apply the age range 0-18 years and classify as off-label
SmPC does not provide neonatal (0-27 days) doses	Classify use in a neonate as off-label
Medicine administered off-label for only part of the treatment course	Classify as off label
Exact concentrations of inhaled anaesthetic administered not recorded	Assume that the dosage recommendations in the SmPC have been complied with
Intravenous medicines prepared on a ward or in the Central Intravenous Additive Service (CIVAS)	Assume that the preparation recommendations in the SmPC have been complied with
Dosage form likely to have been manipulated before administration	Do not take in to consideration as will not have been recorded consistently
Weight or surface area not recorded but is required to check that doses are authorised	Use the age-related values found in the appendix 'approximate conversions and units' of the BNF-C (Paediatric Formulary Committee, 2008/2009)
Neonates born pre-term	Although it is certainly not the case, assume that all neonates were born at term because gestational age was not recorded in this study

Table 2.4 rules for the classification of specific medicines and groups of medicines

Medicine or medicine group	Rule
Aspirin oral	Assume use is authorised unless being used as an analgesic. SmPC states not to be administered to children unless specifically indicated, main use at this centre is in cardiac cases i.e. specifically indicated
Beclomethasone inhaled	Assume Clenil® brand has been prescribed (this formulation is licensed in children 2-12 years)
Codeine oral	If dose is 15mg, 30mg, 45mg or 60mg might have had tablet or liquid, tablets not licensed in children but liquid is so allocate unknown. If any other dose assume liquid used.
Cytotoxic drugs (medicines in BNF-C section 8.1)	If BNF-C states 'consult local treatment protocol' assume use is authorised provided that the relevant indication is mentioned in the SmPC, if BNF-C states 'not licensed in children' classify use as off-label
Diclofenac oral	Dosage forms >25mg not licensed in children. If dose = 25mg and dose 1-2mg/kg, assume used 25mg tablet i.e. course is authorised. If dose >25mg we do not know if they used 2 x 25mg or 50mg (50mg dispersible are available in our centre) therefore allocate unknown.
Ibuprofen oral	Use BNF-C 2008/09 (Paediatric Formulary Committee, 2008/2009) dose ranges[ii] and categorise all use in children under 3 months as off-label

[ii] Child 3–6 months 50 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses
Child 6 months–1 year 50 mg 3–4 times daily; max. 30 mg/kg daily in 3–4 divided doses
Child 1–4 years 100 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses
Child 4–7 years 150 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses
Child 7–10 years 200 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses
Child 10–12 years 300 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses
Child 12–18 years initially 300–400 mg 3–4 times daily; increased if necessary to max. 600 mg 4 times daily; maintenance dose of 200–400 mg 3 times daily may be adequate

Low birth weight infant supplements	Multivitamins Dalivit® and Abidec®– if dose not recorded assume authorised. Sodium feredetate and folic acid to be categorised as off-label - they are indicated for the treatment of deficiency rather than prevention
Omeprazole oral	If treatment time exceeds 2-4 weeks or indication is anything other than gastro-oesophageal reflux disease (GOR), categorise as off-label
Paracetamol oral	Use BNF-C 2008/09 (Paediatric Formulary Committee, 2008/2009) dose ranges[iii] and refer to the SmPC for details of lower age limit i.e. categorised use in children under 2 months old as off-label and all use except for post-immunisation pyrexia in children under 3 months old as off-label
Paracetamol infusion	Assume licensed product has been administered. Although some doses are packed down by CIVAS it will not be clear from the prescription whether this is the case.

[iii] Child 1–3 months 30–60 mg every 8 hours as necessary
Child 3–12 months 60-120 mg every 4–6 hours (max. 4 doses in 24 hours)
Child 1–6 years 120-250 mg every 4–6 hours (max. 4 doses in 24 hours)
Child 6–12 years 250–500 mg every 4–6 hours (max. 4 doses in 24 hours)
Child 12–18 years 500 mg 4–6 hours (max. 4 doses in 24 hours)

Unlicensed medicines were defined as those without a UK MA and could be one of the types listed in Table 2.5, as per Turner and Choonara (1997). A reference list of unlicensed medicines in use at Alder Hey was obtained from the pharmacy procurement department to assist in the identification of which products had been used. The specific type of unlicensed medicine was not prospectively recorded.

An 'unknown' category was reserved for medicine courses for which inadequate detail was available to decide whether use was authorised, off-label or unlicensed.

Table 2.5 Definitions of unlicensed medicines

1. Modification to licensed medicines (e.g. extemporaneous pharmacy preparations)
2. Licensed medicines in a modified formulation manufactured under a specials manufacturing licence (e.g. a liquid form for ease of administration)
3. New medicines available under a specials manufacturing licence (NB this gives some assurance of the quality of the manufacturing process but not to the standard of a licensed medicine, the safety and efficacy of the product will not have been assessed)
4. Use of chemicals as medicines
5. Medicines used before a licence has been granted
6. Imported medicines (licensed in another country)

2.2.4 Data analysis

Advice on the approach to analysis was obtained from the ADRIC programme statistics team and broadly reflects the approach taken in the cohort study, of which this work is a part. The analysis was carried out by JRB.

2.2.4.1 All first admissions – patient risk factors

Some participants had more than one unplanned admission during the study, in order to avoid including the same patients (and potentially the same medicine courses) repeatedly in the analysis, risk factors were analysed for first admissions only. Using data obtained for each participant who had received at least one prescription medicine course, univariate analysis was performed to compare differences in ADR risk factors for patients with ADRs and those without (age, gender, number of prescription medicines, whether they were oncology patients and off-label/unlicensed prescription medicine use). Categorical outcomes were compared between groups using the chi-square statistic. For normally distributed data, the Student t-test was used to compare groups while for non-normally distributed data, the Mann-Whitney U test was used.

A logistic regression model was used to assess the influence of independent variables (risk factors) on the likelihood of an ADR occurring. Differences were considered significant at the 5% level ($p < 0.05$), and where appropriate, all results were presented with 95% confidence intervals.

Post-hoc, two separate logistic regression models were used to explore two of the significant risk factors identified in the initial logistic regression model; number of medicines and being an oncology patient.

A second logistic regression model was used to assess the influence of the independent variable 'number of medicines' by splitting it into three variables as follows: number of authorised prescription medicines, number of off-label or unlicensed prescription medicines, number of unknown prescription medicines. Consideration was given to splitting this variable further by separating off-label and unlicensed medicines. Since this was a post-hoc analysis, it was known that only around 960 out of 16 551 medicines (6%) were unlicensed and that only 51 of 481 medicines (10.6%) implicated in an ADR were unlicensed, therefore the variable was not split further.

A third logistic regression model was used to assess the influence, in non-oncology patients only, of the variables age, gender, number of authorised prescription medicines, number of off-label or unlicensed prescription medicines and number of unknown prescription medicines.

2.2.4.2 All admissions – medicine courses

The proportions of all prescription medicine courses which were authorised, off-label or unlicensed were calculated for prescription medicine courses administered to all participants on every admission.

To determine the likelihood of medicine courses in each of these categories being implicated in an ADR, the relative risk (with 95% confidence intervals) for off-label and unlicensed medicine courses being implicated in an ADR was calculated for prescription medicine courses administered to all participants on every admission. A p-value of <0.05 was considered to be significant.

The clinical details of ADRs involving off-label and unlicensed medicine courses were described for non-oncology and oncology ADRs.

Post-hoc, the proportion of authorised, off-label or unlicensed prescription medicine courses was calculated for the medicines administered to two patient sub-populations: non-oncology patients and oncology patients. The relative risk (with 95% confidence intervals) for off-label and unlicensed medicine courses being implicated in an ADR was calculated for medicine courses both non-oncology and oncology patients.

Additional post-hoc analysis was undertaken on the descriptive data relating to ADR cases. The difference in proportions (with 95% confidence intervals) for causality, avoidability and severity of ADR cases was compared for two ADR case subgroups: ADRs not involving off-label or unlicensed medicines, ADRs involving at least one off-label or unlicensed medicine.

2.3 Results

2.3.1 Description of medicine courses

The study examined 19975 medicine courses from 6020 separate unplanned admissions of patients who had received at least one medicine course in the two weeks prior to their admission (Figure 2.1). An assessment of the medication histories of all admissions revealed that prescription medicines accounted for 88.9% (17758/19975) of the medicine courses investigated while the remaining 11.1% (2217/19975) were non-prescription. A total of 8.3% (1655/19975) of the medicine courses were administered to patients admitted under the care of oncology but only three (0.2%) of these were non-prescription. Two out of the 2217 non-prescription medicines were implicated in one ADR each.

2.3.2 Analysis of patient characteristics (first admissions only)

2.3.2.1 Univariate analysis

A univariate analysis was carried out using the prescription medicine data of patients on their first admission only (3869 patients); those who had received non-prescription medicines only were excluded. The analysis compared each variable in the group who had experienced at least one ADR with those who had not for: all patients, patients who had been exposed to at least one off-label or unlicensed (OLUL) prescription medicine and patients who had received only authorised prescription medicines.

The results of the univariate analysis are summarised in Table 2.6. There was no significant difference in the proportion of each gender in any of the subpopulations. The median age and median number of prescription medicines was greater in patients who had experienced at least one ADR. However, within the population of patients exposed to authorised prescription medicines only, there was no significant difference in the median age of the patients who had experienced an ADR and those who had not (p=0.968). Oncology patients and patients exposed to off-label and/or unlicensed medicines were significantly more likely to experience an ADR.

Figure 2.1 Medicine courses categorised

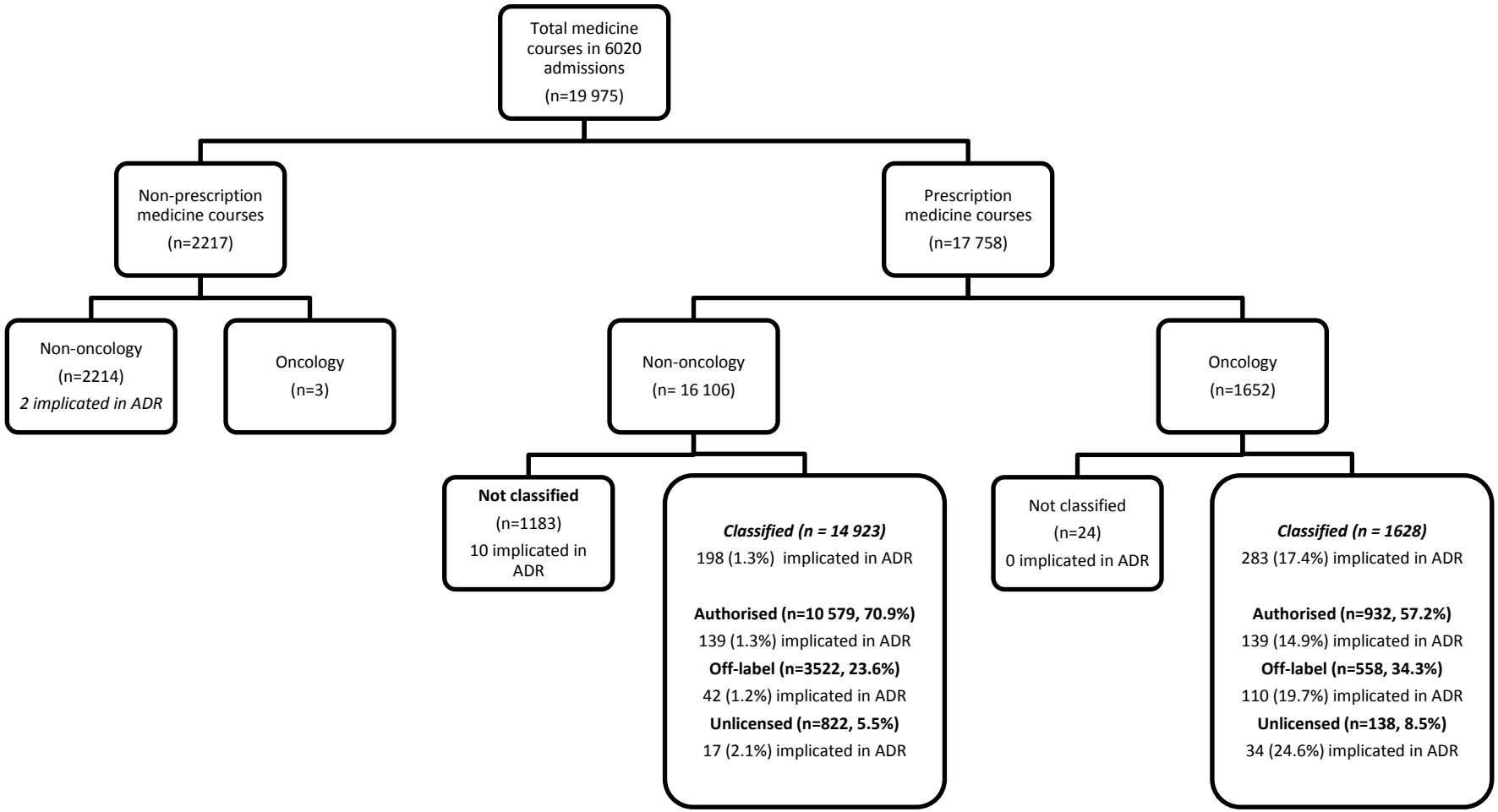


Table 2.6 Univariate analyses of ADRs for all first admissions by gender, age, and number of prescription medicines taken (3869 patients)

Gender	**All**	**No ADR**	**ADR**	**p-value[iv]**
All boys	2247	2172 (96.7%)	75 (3.3%)	0.271
All girls	1622	1557 (96.0%)	65 (4.0%)	
OLUL exposed boys	869	812 (93.4%)	57 (6.6%)	0.920
OLUL exposed girls	627	585 (93.3%)	42 (6.7%)	
Authorised only boys	1321	1303 (98.6%)	18 (1.4%)	0.063
Approved only girls	953	930 (97.6%)	23 (2.4%)	
Age (years, months) [median; Q1, Q3]	**All**	**No ADR**	**ADR**	**p-value[v]**
All	[3y 1m; 8m, 9y] (n=3869)	[3y; 8m, 9y] (n=3729)	[6y; 2y 4m, 11y] (n=140)	<0.001
OLUL exposed	[2y 5m; 3m, 8y] (n=1595)	[2y 1m; 3m, 7y] (n=1496)	[7y; 3y 7m, 12y] (n=99)	<0.001
Authorised only exposed	[3y 8m; 1y, 10y] (n=2274)	[3y 8m; 1y, 10y] (n=2233)	[3y 9m; 5m, 8y 6m] (n=41)	0.968
Number of prescription medicines [median; Q1, Q3]	**All**	**No ADR**	**ADR**	**p-value[v]**
All	[2; 1, 4] (n=3869)	[2; 1, 3] (n=3729)	[6; 3, 9] (n=140)	<0.001
OLUL exposed	[3; 2, 6] (n=1595)	[3; 2, 6] (n=1496)	[8; 5, 11] (n=99)	<0.001
Authorised only exposed	[2; 1, 2] (n=2274)	[2; 1, 2] (n=2233)	[2; 1, 3] (n=41)	0.003
Specialty	**All**	**No ADR**	**ADR**	**p-valueiv**
Oncology	73	32 (43.8%)	41 (56.2%)	<0.001
Non-oncology	3796	3697 (97.4%)	99 (2.6%)	
OLUL exposure	**All**	**No ADR**	**ADR**	**p-value[iv]**
OLUL exposed	1595	1496 (93.8%)	99 (6.2%)	<0.001
Authorised only exposed	2274	2233 (98.2%)	41 (1.8%)	

[iv] Chi-square test
[v] Mann-Whitney U test

2.3.2.2 Multivariate Logistic Regression

Logistic regression analysis indicated that patients admitted into the care of the oncology specialty were more likely to have experienced an ADR, (odds ratio (OR) 25.07, 95% CI 14.53, 43.26, p<0.001) as were patients who had been exposed to a greater number of prescription medicines (OR 1.20, 95% CI 1.15, 1.26, p<0.001). In addition, increasing age was associated with an increased risk of ADR; (OR 1.05, 95% CI 1.01, 1.09, p=0.017). Although the results did not reach statistical significance, there was trend towards an increased ADR risk with exposure to an off-label or unlicensed medicine; (OR 1.43, 95% CI 0.91, 2.27, p=0.124) and there was a trend towards males being less likely to experience an ADR than females (OR 0.73, 95% CI 0.50, 1.07, p=0.106) (Table 2.7).

Table 2.7 Multivariate logistic regression analysis for all first admissions (3869 patients)

Variable	Odds Ratio (OR)	Standard error of OR	95% CI for OR	p-value
Gender (male)	0.73	0.196	0.50, 1.07	0.106
Specialty (oncology)	25.07	0.278	14.53, 43.26	<0.001
No. of prescription medicines	1.20	0.024	1.15, 1.26	<0.001
OL/UL Exposure	1.43	0.234	0.91, 2.27	0.124
Age in years	1.05	0.019	1.01, 1.09	0.017

We dissected the variable 'number of medicines' to determine the relative influences of the number of authorised, and the number of off-label and unlicensed medicines (Table 2.8). Each additional authorised medicine administered in the two weeks before admission increased the risk of an ADR by 25% and each additional off-label or unlicensed medicine increased the risk by 23%; both variables were significant predictors.

Table 2.8 Multivariate logistic regression analysis for all first admissions, number of authorised and number of off-label and unlicensed prescription medicines (3869 patients)

Variable	Odds Ratio (OR)	Standard error of OR	95% CI for OR	p-value
Gender (male)	0.74	0.196	0.51, 1.09	0.130
Specialty (oncology)	25.70	0.290	14.56, 45.38	<0.001
No. of authorised medicines	1.25	0.037	1.16, 1.35	<0.001
No. of off-label/unlicensed medicines	1.23	0.054	1.10, 1.36	<0.001
No. of unknown medicines	0.84	0.175	0.59, 1.18	0.303
Age in years	1.04	0.019	1.00, 1.08	0.045

Since the influence of a patient being admitted under the care of the oncology specialty was so significant, multivariate analysis was repeated after excluding oncology patients (to leave 3796 patients). Each additional authorised prescription medicine increased ADR risk by 33% ($p<0.001$). The number of off-label/unlicensed prescription medicines was not a significant predictor of ADR risk ($p=0.627$) Older patients were more likely to experience an ADR (OR 1.05, 95% CI 1.01-1.09 $p=0.023$). There was still a trend towards males being less likely to experience an ADR, (OR 0.71, 95% CI 0.47, 1.08, $p=0.107$) (Table 2.9).

Table 2.9 Multivariate logistic regression analysis for all non-oncology first admissions (3796 patients)

Variable	Odds Ratio (OR)	Standard error of OR	95% CI for OR	p-value
Gender (male)	0.71	0.211	0.47, 1.08	0.107
No. of authorised medicines	1.33	0.040	1.23, 1.44	<0.001
No. of off-label/unlicensed medicines	1.04	0.079	0.89, 1.12	0.627
No. of unknown medicines	0.79	0.202	0.53, 1.17	0.233
Age in years	1.05	0.020	1.01, 1.09	0.023

2.3.3 Analysis of medicine courses (all admissions)

Considering the 17758 prescription medicine courses, 1207 (6.8%) of these could not be categorised because insufficient information about the patient or the medicine had been recorded, for example no patient weight or no medicine frequency (Figure 2.1). Considering the 16551 medicine courses which could be categorised, off-label or unlicensed medicines were more likely to be implicated in an ADR than authorised medicines (relative risk (RR) 1.67, 95% CI 1.38, 2.02, p<0.001).

14923 of 16106 medicine courses administered to non-oncology patients could be categorised (Figure 2.1). Of these, 70.9% were authorised, 23.6% off-label and 5.5% unlicensed. Off-label or unlicensed medicines were not more likely to be implicated in an ADR than authorised medicines, (RR 1.03, 95% CI 0.72, 1.48, p=0.830).

In comparison, among the 1652 medicine courses administered to oncology patients, 1628 could be classified and 57.2% were authorised, 34.3% off-label and 8.5% unlicensed (Figure 2.1). Off-label or unlicensed medicines were more likely to be implicated in an ADR than authorised medicines, (RR 1.39, 95% CI 1.12, 1.71, p=0.02).

2.3.4 Description of ADRs in which off-label and unlicensed medicines were implicated

2.3.4.1 All ADRs in which off-label and unlicensed medicines were implicated

Of 247 ADRs, 45 (18.3%) were attributed to off-label or unlicensed medicines alone, 96 (38.9%) to authorised medicines alone and 98 (39.7%) to a combination of off-label or unlicensed *and* authorised medicines. The remainder involved at least one medicine which could not be categorised. Table 2.10 summarises the characteristics of these 247 ADRs in terms of severity, avoidability and causality and the number of medicines involved in each.

2.3.4.2 Non-oncology ADRs in which off-label and unlicensed medicines were implicated

48 of 127 non-oncology ADRs involved at least one off-label or unlicensed medicine (see Appendix 2 for details). Of these, 37 involved two or more medicines. In the nine cases where three medicines were implicated, at least one of these was always an authorised medicine. In the 29 cases where two medicines were implicated, 23 involved at least one authorised medicine as well, three involved off-label only, two involved off-label and unlicensed and one involved only unlicensed.

The following list provides reasons for the off-label and unlicensed categorisation of medicines implicated in non-oncology ADRs (Appendix 2).

- Acetazolamide oral – for intra-cranial hypertension, not authorised for this indication via this route.
- Anakinra injection –administered to a child, not authorised for use in children.
- Contraceptive Mercilon® oral - to regulate menstruation in a patient with polycystic ovary disease, not authorised for this indication.
- Dexamethasone injection - for the prevention of post-operative vomiting and/or post-tonsillectomy pain, not authorised for use in children for this indication.
- Diclofenac by mouth – for post-operative pain in children, not authorised for use in children for this indication.
- Dihydrocodeine by mouth - recipient three years old, preparation not authorised for use in children under four years old.
- Fentanyl infusion - patient-controlled analgesia infusion, not authorised for this indication
- Ibuprofen by mouth - dose not authorised (see Table 2.4).
- Infliximab infusion - to facilitate fistula healing in a two year old without Crohn's disease, not authorised for children under six years old or for this indication.
- Methotrexate by mouth – recipient nine years old with juvenile idiopathic arthritis (JIA), not authorised for this indication.
- Methotrexate infusion – for juvenile idiopathic arthritis (JIA), not authorised for this indication.
- Mycophenolate by mouth - for systemic lupus erythematosus (SLE) and for prevention of hepatic transplant rejection in a thirteen year old, not authorised for these indications.
- Ondansetron injection – for vomiting not induced by anaesthetic (PONV) or chemotherapy (CINV), not authorised for this indication.
- Oxybutynin by mouth – recipient two years old, not authorised for children under 5 years old.
- Propranolol oral –for the management of haemangioma, not authorised for this indication.
- Tacrolimus by mouth - to prevent rejection of lung transplant, not authorised for this indication.

2.3.4.3 Oncology ADRs in which off-label and unlicensed medicines were implicated

93 of 120 oncology ADRs involved at least one off-label or unlicensed medicine (see Appendix 3 for details). Of these, seven involved only one medicine; four were due to an off-label medicine and three were due to an unlicensed medicine. 28 ADRs did not involve any authorised medicines. The remaining 58 ADRs involved between two and six medicines made up of a combination of authorised, off-label and unlicensed medicines.

The following list provides reasons for the off-label and unlicensed categorisation of medicines implicated in oncology ADRs (Appendix 3).

- Carboplatin infusion - administered to a child, not authorised for use in children.
- Cyclophosphamide infusion - administered to a child, not authorised for use in children.
- Doxorubicin – administered to a child, not authorised for use in children.
- Etoposide infusion – administered to a child, not authorised for use in children.
- Ifosfamide infusion – for primitive neuroectodermal embriogenic tumour, not authorised for this indication.
- Imatinib tablets – for relapsed neuroblastoma, not authorised for this indication.
- Ondansetron oral - frequency not authorised.
- Prednisolone – for haemangioma, not authorised for this indication (NB this patient was under the care of oncology for treatment of a steroid unresponsive haemangioma).

Table 2.10 Characteristics of ADRs which involved at least on off-label or unlicensed medicines

ADR type	Severity[vi] count of ADRs (%)					Avoidability count of ADRs (%)			Causality count of ADRs (%)			Total number of medicines implicated count of ADRs (%)			Number of OLUL medicines implicated count of ADRs (%)		
	1	2	3	4	5	Unavoidable	Possibly avoidable	Definitely avoidable	Possible	Probable	Definite	1	2	>3	1	2	>3
Non-oncology (n = 48)	1 (2.1)	1 (2.1)	41 (85.4)	5 (10.4)	0	40 (83.3)	7 (14.6)	1 (2.1)	33 (68.8)	12 (25.0)	3 (6.3)	11 (22.9)	29 (60.4)	8 (16.7)	36 (75)	12 (25.0)	0
Oncology (n = 93)	4 (4.3)	0	88 (94.6)	0	1 (1.1)	88 (94.6)	5 (5.4)	0	6 (6.5)	20 (21.5)	67 (72.0)	7 (7.5)	41 (44.1)	45 (48.4)	42 (45.2)	44 (47.3)	7 (7.5)

[vi] **Modified Hartwig scale (Hartwig, Siegel and Schneider, 1992)**

Severity level	Description
1	Required no change in treatment
2	Drug dosing or frequency changed
3	Required treatment, or drug administration discontinued
4	Result in patient transfer to higher level of care
5	Caused permanent harm to patient or significant haemodynamic instability
6	Directly or indirectly resulted in patient death

2.3.5 Causality, avoidability and severity of ADRs

In terms of causality, ADRs in which at least one off-label or unlicensed medicine was implicated were more likely to be classified as definite or probable (difference in proportions 12%, 95% CI 0.4%, 25%, p = 0.047, Table 2.11). ADRs involving off-label or unlicensed medicines were more likely to be classified as unavoidable than ADRs involving only authorised medicines (difference in proportions 30%, 95% CI 20%, 40%, p < 0.001, Table 2.11). Finally, there was no difference in the severity of ADRs involving only authorised medicines when compared to ADRs involving at least one off-label or unlicensed medicine (difference in proportions 6%, 95% CI -0.5%, 12%, p = 0.066, Table 2.11).

In a comparison of oncology and non-oncology ADRs, oncology ADRs were more likely to involve at least one off-label or unlicensed medicine (difference in proportions 40%, 95% CI 32%, 48%, p < 0.01, Table 2.12). Oncology ADRs were also more likely to have been definite or probable (difference in proportions 50%, 95% CI 40%, 60%, p<0.001, Table 2.12). In addition, oncology ADRs were more likely to have been unavoidable (difference in proportions 29%, 95% CI 24%, 34%, p<0.001, Table 2.12). Oncology ADRs were less likely to have been severe (Hartwig score 4 or 5) than non- oncology (difference in proportions 3%, 95% CI 1%, 13%, p = 0.032, Table 2.12).

Table 2.10 Comparison of causality, avoidability and severity assessments for ADRs involving off-label and unlicensed medicines and those which did not

Assessment	Score	ADRs not involving off-label or unlicensed medicines (n=106)	Count for ADRs involving at least one off-label or unlicensed medicine (n=141)	p-value[vii]
Causality	Definite & Probable	64	102	0.047
	Possible	42	39	
Avoidability	Definitely & possibly avoidable	41	13	<0.001
	Unavoidable	65	128	
Severity	1,2,3	95	135	0.066
	4,5	11	6	

[vii] difference in proportions

Table 2.11 Comparison of causality, avoidability and severity assessments of non-oncology and oncology ADRs

Assessment	Score	Non-oncology ADRs (n=127)	Oncology ADRs (n=120)	p-value[vii]
Causality	Definite & Probable	55	111	<0.001
	Possible	72	9	
Avoidability	Definitely & possibly avoidable	46	8	<0.001
	Unavoidable	81	112	
Severity	1,2,3	114	116	0.032
	4,5	13	4	

2.4 Discussion

This is the first large scale study of the contribution of off-label and unlicensed prescribing to the risk of ADR-related hospital admissions. In this study exposure to off-label and/or unlicensed medicines, in the two weeks before admission, was not a significant predictor of ADR risk. However both the number of authorised and the number of off-label or unlicensed medicines administered in the two weeks before admission were significant predictors of ADR risk. This increased risk associated with off-label and unlicensed medicine use was also seen in the analysis of medicine courses; off-label and unlicensed medicines were more likely to be implicated in an ADR than authorised medicines. Given that oncology drugs were a major risk factor in causing ADRs in this study, further analyses showed that, when oncology patients were excluded, the number of off-label or unlicensed medicines was not a significant predictor of ADR risk and the risk of an unlicensed or off-label medicine being implicated in an ADR was not significantly greater than that for an authorised medicine. This shows that the data from our whole population was strongly influenced by the characteristics of the oncology sub-population with its high rate of off-label and unlicensed medicine use and by the therapeutic regimens for which we would anticipate toxicity.

The results described here cannot be compared easily with those of similar studies since this is the first large admissions study of this type. Furthermore, the statistical methods employed by previous authors have varied. Although 17.7% of our ADRs were due to medicines prescribed in community settings, 82.3% (205/247) of ADRs involved prescription medicines originating from hospital and so we will also compare our findings to previous hospital-based studies. Compared here are the findings of seven prospective studies: one study of admissions, four studies of inpatients and two community-based studies.

In a prospective study of ADRs causing admission (Posthumus et al., 2012), the off-label or unlicensed status of the medicines implicated in ADRs was reported. 683 acutely admitted patients were separated into two groups, ADRs were reported for those exposed to cancer chemotherapy and those not exposed. The overall ADR rate was 6.9%, compared to our 2.2%. The definitions of off-label and unlicensed medicine use were the same as in this study. Amongst 47 patients exposed to cancer chemotherapy there were 32 ADRs of which 84% involved off-label or unlicensed drugs. Of 636 patients not exposed to cancer chemotherapy, 15 were admitted due to an ADR. 33% of these ADRs were due to off-label or unlicensed drugs. Medicines not involved in ADRs were not classified so no change in

ADR risk associated with off-label or unlicensed medicine use could be calculated. The results of this study, like ours, are indicative of the influence of oncology treatment on studies of off-label and unlicensed medicine use and ADRs - a greater proportion of oncology ADRs involved off-label and unlicensed medicines.

There have been three previous prospective inpatient studies of off-label and unlicensed medicine use and ADRs, all of which reported a higher ADR incidence than this study. In agreement with our findings, Turner et al. (1999) reported that off-label and unlicensed medicines were more likely to be implicated in an ADR than authorised medicines (RR 1.46, 95% CI 1.11, 1.93). Multivariate analysis demonstrated a non-significant relationship between off-label and unlicensed drug use and ADR risk, (RR 1.74, 95% CI 0.89, 3.41, p=0.106). The incidence of ADRs in their study was 116/1046 (11%) and the proportion of off-label and unlicensed prescriptions was similar to that in our study 1574/4455 (35%). However, they did not include oncology patients. In contrast with our findings, Neubert et al. (2004) reported no significant difference in the number of off-label or unlicensed medicines implicated in ADRs compared to the number of medicines not defined as off-label or unlicensed (RR 1.08. 95% CI 0.50, 2.35). Patients receiving at least one off-label or unlicensed medicine experienced an ADR significantly more frequently than those receiving only medicines not defined as off-label or unlicensed, (RR 3.62, 95% CI 2.23, 5.85). Their finding that exposure to off-label and/or unlicensed medicines increased ADR risk reflects the higher proportion of patients exposed (59% compared to our 40%) and a higher ADR incidence (12.5%). Theirs was a much smaller study (156 patients) and oncology patients were not included. A Brazilian hospital-based study demonstrated that exposure to at least one off-label medicine was associated with an increased ADR risk (RR 2.44, 95% CI 2.12, 2.89) which reflects a higher incidence of off-label and unlicensed medicine use (45.1% of prescriptions) and a higher ADR incidence (19.9%), amongst 265 non-oncology patients (Santos et al., 2008). A fourth hospital-based study included ADRs to medicines administered before admission as well as those to medicines administered in hospital. It included 1619 patients of whom 12 were admitted due to an ADR. No significant association between ADR risk and off-label medicine use was reported (Impicciatore et al., 2002).

In a prospective community-based study, Horen et al. (2002) reported that ADR risk was related to off-label drug use (RR 3.44, 95% CI 1.26, 9.38). In comparison to this study, they recorded a lower proportion of off-label prescriptions (18.9%) as well as a lower ADR incidence (1.41%). In a second community-based study, Kramer et al. (1985) examined only one aspect of off-label use; the administration of a total daily dose greater than that recommended by the manufacturer whether prescribed or secondary to parental overtreatment (NB the latter could be considered an error rather than off-label use). They found that medicines used in this way were more likely to be implicated in an ADR (RR 1.63, 95% CI 1.23, 2.16, $p<0.001$). They did not describe the proportion of patients who had received off-label or unlicensed medicines or the incidence of ADRs.

Multivariate analysis showed that exposure to off-label or unlicensed medicines was not a significant predictor for the development of an ADR which is in accordance with one previous inpatient study (Turner et al., 1999) but contradicts two others (Neubert et al., 2004, Santos et al., 2008). This method of analysis treats exposure to off-label or unlicensed medicines as a characteristic of the patient and fails to take into the account whether those medicines directly contributed to the ADRs. It may be that the predictor variable 'off-label and/or unlicensed medicine exposure' is actually telling us something else about our patients. Previous studies have shown that children who receive these types of medicines may be more likely to be neonates or infants, to consult their general practitioner more often, to receive more prescriptions, to have more specialist referrals or to be cared for by certain specialties e.g. dermatology, cardiology or ophthalmology (Schirm, Tobi and de Jong-van den Berg, 2003, 't Jong et al., 2003, 't Jong et al., 2002a). We conducted an alternative multivariate analysis in which the number of authorised medicines and the number of off-label or unlicensed medicines were predictor variables. Both were significant predictors of ADR risk and the odds ratios were similar (1.25 and 1.23 respectively) which suggests that the number of medicines is a more important predictor than whether they are authorised or not.

From the analysis of medicine courses, off-label and unlicensed medicines were more likely to be implicated in ADRs than authorised medicines. Before discussing this finding further, it is important to highlight that 87.2% of ADRs which involved at least one off-label or unlicensed also involved at least one other medicine (Appendices 2 & 3). Our calculation of relative risk for individual medicines does not describe the relative contribution of individual medicines to each ADR. In some cases the off-label or unlicensed medicine may

not have caused the ADR in the absence of the authorised medicine. Oncology ADRs made up 48.6% of all ADRs but they were significantly more likely to involve at least one off-label or unlicensed medicine than non-oncology ADRs. Hence, oncology ADRs made a substantial contribution to the likelihood of off-label and unlicensed medicines being implicated in an ADR.

ADRs involving off-label and/or unlicensed medicines were more likely to have been classified as unavoidable and their causality was more likely to have been probable or definite (Table 2.12). This can be explained by the fact that oncology ADRs were more likely to involve off-label or unlicensed medicines and were also more likely to be unavoidable and probable or definite (Table 2.13). The majority of oncology ADRs resulted from the unwanted effects of medicines used to treat malignant disease, because of the severity of the disease and the limited treatment options available, many of these reactions were unavoidable. Oncology ADRs were frequently classified as probable or definite because we had confidence in many cases that there was no other likely cause for the signs and/or symptoms. These ADRs are, in general, well characterised and predictable. Since the same medicine was administered intermittently over a period of weeks or months, in accordance with the treatment protocol for these patients, there was a positive re-challenge in many cases and therefore an increased likelihood that the ADR would be classified as 'definite'.

The prospective design of the cohort study had limitations. The recording of a medication history for each participant was recorded at the point of admission by the admitting clinician and clarified soon after admission by the study team. It relied on parents and/or patients recalling and communicating accurately all medicines administered in the preceding two weeks. Clearly there was scope for errors and omissions in this process. The detection of suspected ADRs by the study team relied on two things: a) signs and symptoms associated with the ADR being recorded by the clinical team looking after the patient; and b) the study team suspecting a link between signs and symptoms recorded and the medicines administered before admission. Where signs and symptoms were not recorded or the study team missed the link, the ADR will not have been highlighted or evaluated. The result of these limitations would be an underestimate of ADR incidence, an inaccurate estimate of medicine use and of the contribution of off-label and unlicensed medicines to ADR risk. The classification of medicine courses as authorised, off-label or unlicensed was done retrospectively using information about recent medicine use which had been collected prospectively. A consequence of this approach was that assumptions had to be

made in the classification process (Tables 2.3 & 2.4) and 6.8% of medicine courses could not be classified. It seems unlikely that classification of medicine courses at the time of data collection would have overcome these problems because the requisite details of a medicine used up to two weeks previously may still not have been available. An assumption which may have led to an overestimate of off-label and unlicensed medicine use was the necessity to categorise a course as off-label even if only part of that course had been off-label. Assumptions which may have led to an underestimate of off-label and unlicensed medicine use included the expectation that inhaled anaesthetic use was authorised and that CIVAs doses were prepared in accordance with manufacturers' instructions. The assumption that all neonates were born at term prevented the exploration of off-label medicine use in pre-term infants and may have led to an underestimate of off-label use. Assumptions about intravenous paracetamol, inhaled beclomethasone and cytotoxic drugs may have all led to an underestimate of off-label and unlicensed medicine use. Employing standard rather than actual weight and surface area for some children may have under- or overestimated off-label medicine use.

Our results must be considered in the context of the diversity of off-label and unlicensed medicines and the complexity of the ADRs detected. Different off-label and unlicensed medicines have different propensities to cause ADRs. There are various categories of off-label and unlicensed medicine use (Tables 2.2 & 2.5) some of which may carry a greater risk of being implicated in an ADR than others. For example, Horen et al. (2002) found that there was a significant increase in ADR risk when medicines were used for a different indication than recommended. We must also consider that the same medicine may be classified as off-label or authorised, even in the same patient, depending on the context of its use. The pharmacological and pharmacokinetic profiles of off-label and unlicensed medicines are diverse. A key consideration is whether off-label and unlicensed medicines would be any less likely to be implicated in an ADR if their use was authorised. Finally, in this study, ADRs rarely resulted from the unwanted effects of a single medicine administered to a mildly unwell child. They were more often a result of the administration of multiple medicines to a child unwell enough to require admission to hospital. In these complex cases there was potential for both drug-drug and drug-disease interactions which could not be investigated in the analyses conducted here.

2.5 Conclusion

There is some indication that the use of off-label and unlicensed medicines may contribute to ADR risk in children admitted to hospital but this needs to be investigated in more detail. This finding is influenced by the inclusion of oncology ADRs in this study. Off-label and unlicensed medicines should not be treated as a homogenous group but should be considered according to their individual characteristics both in terms of their propensity to contribute to ADRs and the reasons that they are classified as off-label or unlicensed. A more detailed examination of the characteristics of medicines implicated in ADRs, inclusive of a comparison with those not implicated in ADRs, could inform an understanding of why off-label and unlicensed medicines may be more likely to be implicated in ADRs.

3 ADRs detected in paediatric inpatients – contribution of off-label and unlicensed medicine use to ADR risk

3.1 Introduction

Adverse drug reactions in paediatric inpatients have an incidence ranging from 0.6% to 16.8% (Smyth et al., 2012). The wide variation in incidence can be explained by a number of factors. Although all the studies included children who were inpatients, there was variation in the study settings, for example some were undertaken on paediatric intensive care units whereas other were undertaken on general paediatric wards or surgical wards. In these various settings there would be variation in the extent and severity of the underlying disease for individual patients as well and in the types of medicine being used, both of these factors would be expected to have an impact on ADR rate. The approach to ADR detection varied between studies with some employing multiple approaches in combination, for example case record review, screening of laboratory results and prescription charts, spontaneous reports and ward round attendance. Clearly, some of these approaches are more thorough and systematic than others, this would affect how many ADRs were detected. An understanding of the risk factors for ADRs in this population will inform the development of measures to reduce the burden of ADRs.

Off-label and unlicensed medicine use in children is a potential risk factor for ADRs. In paediatric hospital settings, between 18 and 65% of prescriptions are off-label while 1 to 48% of prescriptions are for unlicensed medicines (Kimland and Odlind, 2012). Three previous studies have investigated the contribution of off-label and unlicensed medicine use to ADR risk in paediatric inpatients. Turner et al. (1999) found that the proportion of unlicensed and off-label medicines administered to paediatric inpatients was significantly associated with ADR risk. Another inpatient study identified that patients who received at least one off-label or unlicensed medicine were more likely to experience an ADR than those who did not (Neubert et al., 2004) while a third study identified that off-label drug use was significantly associated with ADR risk in paediatric inpatients (Santos et al., 2008).

These previous studies did not report any attempt to find reasons for their findings, for example by scrutiny of the types of off-label medicine use or the drug types implicated in ADRS. With the knowledge that off-label and unlicensed medicines are a diverse group of medicines, this study extends the methodology described in the previous chapter. We

hypothesise that some types of off-label or unlicensed medicine use may carry a greater risk than others.

This study aims to describe the contribution of the different types of off-label and unlicensed medicine use to the risk of ADRs in paediatric inpatients.

3.2 Methods

3.2.1 Setting & participants

This was a nested case-control study within a twelve month prospective cohort study of 6601 admissions in a paediatric tertiary referral centre in the UK (Thiesen et al., 2013). The cohort study was carried out between 1st October 2009 and 30th September 2010 and included all patients aged 0-16 years who were inpatients for longer than 48 hours. Patients were not observed in theatre, recovery, the department of radiology, paediatric intensive care unit (PICU), the hospital's transitional care unit (for patients on long term ventilation) or the psychiatry unit. Patients with missing prescription details for their entire stay were excluded. Patients with part of their prescription details missing were assessed on a case-by-case basis and a decision was made on whether to include or exclude them. Some patients had multiple admissions over the study period. The cases for the nested case control study were defined as children on their first admission who had experienced at least one probable or definite ADR (n=694). Cases were matched 1:1 to controls defined as children on their first admission who had not experienced any possible, probable or definite ADRs, but may have had a suspected ADR assessed as unlikely. Matching was by closest date and time of admission, see Appendix 4 for details. A nested-case control design was chosen because the resources were not available to allow us to include all patients from the cohort study. This approach was preferable because it exploited ADR data from all first admissions that experienced at least one probable or definite ADR. The use of a random sample would have resulted in the loss of potentially valuable data from ADR cases not included. This study was part of a larger study which used routinely collected clinical data in an anonymised format. The Chair of Liverpool Paediatric REC informed us that this study did not require individual patient consent or review by an Ethics Committee (Appendix 13).

3.2.2 Data collection

Patients were identified on a daily basis by the use of a twice-daily download from the hospital electronic medical records system (MEDITECH). This file contained details of all admissions whose stay had reached 48 hours since the previous download. The file contained the details required for the patient to be identified and located within the hospital: name and ward, and also details that were required for the final analysis: age, sex and admitting specialty. Each eligible patient was identified by this process and subsequently reviewed every 48 to 72 hours until they were discharged. Reviews were undertaken by one member of a multidisciplinary team which comprised a paediatrician, a paediatric nurse and at least one pharmacist (JRB was one of the pharmacists on the team for the duration of the study). The aim of the initial review was to record the patient's medical and surgical history, reason for admission and medicines administered since admission as well as to identify any suspected ADRs which had occurred since admission. Subsequent reviews aimed to record medicines administered and to identify any ADRs suspected since the last review. Details of medicines administered were recorded for each day of the patient's stay: drug name, dose, frequency, and indication (if this was thought to require clarification). The data required were obtained from one or more of the following sources at the study team's discretion: hospital electronic medical records system (MEDITECH), patient's case notes or bedside charts, the clinical team, the patient themselves or their carer. If an ADR was suspected, these cases were taken through further evaluation by the study team. A case report was compiled by one member of the study team; this described in detail the suspected ADR inclusive of the results of any investigations, any action taken by the clinical team and its outcome. Each suspected ADR report was then subjected to the following assessments: causality using the Liverpool Causality Assessment Tool (LCAT) (Gallagher et al., 2011) and severity using the Hartwig scale (Hartwig, Siegel and Schneider, 1992). JRB prepared the case report for, and evaluated 984 of 2933 ADR cases, JRB also contributed to the causality assessment of case reports prepared by other members of the team.

3.2.3 Classification of Medicines

For each of the 1388 cases and controls, JRB updated the record of medicines administered was updated to include a detailed off-label or unlicensed category for each medicine on each day it was administered. There were 28 possible off-label categories and five unlicensed medicine categories (Tables 3.1 & 3.2).

Table 3.1 Off-label categories

Category	Definition
1	Authorised - medicine used within the terms of its MA
2	Contraindication exists
3	Dose greater than recommended
4	Dose greater than recommended and contraindication exists
5	Not licensed in child of this age (or child below minimum weight stated)
6	Not licensed in child of this age and contraindication exists
7	Not licensed by this route
8	Not licensed by this route and contraindication exists
9	Not licensed by this route or in a child of this age
10	Not licensed by this route or in a child of this age and contraindication exists
11	Not licensed for this indication
12	Not licensed for this indication and contraindication exists
13	Not licensed for this indication or at this dose
14	Not licensed for this indication or at this dose and contraindication exists
15	Not licensed for this indication or at this age
16	Not licensed for this indication or at this age and a contraindication exists
17	Not licensed for this indication or by this route
18	Not licensed for this indication or by this route and a contraindication exists
19	Not licensed for this indication or by this route or at this age
20	Not licensed for this indication or by this route or at this age and a
21	Not licensed for use in children
22	Not licensed for use in children and, a contraindication exists
23	Not licensed for use in children or in adults by this route
24	Not licensed for use in children or in adults by this route and a contraindication
25	Not licensed for use in children or in adults for this indication
26	Not licensed for use in children or in adults for this indication and a
27	Not licensed for use in children or in adults for this indication or in adults by this
28	Not licensed for use in children or in adults for this indication or in adults by this route and a contraindication exists.
29	Category cannot be assigned
30	Theatre medicine

Table 3.2 Unlicensed categories

Category	Definition
31	Prepared extemporaneously
32	Manufactured under a specials manufacturing licence
33	Chemical
34	Import
35	Awaiting a MA (e.g. previous trial medicine)

3.2.3.1 Off-label categories

Off-label use was defined as the use of a medicine outside the terms of its UK marketing authorisation (MA).

The categories for off-label use (Categories 2-28, Table 3.1) were allocated for each medicine according to the reason(s) why their use was deemed off-label when compared to the terms of the MA for that medicine. The terms of the MA were found in the Summary of Product Characteristics (SmPC) available online from the Electronic Medicines Compendium (DataPharm Communications Ltd., 2010). The version of the SmPC which was the most up to date during the study was referred to. The 'date of revision of the text' at the end of the electronic SmPC indicated when the information was last updated, if the document had been updated since the date that the medicine was administered, a paper version of the contemporaneous SmPC was used. If no SmPC was available, the British National Formulary for children (BNF-C) (Paediatric Formulary Committee, 2009/2010) was consulted for details of the product MA. If neither reference source provided adequate clarity of information, the manufacturer of the medicine was contacted.

Off-label categories were assigned by using 'decision trees' which required the user to consider each aspect of medicine use as they followed the diagram in order that the resultant category would describe in detail the type of off-label use (Appendix 5). Category 29 'category cannot be assigned' was used if insufficient information was available to allocate a category. Category 30 'theatre medicine' was introduced because the prospective cohort study did not record theatre medicines for controls and only recorded them for cases where they were implicated, for example in post-operative vomiting). Therefore any theatre medicines which were recorded were highlighted and subsequently excluded. As in the admissions study reported in Chapter 2, rules for the classification of medicines were established. The rules for specific scenarios were those in Table 2.3 (previous chapter) and the additional rules outlined here (Table 3.3). Similarly, the rules for specific medicines and groups of medicines were those outlined in Table 2.4 (previous chapter) and the additional rules outlined here (Table 3.4).

Table 3.3 Additional rules for the classification of licensed medicines by reference to the SmPC

Scenario	Rule
SmPC states 'should be administered to children only if the potential benefits outweigh the risks'	Classify as off-label
Paracetamol dose has been rounded up or down e.g. paracetamol infusion 15mg/kg in a 16.5kg child = 247.5mg rounded up to 250mg	Classify as authorised if difference between calculated and prescribed doses less than or equal to 10% (Johnson et al., 2011)
Medicine administered at greater frequency or for a longer period than the maximum recommended	Consider frequency and duration to be part of the 'dose' recommendation therefore this would be off-label
Dose less than that recommended	Classify as authorised
Prescription record indicates that medicine was administered via a nasogastric tube (NGT)	Ignore this during classification process, prescription records seem to be unreliable, that is the route is often not amended to oral when the NGT is removed

Table 3.4 Additional rules for the classification of specific medicines and groups of medicines

Medicine or medicine group	Rule
Ciprofloxacin + Metronidazole to treat an exacerbation of Crohn's disease	Classify as authorised. Although not an explicit indication, the principle is to use these agents to treat any bacterial contribution to the exacerbation.
Fentanyl injection	Use for post-operative analgesia by continuous infusion in an NCA or PCA should be classified as off-label. It is licensed for use in children >2 years for anaesthesia / intraoperative analgesia.
Flucloxacillin	Classify dose as off-label if it is above the relevant age- and indication-specific range recommended by the BNF-C. The SmPC information on dose is unclear.
Heparin	No preparations in the eMC are indicated for any indication apart from the treatment of thrombotic episodes. Therefore assume that a preparation licensed for use in children has been used but if it is for prophylaxis, consider it to be off-label.
Gentamicin	Follow these recommendations for authorised use: premature infants or neonates up to 2 weeks 3mg/kg 12 hourly and children 2 weeks to 12 years 2mg/kg 8 hourly. Daily paediatric dosing was added to the SmPC in November 2010 after the end of the study.
Ketamine	Use for post-operative analgesia should be classified as off-label. It is licensed for use in children for anaesthesia.
Magnesium sulphate injection	Use in the treatment of acute exacerbations of asthma is off-label. For other indications the maximum single licensed dose is 2g.
Metronidazole	SmPC updated January 2011 to include dosing for children <8 weeks and >8 weeks but BNF-C for the period of the study stated: not licensed for use in neonates or children under one year, so classify as off-label in children under one year.
Morphine injection	One preparation (Minijet™) is licensed for IM, SC, IV injection and IV infusion in children. The SmPC for all other preparations state that use is not recommended in children and one (Hameln brand) specifies that it is not recommended in children <12years. During the period of the study, Martindale and Hameln brands were in use. Therefore, assume Hameln brand was used. If child is <12 years assign category '5' (not licensed in a child of this age) if other aspects of use are authorised. If child is >12 years assign category '1'(authorised) if other aspects of use are authorised

Medicine or medicine group	Rule
Ondansetron intravenous for PONV[viii]	In children >2 years old, any doses which are in addition to a single intra-operative dose + a single post-operative dose are off-label. Amended prescribing recommendations were added to SmPC in December 2010 after the end of the study.
Ondansetron intravenous for CINV[ix]	In children >2 years old, any doses which are in addition to a single pre-chemotherapy dose + two post-chemotherapy doses are off-label. Amended prescribing recommendations were added to SmPC in December 2010 after the end of the study.
Oseltamivir	Over the period of the study, Alder Hey was using oseltamivir capsules and both the licensed Tamiflu 60mg/mL and the unlicensed, Department of Health (DH) product, oseltamivir 15mg/mL which is a manufactured special. Since this product was dispensed for individual patients rather than held as ward stock, refer to pharmacy records for the exact product dispensed for individual patients and categorise accordingly.
Phenytoin doses (including intravenous loading)	Classify dose as off-label if it is above the relevant age- and indication-specific range recommended by the BNF-C. The SmPC information on dose is unclear.

[viii] Post-operative nausea and vomiting
[ix] Chemotherapy-induced nausea and vomiting

3.2.3.2 Unlicensed categories

Unlicensed medicines were defined as those without a UK MA.

A list of each of the unlicensed medicines recorded in the study was produced and with the assistance of a member of the hospital pharmacy staff responsible for the procurement of these products, this list was updated to indicate the type of unlicensed medicine in accordance with one of the five categories outlined (Appendix 6).

3.2.4 Data analysis

Advice on the approach to analysis was obtained from the ADRIC programme statistics team and broadly reflects the approach taken in the cohort study with the exception of the nested case-control design. The analysis of medicines courses was carried out by JRB. The datasets for the univariate and multivariate analyses within the case-control study were prepared by JRB, the analysis was carried out by the statistics team.

The odds ratio with 95% confidence intervals (95% CI) for off-label and unlicensed medicines being implicated in a probable or definite ADR was calculated for all medicines administered in the nested case-control study. The odds ratios (with 95% CI) for each of the off-label and unlicensed categories being implicated in a probable or definite ADR were also calculated. It was recognised that some types of off-label and unlicensed medicine use are rarer than others, for example imported medicines are used infrequently. It was acknowledged that if there were too few medicine courses in a category or if no medicines within a category were implicated in an ADR, it would not be possible to determine the odds ratio for that category.

A univariate analysis was undertaken; time to first ADR was compared between groups using a log-rank test and Kaplan-Meier curves were estimated. The following categorical variables were compared: gender, age category and oncology status. A Cox univariate regression analysis was undertaken to compare ADR risk in the group that had received a GA and those who had not (categorical time-varying variable). A multivariate Cox proportional hazards regression model was fit to the data to assess the influence that off label and unlicensed medicine use has on the hazard of an ADR occurring (discrete time-varying). In addition to the number of off-label and unlicensed medicines administered during the admission, the following risk factors were included in the model: age, gender, having received a general anaesthetic (GA) during the admission, oncology patient status

and the number of authorised medicine courses administered during the admission. Due to their clinical importance, all risk factors remained in the final model. Results are given in terms of the hazard ratio (HR) together with the accompanying 95% CI and p-value. The analysis was carried out using the statistical software package R (version 2·13·2) using a significance level of 0·05 (5%) throughout.

3.3 Results

3.3.1 Participants & descriptive data

In this study, there were 754 male and 634 female patients, 21.2% were < 1 year old, 24.6% were 1-4 years, 27.7% were 5-11 years and 26.6% were teenagers (> 12 years). The median age of patients was 5.96 years (inter-quartile range (IQR) 1.36-12.43 years). There were 43 oncology patients (3.1% of all patients) and 873 patients (62.9% of all patients) received a general anaesthetic. The median daily number of medicines was 3 (IQR 1-5), the median daily number of authorised medicines was 2 (IQR 1-3) and the median daily number of off-label and unlicensed medicines was 1 (IQR 0-2).

3.3.2 Medicine courses

10,699 medicine courses were administered to the 1388 patients included in this study. There were 723 probable and 62 definite ADRs which involved 694 patients. Of these ADRs, 505 involved one medicine course, 172 involved two medicine courses, 77 involved three medicine courses and the remaining ADRs involved four or more medicine courses. Of the 10, 699 medicine courses, 10, 145 could be categorised using one of the definitions listed in Tables 3.1 and 3.2. The reason that 554 (5.2%) of courses could not be categorised was that the prescription record did not provide the required information, for example missing dose information or insufficient detail about the exact preparation used. 301 (38%) of ADRs involved only off-label or unlicensed medicines, 290 (37%) of ADRS involved only authorised medicines, 160 (20.4%) involved a combination of off-label or unlicensed and authorised medicines and the remaining 34 (4.3%) involved at least one medicine for which the category was unknown.

6990 (68.8%) of all medicine courses were authorised, 2407 (23.7%) were off-label and 758 (7.5%) were unlicensed. 435 (6.2%) of all authorised medicine courses were implicated in at least one probable or definite ADR compared with 298 (12.4%) of off-label medicine courses and 113 (14.9%) of unlicensed medicine courses. The odds ratio (OR) of an

unlicensed or off-label medicine being implicated in an ADR when compared with an authorised medicine course was 2.25 (95% CI 1.95, 2.59, p<0.001).

The three most common categories of off-label medicine use represented 85.2% of all off-label medicine courses. In order of frequency they were: Category 11: not licensed for this indication, Category 3: dose greater than recommended and Category 5: not licensed in a child of this age, or child below minimum weight stated. Category 11 was the most common off-label category (764 courses). 257 courses were ondansetron for indications other than post-operative or cytotoxic-induced nausea and vomiting (CINV or PONV). 136 courses were fentanyl by intravenous infusion for post-operative analgesia. 105 courses were intravenous dexamethasone for the management of nausea and vomiting or oral dexamethasone for the management of nausea and vomiting other than CINV and 78 courses were ketamine by intravenous infusion for post-operative analgesia. The second most common category was Category 3 (698 courses) of which 484 were paracetamol at a dose of 15-20mg/kg. This weight-based dosing frequently resulted in a greater dose being prescribed and administered than that recommended, by age band, in the BNF-C. We referred to the contemporaneous BNF-C age-related dose recommendations to categorise paracetamol courses (Paediatric Formulary Committee, 2009/2010). 79 Category 3 medicine courses were nebulised or inhaled salbutamol at a greater frequency than recommended in the SmPC. Salbutamol nebules were administered every 20–30 minutes or as necessary and metered dose inhalers were used to deliver 100mcg every 15–30 seconds up to a maximum of 10 puffs, both in accordance with British Thoracic Society Guidelines as summarised in the BNF-C at that time (Paediatric Formulary Committee, 2009/2010). 69 of the Category 3 courses were intravenous gentamicin as a single daily dose. The third most common category was Category 5 (588 courses). 186 of these were morphine by continuous intravenous infusion, the SmPC for the morphine brand in use during the study stated that it was not suitable for use in children younger than 12 years old. 111 of the Category 5 courses were oral paracetamol; these were courses of oral paracetamol in children younger than 2 months.

The most common category of unlicensed medicine use was Category 32: manufactured under a specials licence (577 courses) which represented 76% of all unlicensed medicine courses: 142 diclofenac 10mg dispersible tablet, 106 fentanyl + levobupivicaine epidural, 69 spironolactone oral suspension and 58 midazolam oral or buccal solution (Table 3.5).

The proportion of medicine courses from each category which were implicated in at least one probable or definite ADR (PD ADR) was calculated and this was compared to the 6.2% of authorised medicine courses implicated (Table 3.5). Eighteen off-label and unlicensed categories were utilised (excluding 'authorised', 'unknown' and 'theatre medicine'). There were seven categories in which none of the medicine courses were implicated in an ADR and one in which only one of courses was implicated, the largest of these categories contained 21 medicine courses. There were four categories which contained small numbers of medicine courses, the largest of these contained 61 medicine courses. In two of these categories the confidence interval for the odds ratio demonstrated non-significance and in the remaining two it was indicative of imprecision, a consequence of the small number of courses identified. Considering only the remaining six categories, medicines licensed for use in children but given at a dose greater than recommended (Category 3) had a lower risk of being implicated in an ADR than authorised medicines (2.7% implicated, OR 0.42, 95% CI 0.26, 0.67). Medicines licensed in children but given to a child below the minimum age or weight had the greatest risk of being implicated in an ADR (19.0% implicated, OR 3.54, 95% CI 2.82, 4.44) followed by medicines not licensed for use in children at all (18.6% implicated, OR 3.44, 95% CI 2.41, 4.91). Medicines administered for a different indication were more likely to implicated in an ADR than authorised medicines (14.3% implicated, OR 2.50, 95% CI 2.00, 3.13). Amongst unlicensed medicines, medicines manufactured under a specials licence were the most likely to implicated in an ADR (14.9% implicated, OR 2.64, 95% CI 2.05, 3.38), followed by medicines prepared extemporaneously (14.7% implicated, OR 2.59, 95% CI 1.61, 4.16).

Table 3.5 Number of medicine courses in each authorised, off-label or unlicensed category and number implicated in at least one PD ADR

Category	Definition	Number of medicine courses	% of courses implicated in at least one PD ADR	Odds ratio of ADR vs. Authorised	95% confidence interval
1	Authorised	6980	6.2	1.00	-
2	Contra-indication exists	1	0	-	-
3	Dose greater than recommended	698	2.7	0.42	0.26, 0.67
5	Not licensed in a child of this age (or child below minimum weight stated)	588	19.0	3.54	2.82, 4.44
6	Not licensed in a child of this age and a contraindication exists	1	0	-	-
7	Not licensed by this route	61	9.8	1.64	0.70, 3.83
11	Not licensed for this indication	764	14.3	2.50	2.00, 3.13
13	Not licensed for this indication or at this dose	8	0	-	-
15	Not licensed for this indication or at this age	35	25.7	5.21	2.43, 11.18

Category	Definition	Number of medicine courses	% of courses implicated in at least one PD ADR	Odds ratio of ADR vs. Authorised	95% confidence interval
17	Not licensed for this indication or by this route	21	0	-	-
19	Not licensed for this indication or by this route or at this age	2	0	-	-
21	Not licensed for use in children	215	18.6	3.44	2.41, 4.91
22	Not licensed for use in children and, a contraindication exists	1	100.0	-	-
23	Not licensed for use in children or, in adults by this route	1	0	-	-
25	Not licensed for use in children or, in adults for this indication	11	18.2	3.34	0.72, 15.52
31	Prepared extemporaneously	143	14.7	2.59	1.61, 4.16
32	Manufactured under a specials manufacturing licence	577	14.9	2.64	2.05, 3.38
33	Chemical	1	0	-	-
34	Import	37	16.2	2.91	1.21, 7.02

For medicine types with more than 100 courses administered, the proportion of medicine courses implicated in a probable or definite ADR is presented alongside the proportion of those courses which were categorised as off-label or unlicensed (Table 3.6). Fentanyl via any route excluding epidural administration had the greatest proportion of courses implicated in an ADR (48.0%) and 99.3% of courses were off-label. 44.3% of epidural fentanyl courses were implicated in an ADR with 100% of courses categorised as unlicensed. 39.6% of morphine courses were off-label or unlicensed. 28.5% of authorised morphine courses and 44.9% of off-label and unlicensed courses were implicated in at least one ADR.

Table 3.7 shows the four most frequently implicated medicines and which off-label and unlicensed categories were assigned to them. These medicines were intravenous fentanyl, epidural levobupivicaine + fentanyl, morphine by any route and codeine by any route. The details of the ADRs in which these four medicines were implicated are as follows:

Intravenous fentanyl: 48% of fentanyl courses (all off-label) were implicated in 136 ADRs, most commonly pruritus (49), constipation +/- abdominal pain (22) and vomiting (19). We examined the use of fentanyl leading to severe ADRs (Hartwig scale 4-6). There were only two severe ADRs secondary to fentanyl, both were severity level 4 (resulted in patient transfer to a higher level of care). One case was a respiratory arrest in a 9 year old; drugs received for general anaesthesia were also implicated in the ADR. The second case was respiratory depression in a 15 year old, intravenous ketamine infusion was also implicated. Both patients were receiving fentanyl at a rate of 1mcg/kg/hr.; the record of bolus doses was unreliable.

Fentanyl + levobupivicaine epidural: 47 courses of fentanyl + levobupivicaine via the epidural route (all manufactured under a specials licence) were implicated in 106 ADRs, most commonly: pruritus (26), constipation +/- abdominal pain (20) and vomiting (19). There were no severe ADRs (Hartwig scale 4-6) secondary to fentanyl + levobupivicane via the epidural route.

Morphine via any route: Amongst the authorised morphine courses, 60.3% were administered to children aged 12 years or older. Almost all of the off-label morphine courses were administered to children younger than 12 years (99%). 28.5% of authorised morphine courses were implicated in 142 ADRs, most commonly pruritus (42), constipation +/- abdominal pain (39) and vomiting (29). 44.9% of off-label morphine courses were implicated in 173 ADRs, and the most common ADR types were the same as those caused by authorised morphine courses: pruritus (78), vomiting (31) and constipation +/- abdominal pain (15). There were no severe ADRs (Hartwig scale 4-6) secondary to morphine.

Codeine via any route: 13.2% of codeine courses were implicated in 101 ADRs (all implicated courses were oral). 49/483 (10.1%) of authorised courses were implicated in 67 ADRs and 80.6% of these ADRs were constipation. 31.2% of codeine courses could not be categorised because the preparation used was not recorded on the prescription. 33/257 (12.8%) of uncategorised courses were implicated in 34 ADRs and 73.5% of these were constipation. There were no severe ADRs (Hartwig scale 4-6) secondary to codeine.

Table 3.6 Medicines course frequency administered, implicated and off-label, unlicensed or unknown. Greatest proportion of courses implicated first (only medicines with > 100 courses shown, n=7007)

Medicine	No. of courses	% of courses implicated	No. of courses off-label	No. of courses unlicensed	% of courses off-label	% of courses unlicensed	No. of courses unknown
Fentanyl	150	48.0	149	0	99.3	0	0
Fentanyl & Levobupivicaine epidural	106	44.3	0	106	0	100	0
Morphine	500	35.0	197	1	39.4	0.2	0
Codeine Phosphate	752	13.2	9	3	1.2	0.4	257
Furosemide	123	9.8	13	0	11.8	0	0
Cefotaxime	388	9.0	0	0	0	0	0
Salbutamol	146	8.9	84	0	56.8	0	0
Metronidazole	257	7.8	21	0	8.2	0	0
Cefalexin	148	7.4	9	0	6.1	0	0
Dexamethasone	166	6.6	107	0	64.5	0	7
Ondansetron	550	5.8	290	0	52.7	0	48
Cefuroxime	245	4.5	0	0	0	0	1
Lactulose	272	2.2	13	0	4.8	0	0
Diazepam	107	1.9	2	0	1.9	0	0
Diclofenac	331	1.5	7	142	2.1	42.9	159
Ranitidine	109	0.9	65	0	59.6	0	0
Ibuprofen	545	0.7	26	0	4.8	0	0
Chlorphenamine	339	0.3	1	0	0.3	0	1
Paracetamol	1786	0.1	596	0	33.4	0	2

Table 3.7 Off-label and unlicensed category proportions for medicines with >10% of courses implicated

Category	Definition	Count of medicine courses (count of courses implicated in an ADR)			
		Fentanyl	Fentanyl & Levobupivicaine Epidural	Morphine	Codeine
1	Authorised	1 (0)	-	302 (86)	483 (49)
3	Dose greater than recommended	-	-	2 (0)	-
5	Not licensed in a child of this age (or child below the minimum weight stated)	1 (0)	-	189 (88)	9 (0)
11	Not licensed for this indication	136 (66)	-	6 (1)	-
15	Not licensed for this indication or at this age	12 (6)	-	-	-
29	Category cannot be assigned	-	-	-	257 (33)
32	Manufactured under a specials manufacturing licence	-	106 (47)	1 (0)	3 (0)
	Total	**150 (72)**	**106 (47)**	**500 (175)**	**752 (99)**

3.3.3 Univariate analysis

Gender, age, oncology patient status and receipt of a general anaesthetic (GA) were the variables examined in the univariate analysis (Table 3.8 & Figures 3.1-3.3). There was no difference in the time to first ADR between males and females; children in the teenage category (>12 years) were at greatest risk of experiencing an ADR, with neonates at the lowest risk. Oncology patients were more likely to experience an ADR than non-oncology patients and patients who had received a GA were more likely to experience an ADR than those who had not.

Table 3.8 Univariate analysis

Variable		ADR	No ADR	Kaplein-Meir Curve	p-value
Gender	**Male**	382	372	Figure 1	0.446[x]
	Female	312	322		
Age	**Infant: < 1 years**	78	322	Figure 2	<0.001[xi]
	Pre-school: 1 to 4 years	155	186		
	School-aged: 5 to 11 years	231	153		
	Teenage: >12 years	230	139		
Oncology status	**Oncology**	38	5	Figure 3	<0.001[xi]
	Non-oncology	656	689		
GA exposure	**GA**	533	340	-	< 0.001[xi]
	No GA	161	354		

[x] Log-rank test for significant difference between curves
[xi] Cox univariate regression for significant difference between curves

Figure 3.1 Univariate analysis of gender

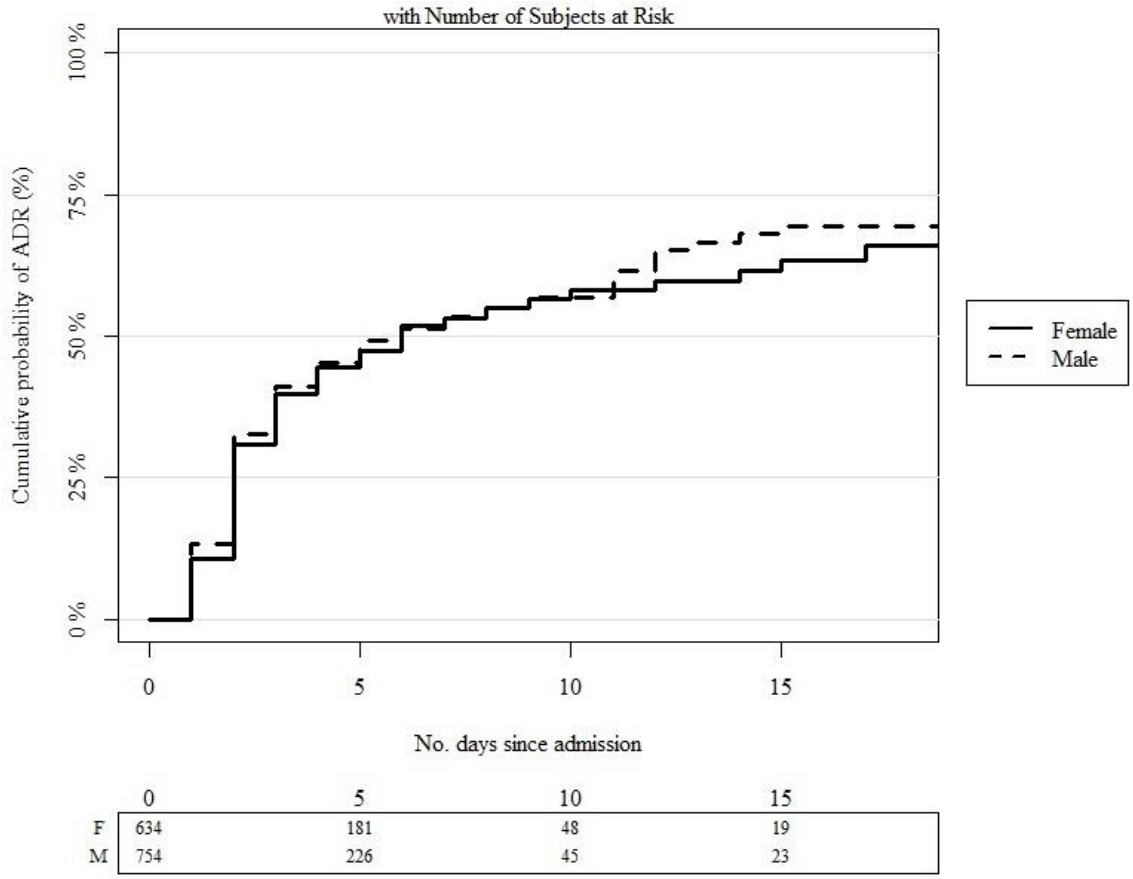
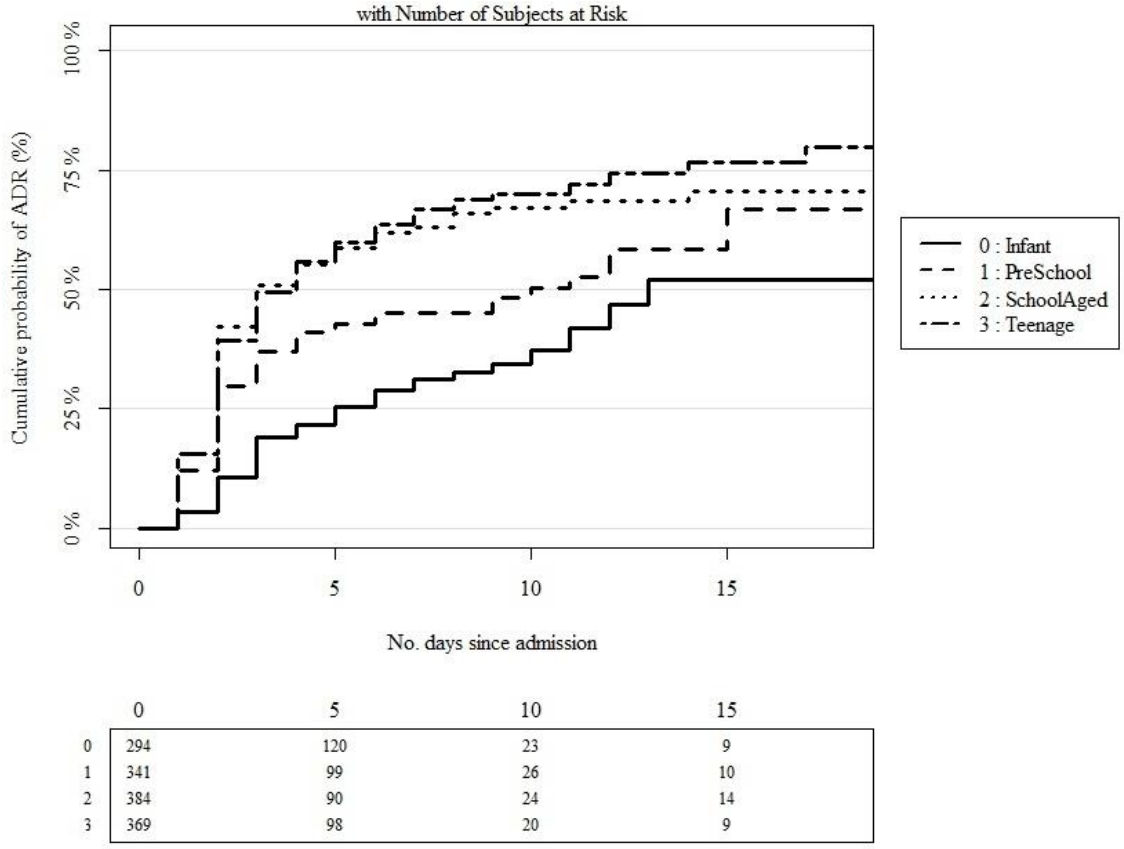


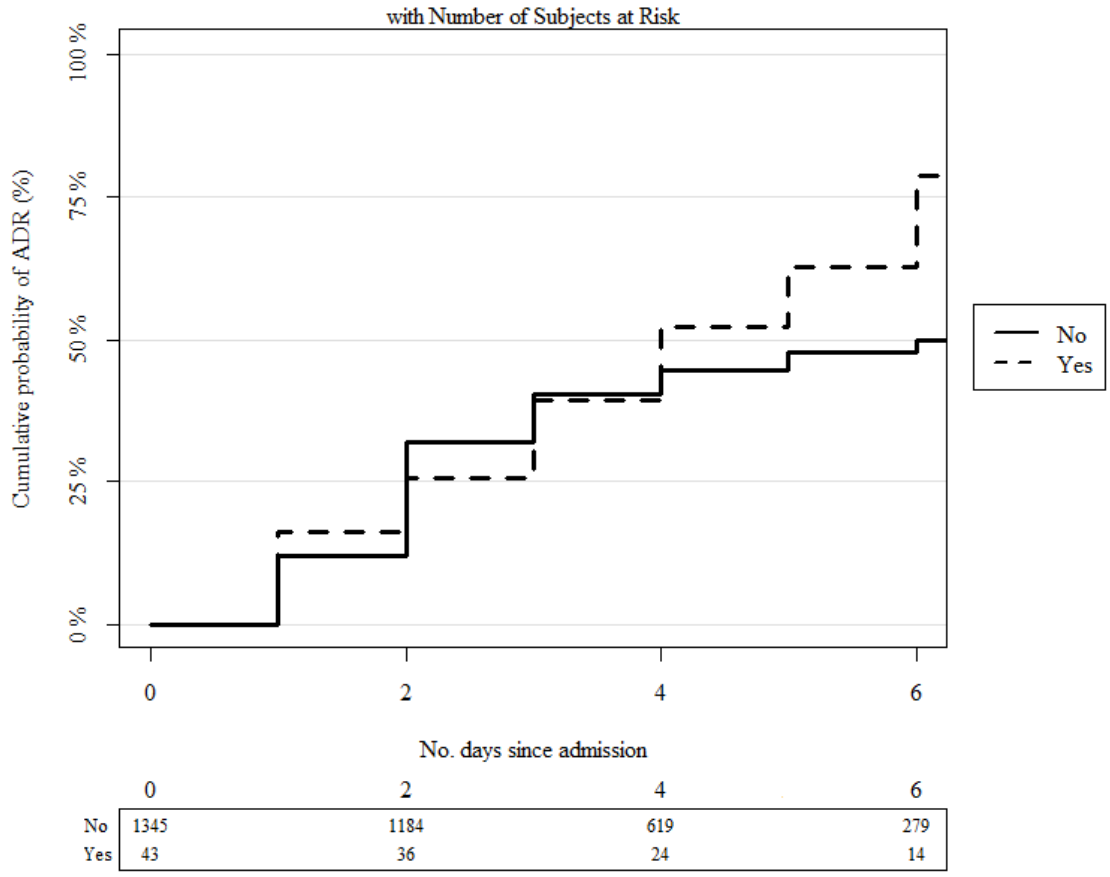
Figure 3.2 Univariate analysis by age category[xii]



	0	5	10	15
0	294	120	23	9
1	341	99	26	10
2	384	90	24	14
3	369	98	20	9

[xii] Infant: < 1 years, Pre-school: 1 to 4 years, School-aged: 5 to 11 years, Teenage: >12 years

Figure 3.3 Univariate analysis by oncology patient status[xiii]



[xiii] No = non-oncology patient, Yes = oncology patient

3.3.4 Multivariate analysis

All patients (n=1388) were included in the multivariate analysis. All variables included in the univariate analysis were included in the model due to their clinical importance, the number of authorised, off-label or unlicensed and unknown medicines per day were also included. Age on admission and receipt of a GA each had a significant effect on ADR risk. The risk of an ADR increased with each year increase of age. Gender and oncology patient status did not have a significant effect on the hazard of an ADR. Each additional off-label and/or unlicensed medicine given per day significantly increased the risk of an ADR (HR 1.27, 95% CI 1.20, 1.34, p<0.001). Similarly, each unit increase in the number of authorised medicines in a single day also significantly increased the hazard of an ADR (HR 1.22, 95% CI 1.17, 1.26, p <0.001) (Table 3.9).

Table 3.9 ADR risk factors assessed by multivariate analysis

Predictor		HR (95% CI)	p-value
Gender	**Female**	1	0.152
	Male	0.90 (0.77, 1.04)	
Age on admission (years)		1.04 (1.02, 1.05)	<0.001
Received a GA	**No**	1	<0.001
	Yes	5.30 (4.42, 6.35)	
Oncology	**No**	1	0.655
	Yes	0.93 (0.66, 1.30)	
Number of authorised medicines		1.22 (1.17, 1.26)	<0.001
Number of OLUL medicines		1.27 (1.20, 1.34)	<0.001
Number of uncategorised medicines		1.14 (0.97, 1.34)	0.116

3.4 Discussion

This is the largest study of this kind undertaken. Off-label and unlicensed medicines were significantly more likely to be implicated in a probable or definite ADR than authorised medicines. In a survival analysis model, the number of off-label and/or unlicensed medicines administered was a significant predictor of ADR risk but so was the number of authorised medicines.

One of the key limitations of the observational study design was that signs, symptoms or measurements indicative of an ADR which were not detected and recorded by the clinical team looking after the child could not be detected by the study team. A nested case-control design was appropriate to test our hypotheses in the context of the resources we had available and the detailed evaluation of each prescription that was required. Controls were matched to cases using the nearest date and time of admission in order to avoid using as matching criteria any of the variables we planned to examine. As this study takes much of its dataset from a larger prospective study, there is no reason to suppose that the quality of data available for our variables of interest was any different between cases and controls. The study may have had greater power to detect differences between patients who experienced an ADR and those who did not if cases had been matched to controls in a ratio of 1:2 or 1:3 rather than 1:1. This limitation is illustrated in this study by the fact that, in contrast to the main cohort study (Thiesen et al., 2013), we did not demonstrate a significant difference in ADR risk between oncology and non-oncology patients. Another limitation was the necessity for a minimum amount of information to be available for medicine categorisation, this led to 5.2% of medicine courses not being categorised and consequently being excluded from the risk analysis. This limitation could only have been overcome by requesting a change to prescribing practice i.e. recording of drug name and preparation on every prescription; this was not achievable. Further limitations result from the assumptions outlined in the methodology which pertain to the SmPC definitions of age, gestational age and the classification of cytotoxic medicines.

In our study, 23.7% of medicine courses were off-label and 7.5% were unlicensed. The percentage of off-label prescriptions in observational studies of paediatric inpatient prescribing ranges from 18 to 60%, the percentage of unlicensed prescriptions in these studies ranges from 3.4 to 36% (Cuzzolin, Atzei and Fanos, 2006). Turner et al. (1999) conducted a similar study at Alder Hey which was published in 1999, they found that 35% of prescriptions were off-label or unlicensed. With the introduction of the paediatric

regulation in 2007 (The European Parliament and the Council of the European Union, 2006) it might be assumed that, 5 years on, the incidence of off-label and unlicensed prescribing would be less, our results show that this is not the case. The European Medicines Agency Paediatric Committee's 5-year report to the European Commission indicated that by the end of 2011, 29 PIPs had been completed leading to new paediatric indications for 24 medicines and to new pharmaceutical forms appropriate for children for 7 medicines. Between 2008 and 2012, 10 out of 113 new centrally authorised medicinal products received a paediatric indication (out of 113 new active substances in total). For one of these products, a Paediatric Use Marketing Authorisation (PUMA) was granted. For medicines already authorised centrally or nationally, 18 and 12 respectively, received a new paediatric indication (European Medicines Agency with its Paediatric Committee, 2012).

In our study, based in a large paediatric tertiary referral centre, off-label and unlicensed medicines were significantly more likely to be implicated in an ADR than medicines used within the terms of their MA, OR 2.25 (95% CI 1.95, 2.59). This was a greater increase in risk than that reported in previous inpatient studies. In their study of paediatric outpatients, Horen et al. (2002) reported a similar risk for off-label medicines (RR 3.44 95% CI 1.26, 9.38) however the design and setting of this study were dissimilar to ours. The odds ratio reported here summarises the likelihood of individual medicines being implicated in an ADR but it does not reflect the complexity of the dataset. 20.4% of ADRs involved a combination of off-label and/or unlicensed and authorised medicines and some medicines were involved in multiple ADRs. The authors of two previous prospective inpatient studies have reported on the likelihood of off-label and unlicensed medicines being implicated in ADRs. Turner et al. (1999) found a smaller but still significant increase in ADR risk associated with off-label and unlicensed medicines (relative risk 1.46, 95% CI 1.11, 1.93). We used the same definitions of off-label and unlicensed medicine but included more than twice the number of medicine courses. Although carried out at the same centre as ours, their study was carried out on fewer wards and included some different ward types: PICU, cardiac ICU, neonatal surgery, a medical ward and a surgical ward; their cohort of patients may have a different medicine use profile and/or susceptibility to ADRs. Neubert et al. (2004) reported a small non-significant increase in ADR risk with off-label and unlicensed medicine use (relative risk of 1.08, 95% CI 0.50, 2.35). Theirs was a smaller study based on a single paediatric isolation ward, this is reflected in the nature of the adverse drug reactions they observed and the medicines implicated in them. They used different definitions of off-label and unlicensed medicine use, they compared the official licence information with the

patient's age, the dose of the medicine given and the route it was given by but indication was not considered.

The three most common categories of off-label medicine use in our study were: Category 11: not licensed for this indication, Category 3: dose greater than recommended and Category 5: not licensed in a child of this age, or child below minimum weight stated. The most common category of unlicensed medicine use was Category 32: manufactured under a specials licence. Two previous inpatient studies have described in detail the categories of off-label and unlicensed medicine use. Santos et al. (2008) used different definitions to ours; unlicensed medicines were those contraindicated in children, extemporaneous products and medicines for which safety and efficacy have not been established in children. In their off-label assessment they considered age or weight, dose or frequency, route and formulation. They found that the most frequent off-label reason was dose/frequency different from that recommended in local pharmaceutical references followed by age/weight different from that recommended and that the most frequent type of unlicensed medicine was 'safety and efficacy have not been established in children'. The categories used by Neubert et al. (2004) are outlined earlier in this discussion, they reported that the only type of unlicensed medicine use was modification to licensed medicines and the most common type of off-label use was use at an inappropriate age, they did not consider indication.

To our knowledge, there are no previous inpatient studies which compare ADR risk for authorised and off-label and unlicensed medicine use categories. In a community-based study Horen et al. (2002) reported that a significant increase in ADR risk with medicines used for different indication, the risk was greater than that found in our study (RR 4.42 95% CI 1.60, 12.25). Jonville-Bera et al. (2005) studied medicines implicated in spontaneous ADR reports and found that the most common categories were indication not authorised and precautions for use not being respected. Our ability to consider the odds of each category being implicated in an ADR was limited by the low number of courses in some categories. Medicines given at a dose greater than recommended (Category 3) had a lower risk of being implicated in an ADR than authorised medicines; this can be explained by the fact that this category is dominated by paracetamol courses which were frequently off-label (but followed national peer-reviewed guidance (Anonymous 2012)), only one paracetamol course was implicated in an ADR. When the analysis was repeated without any paracetamol courses, the proportion of authorised medicines implicated in an ADR increased from 6.2%

to 7.5% and Category 3 medicines had a greater risk of being implicated in an ADR than authorised medicines, 8.9% courses were implicated (OR 1.20, 95% CI 0.74, 1.94).

We examined, with reference to their off-label or unlicensed status, the use of the four medicine types for which more than 10% of courses were implicated in at least one ADR (Table 3.7). Notably, these medicines are all opioids mainly used in the management of post-operative pain. This is reflective of the case-mix within this study; 873 of 1388 (62.9%) patients received a general anaesthetic. We can assume that, within a tertiary care setting and with the inclusion of only those patients who had been in hospital for longer than 48 hours, the majority of these general anaesthetics were given for major operative procedures following which opioids were required to provide adequate analgesia.

Intravenous fentanyl: 99.3% of intravenous fentanyl courses were off-label because the commonly used infusion and bolus doses used for nurse- and patient-controlled post-operative analgesia (NCA and PCA) are not found in the SmPC for this medicine. The use of fentanyl in this way is not mentioned in the BNF-C but is recommended at a rate of 0.5-2.5mcg/kg/hr. in a UK peer-reviewed guideline. (Anonymous 2012, Monitto et al., 2000) Although the administration of fentanyl via NCA or PCA is off-label using our definition, there is an evidence base for its use. If this use was authorised there is no obvious reason why the frequency of the most common ADRs (pruritus, constipation and vomiting) would be diminished. There may be other characteristics of these patients which made them susceptible to these ADRs, for example underlying disease, but these have not been investigated here.

Fentanyl + levobupivicaine epidural: All fentanyl + levobupivicaine epidural courses were unlicensed. Peer-reviewed guidelines (Anonymous 2012) recommend the use of fentanyl + levobupivicaine via the epidural route at a rate of 0.3-0.8mcg/kg/hr. to manage post-operative pain, following certain procedures in children. Local guidelines in use during this study recommended a rate of 0.1-0.3mcg/kg/hr. If we assume that the epidural infusion we use delivers an accurate dose there is no reason to suppose that the use of a licensed infusion would result in fewer ADRs.

Morphine via any route: 35% of morphine courses (via any route) were implicated in an ADR (Table 3.6). The most common route was via NCA or PCA. A UK peer-reviewed, evidence-based guideline (Anonymous 2012) recommends: NCA background 0-0.02mg/kg/hr. (0mg/kg/hr. if patient <5kg), 0.01 – 0.02 mg/kg bolus with a 20-30 minute

lock-out period, PCA background 0.004mg/kg/hr., 0.01-0.02mg/kg bolus with a 5-10 minute lock-out. Morphine NCA and PCA guidelines at Alder Hey correspond to this with the exception that the NCA guideline recommends a background infusion from birth (regardless of patient weight) and a 15 minute lock-out period. Authorised and off-label morphine courses were not uniformly distributed across the age groups in our study population. Only one off-label course was administered to a child 12-16 years old whereas amongst 316 courses given to children under 12 years old, 196 (62.0%) were off-label. Our data indicate that off-label morphine courses are more likely to be implicated in an ADR. One possible interpretation of this is that children under 12 years old are more susceptible to ADRs. However, on closer inspection of the data, the proportion of morphine courses implicated in an ADR was similar in both age groups: 110/316 (34.8%) in children <12 years old and 65/184 (35.3%) in children 12-16 years old. In children under 12 years old, 88/197 (44.7%) of off-label courses and 22/119 (18.5%) of authorised courses and were implicated in at least one ADR (Chi-square test for difference in proportions $p<0.001$). Amongst children under 12 years old, the mean age of those who received off-label morphine was less than the mean age of children who received authorised morphine; 4.9 years (SD 3.8) vs. 6.2 years (SD 3.5), Student's t-test for difference between means $p = <0.001$. Therefore, off-label morphine was more likely to be implicated in an ADR and younger children were more likely to receive off-label morphine. Because of developmental differences in pharmaco - kinetics and – dynamics, younger children may be more likely to experience an ADR to morphine. In terms of metabolism, glucuronidation of morphine occurs in the liver of neonates and infants but it is unclear whether the capacity of the liver is fully mature (Kart, Christrup and Rasmussen, 1997a). The half-life of morphine decreases and its elimination increases up to the age of two months; in children older than this these parameters are similar to those in adults (Kart, Christrup and Rasmussen, 1997a). The quantity and location of opioid receptors and their affinity for morphine may change with age and the immature blood-brain barrier in very young children may also influence the effects of morphine (Kart, Christrup and Rasmussen, 1997b). In a large-scale clinical study of morphine NCA use in children, neonates were significantly more likely than older children to experience serious adverse events (respiratory depression or over-sedation for which active resuscitation measures were taken and naloxone was administered) (Howard et al., 2010). Conversely, the risk of 'non-serious' cases of respiratory depression and sedation and post-operative nausea and vomiting increased with increasing age. The incidence of pruritus was similar across all ages (with the exception of neonates, amongst whom the incidence was low). Data on the incidence of constipation was not collected. As in the case of fentanyl, there

are likely to be other pre-disposing patient-related factors which we have not examined here. For example, morphine pharmacokinetic parameters may be affected by surgery or cardiac state (Kart, Christrup and Rasmussen, 1997a). The pharmacodynamics of morphine may also affected by the clinical state of the patient if severe illness alters the pattern of opioid receptor expression and affinity (Kart, Christrup and Rasmussen, 1997b).

Codeine via any route: None of the nine off-label codeine courses were implicated in an ADR. If we assume that the majority of 'unknown' courses were authorised, authorised codeine courses were more likely to be implicated in an ADR than off-label courses. If we assume that the majority of 'unknown' courses were off-label, the proportion of authorised and off-label courses implicated in at least one ADR is similar. Therefore, we do not have any evidence that ADRs are more likely with off-label codeine use. Codeine was implicated alongside at least one other medicine in 81/101 ADRs, most commonly fentanyl or morphine in cases of constipation. This exemplifies how the involvement of multiple medicines in one ADR can limit our ability to evaluate the contribution of individual drugs, inclusive of their category.

Multivariate analysis indicated that the number off-label and unlicensed medicines administered per day has a similar influence on ADR risk as the number of authorised medicines administered per day. Two previous inpatient studies have considered off-label and unlicensed medicine use as an ADR risk factor in multivariate analyses. Turner et al. (1999) used a binary variable; patient exposed to at least one off-label or unlicensed medicine or not, they did not demonstrate a significant contribution of off-label or unlicensed medicine exposure to ADR risk, RR 1.74, 95% CI 0.89, 3.41, $p<0.06$. Santos et al. (2008) found that off-label medicine use was significantly associated with ADR risk, RR 2.44, 95% CI 2.12, 2.89, we have described above how their definitions of off-label and unlicensed medicine use were disparate from ours. Our method of analysis differs from that in these two previous studies and allows us to examine the influence of the number of off-label medicines and compare this to the influence of the number of authorised medicines. Our findings indicate, in accordance with the results of previous studies, (Turner et al., 1999, Neubert et al., 2004, Davies et al., 2009) that the overall number of medicines is a significant predictor of ADR risk. This may result from the increased risk of drug-drug interactions or may also be a reflection of the fact that patients on more medicines are more likely to be seriously unwell or have on-going complex medical needs.

The risk of ADRs was greater with off-label and unlicensed medicines but we have no evidence that if these medicines were used in accordance with a MA they would be implicated in fewer ADRs. The terms of a MA are derived from the data submitted as part of the drug regulatory process and may subsequently be updated with data obtained from post-marketing evaluation. If a MA does not cover some or all use in children it is because, in that specific circumstance, there is evidence that the medicine is not efficacious and/or not safe or because there is a lack of evidence that the medicine is efficacious and/or safe. Therefore, when the use of a medicine is categorised as 'off-label' this does not provide a consistent indication of the risk associated with that use. Unlicensed medicines need to be used in clinical practice because a suitable authorised medicine does not exist or has not been granted a MA in the UK, the reasons for this are generally commercial or practical and therefore there is no consistent link to the safety of the product.

Off-label medicines given to individuals below the minimum age recommended were the most likely to be implicated in ADRs. For many off-label and unlicensed medicines there is a lack of pharmacokinetic data in children, however off-label prescribing does not consistently equate to off-evidence prescribing, indeed some off-label use is supported by evidence derived from clinical experience or studies (Epstein and Huang, 2012). For some unlicensed medicines there may be a lack of formulation data, which contributes further to the evidence deficit.

It is unequivocal that children should be treated in accordance with the best available evidence. Clinicians incorporate relevant evidence, knowledge and experience into their decision-making regardless of whether this information has been incorporated into the medicine's MA. Information comes from a variety of sources: relevant paediatric studies, extrapolation from adult or less relevant paediatric studies, it is derivative of an understanding of the drug's pharmacology and the patient's underlying illness or clinical experience. The relevance and reliability of these sources of information will vary and the application of this information will be tailored to individual patients. In terms of adverse effects, caution is required when extrapolating data from adult and less relevant paediatric studies. The pharmacokinetic and pharmacodynamic behaviour of a drug may change as a child develops, with the greatest period of development occurring in the first two to three years of life (Kearns et al., 2003, Mulla, 2010). Furthermore, in children, consideration must be given to adverse effects relating to growth and development and to the potential for adverse effects associated with long term use. Knowledge of the pharmacology and

published safety data relating to the authorised formulations of a drug enable clinicians to predict some adverse effects but it may not always be appropriate to extrapolate these data to the use of the drug in an unlicensed formulation. Studies to improve the relevance and reliability of information about medicine use in children are needed. Effective strategies to disseminate and translate this information into clinical practice will help clinicians to optimise the use of medicines in children in terms of both efficacy and safety

3.5 Conclusion

While good quality data on the safe use of some off-label and unlicensed medicines in children may not be available, it is too simplistic to say that this translates directly into an increased risk of ADRs. Using detailed off-label and unlicensed categories, we have described which types of off-label and unlicensed use contributed to ADR risk and we have attempted to discuss the reasons for this. However, our off-label or unlicensed categories do not reveal anything about the pharmacological properties of the medicines. Furthermore, our analysis did not consider any variation in the susceptibility of the patients to ADRs, in terms of physiological development or underlying disease. Both the pharmacological properties of the medicine and the susceptibility of the individual patient influence the likelihood of ADR occurence. In order to target interventions aimed at reducing the risk of ADRs in children, the contribution of individual off-label and unlicensed medicines to this risk must be considered in the context of the evidence available and its appropriate application.

4 ICD-10 Coding of ADRs

4.1 Introduction

National Health Service (NHS) hospitals in the UK use a system of coding alongside the length of hospital stay to determine the chargeable cost of care for each patient. The coding systems used are the International Classification of Disease (ICD-10) codes for signs and symptoms and the Office of Population Census and Surveys (OPCS) codes for interventions and procedures. The process of coding is by case note review, undertaken by trained coders. It relies on diagnoses, procedures and other events being written down by the clinical team caring for the patient. Accurate coding is essential to obtain payment for the treatments and procedures undertaken in a hospital. The data are also submitted to become part of the national hospital episode statistics (HES) which record, for the NHS in England, each episode of admitted patient care. The data are used for research and planning in the NHS.

There are specific ICD-10 codes which relate to either adverse drug events (ADEs) or adverse drug reactions (ADRs) (Tables 4.1 & 4.2) which have been used in surveillance methods in studies of ADEs and ADRs. Some studies have used clinical codes to identify their cases and then examined the casenote record to ascertain that the coding is accurate (Schlienger et al., 1998, Backstrom, Mjorndal and Dahlqvist, 2004, Hougland et al., 2006, Hodgkinson, Dirnbauer and Larmour, 2009). Other studies, in a variety of settings, have used clinical codes as a method of estimating the prevalence of ADRs or ADEs without validation of those codes (Waller et al., 2005, Patel et al., 2007, Al-Malaq, Al-Aqeel and Al-Sultan, 2008, Shamliyan, 2010, Bourgeois et al., 2009, Carrasco-Garrido et al., 2010, Kane-Gill, Van and Handler, 2010, Wu et al., 2010, Stausberg and Hasford, 2011). There are some studies which identified ADR cases by searching for the relevant ICD code and compared these with spontaneously reported cases. They found that not all ADRs were identified by both methods and concluded that neither method in isolation was reliable for ADR surveillance. In general, they comment that spontaneous reports and hospital administrative data could be used in conjunction to increase the, currently suboptimal, detection of ADRs overall. (Cox et al., 2001, Lugardon et al., 2006, Batz et al., 2011, Mahe et al., 2013, Verriere et al., 2013). None of the approaches described above allowed an examination of whether coding provided a good estimate of ADE or ADR prevalence. Three studies in the adult population have identified ADRs or ADEs either by retrospective case note review or by prospective monitoring, and then reviewed the ICD codes for these cases;

these studies showed that, in the majority of cases, ADRs and ADEs had not been coded properly (Juntti-Patinen et al., 2006, Brvar et al., 2009, Hohl et al., 2012).

When undertaking research which uses data derived from administrative healthcare databases it is essential to first consider the reliability of those data. A systematic review of studies which compared discharge codes with the medical record for hospitals in the UK found a median coding accuracy rate of 91% for diagnostic codes and of 69.5% for operation or procedure codes in England and Wales and of 82% for diagnostic codes and 98% for operation or procedure codes in Scotland (Campbell et al., 2001). This finding implies good accuracy of the coding system but many of the studies that were included looked only at specific diagnoses. Thus the review findings may not actually tell us about the overall accuracy of the system, particularly in the context of pharmacovigilance. Many studies that have used administrative data to provide an estimate of ADR or ADE incidence did not validate their selected codes; they assumed accuracy of the coding system (Waller et al., 2005, Patel et al., 2007, Al-Malaq, Al-Aqeel and Al-Sultan, 2008, Shamliyan, 2010, Carrasco-Garrido et al., 2010, Kane-Gill, Van and Handler, 2010, Wu et al., 2010, Stausberg and Hasford, 2011). A UK study of 'drug-induced disorders' as a cause of hospital admission used HES data to estimate their prevalence but acknowledged that, in comparison to published prospective studies; their methodology underestimated the ADR prevalence (Waller et al., 2005). Other studies of ADR or ADE incidence have validated their findings by going back to the case note record for ADR cases identified by ICD. This method can identify false positives but does not allow the investigators to estimate how many ADRs have been missed by using ICD codes to identify ADR cases (Schlienger et al., 1998, Backstrom, Mjorndal and Dahlqvist, 2004, Hougland et al., 2006, Hodgkinson, Dirnbauer and Larmour, 2009). It is acknowledged that the accuracy of clinical coding is variable which limits its usefulness in the context of clinical studies because its focus is on reimbursement and legal documentation rather than on clinical care. In addition, it provides limited temporal and causal information and may be subject to 'code creep', that is, a bias towards higher paying codes (Bates et al., 2003).

Spontaneous ADR reporting systems have limitations as described in Chapter 1 of this thesis. Furthermore, extensive resources are required to conduct intensive surveillance for ADRs in, for example, prospective cohort studies like those described in Chapters 2 and 3 of this thesis. Therefore, it would be of great benefit if we could rely on hospital administrative data, which is collected routinely and easy to access, for the identification of ADRs. However, this requires ADRs to be coded accurately. The aim of the present study

was to determine whether ADRs in a paediatric population identified prospectively through intensive surveillance were coded appropriately using ICD-10.

Table 4.1 ICD-10 codes which may apply to adverse drug events or adverse drug reactions. Y40-Y59 external cause codes (adverse effects in in therapeutic use)[xiv]

Code	Description
Y40	Systemic antibiotics
Y41	Other systemic anti-infectives/antiparasitics
Y42	Hormones (including synthetic, antagonists)
Y43	Primarily systemic agents
Y44	Agents primarily affecting blood constituents
Y45	Analgesics/antipyretics/anti-inflammatories
Y46	Antiepileptics/antiParkinsonism drugs
Y47	Sedatives, hypnotics, antianxiety drugs
Y48	Anaesthetics, therapeutic gases
Y49	Psychotropic drugs
Y50	CNS stimulants
Y51	Drugs affecting autonomic nervous system
Y52	Agents primarily affecting cardiovascular system
Y53	Agents primarily affecting gastrointestinal system
Y54	Agents affecting water/mineral balance/uric acid
Y55	Agents affecting muscle/respiratory system
Y56	Topical agents affecting skin, ENT, dental
Y57	Other and unspecified medicaments
Y58	Bacterial vaccines
Y59	Other vaccines/biologicals

[xiv] Waller et al. 2005

Table 4.2 ICD-10 codes which may apply to adverse drug events or adverse drug reactions – codes including the word 'drug induced'[xiv]

Code	Description
D61.1	Drug-induced aplastic anaemia
D59.0/2	Drug-induced haemolytic anaemia
E03.2	Hypothyroidism due to medicaments
E27.3	Drug-induced adrenocortical failure
F11	Mental disorders due to opioids
F13	Mental disorders due to sedatives/hypnotics
F19	Mental disorders due to multiple psychoactive drugs
G21.0	Malignant neuroleptic syndrome
G21.1	Drug-induced Parkinsonism
G24.0	Drug-induced dystonia
G25.0/4/6	Drug-induced extrapyramidal syndrome/chorea/tics
G72.0	Drug-induced myopathy
H91.0	Ototoxic hearing loss
I42.7	Drug-induced cardiomyopathy
J70.2/3/4	Drug-induced interstitial lung disorders
K71	Drug-induced liver disease
L56.0/1	Drug-induced phototoxicity
M10.2	Drug-induced gout
M32.0	Drug-induced systemic lupus erythematous
M34.2	Drug-induced systemic sclerosis
N14.0/1/2	Drug-induced nephropathy
T88.3	Malignant hyperthermia due to anaesthesia
T88.6	Drug-induced anaphylaxis

4.2 Methods

4.2.1 Detection of ADRs

The method by which the 241 ADRs included in this study were detected and evaluated is described in chapter 2. The study described in this chapter was undertaken by JRB.

For each ADR, the following information was obtained from the dataset to meet the specific objectives of the present study: patient identification, suspected drug(s), a description of the ADR (usually a symptom), ADR type (A or B), severity and causality assessment.

4.2.2 Matching ADRs detected to ICD-10 codes for each admission

The electronic admission abstract recorded in Alder Hey NHS Foundation Trust's electronic medical records system (MEDITECH) displays the ICD-10 codes for that admission. Therefore, the electronic admission abstract for each patient with at least one ADR was examined and a record was made of whether the ADR had been coded using ICD-10 and if so, which code(s) had been used, these will be referred to here as ICD-10 ADR codes. A record was also made of whether the ADR signs and symptoms had been coded using ICD-10 with no acknowledgment of their drug cause. Again the codes used were recorded and will be referred to here as ICD-10 sign and symptom codes.

4.2.3 Comparison of ADR type, severity and causality

A Chi-square test for difference in proportions was used to determine whether there were any differences in the characteristics of coded and uncoded ADRs. The null hypotheses were as follows:

1. Type A and Type B reactions were equally likely to be coded using ICD-10.
2. ADRs of severity 1, 2, 3 and 4, 5 were equally likely to be coded using ICD-10.
3. Possible ADRs were equally likely to be coded as probable and definite ADRs using ICD-10.

4.3 Results

4.3.1 Description of ADRs coded using ICD-10

Of the 241 ADRs evaluated in this study, 76 (31.5%) were coded correctly using at least one ICD-10 code (Table 4.3). One reaction was incorrectly coded, a skin reaction to topical dimeticone, was coded as *Y53.1 Other antacids and anti-gastric-secretion drugs,* the suspected drug had been incorrectly identified during the coding process. Two reactions had two codes as follows:

1. pancytopenia coded as
    a) *Z51.2 other chemotherapy*
    b) *Y43.3 other antineoplastic drugs*
2. post-immunisation irritability coded as
    a) *T88.1 Other complications following immunization*
    b) *Y59.9 Vaccine or biological substance, unspecified*

There were 126 non-oncology ADRs and 115 reactions that involved a patient under the care of the oncologists in this study.

Of the 126 non-oncology ADRs, 6 (4.8%) were coded (see figure 4.1).

Of the 115 oncology reactions, 70 (61%) were coded correctly and without exception, the code *Y43.3 other antineoplastic drugs* was used (see figure 4.2).

Table 4.3 ADRs coded using ICD-10 ordered by reaction frequency (n=76, two reactions had two codes)

Description of reaction (s)	ICD -10 Code	Number of reactions
ADRs secondary to chemotherapy: neutropenia, anaemia, thrombocytopenia, immunosuppression, deranged liver function tests, mouth ulcers, nausea, vomiting, diarrhoea, back pain, fever, deranged renal function	Y43.3 Other antineoplastic drugs	70
Rash secondary to penicillin, Vomiting secondary to penicillin	Y40.0 Penicillins	2
Hyperglycaemia secondary to dexamethasone	Y42.7 Androgens and anabolic congeners	2
Anaemia, immunosuppression, thrombocytopenia, neutropenia	Z51.2 Other chemotherapy	1
Hypoglycaemia secondary to insulin	E16.0 Drug induced hypoglycaemia without coma	1
Irritability following pneumococcal and DTP vaccines	T88.1 Other complications following immunization	1
Irritability following pneumococcal and DTP vaccines	Y59.9 Vaccine or biological substance, unspecified	1

4.3.2 Description of ADR signs and symptoms coded using ICD-10

The signs and symptoms of 212/241 (88%) ADRs were acknowledged by the ICD-10 code(s) for the relevant admission. These 212 ADRs cases were made up of 107 oncology cases of which 70 also had an ADR code and 104 non-oncology cases of which 4 also had an ADR code. There were 20/126 (15.9%) non-oncology ADRs and 8/115 (7.0%) oncology ADRs not acknowledged by either an ADR ICD-10 code or an ICD-10 code pertaining to the signs and symptoms of the ADR (Figures 4.1 and 4.2).

Table 4.4 shows which ICD-10 codes were used to acknowledge the signs and symptoms of the 100 non-oncology ADRs which did not have an ADR specific code.

Table 4.5 shows which ICD-10 codes were used to acknowledge the signs and symptoms of the 37 oncology ADRs which did not have an ADR-specific code.

Figure 4.1 Summary of results for non-oncology ADRs

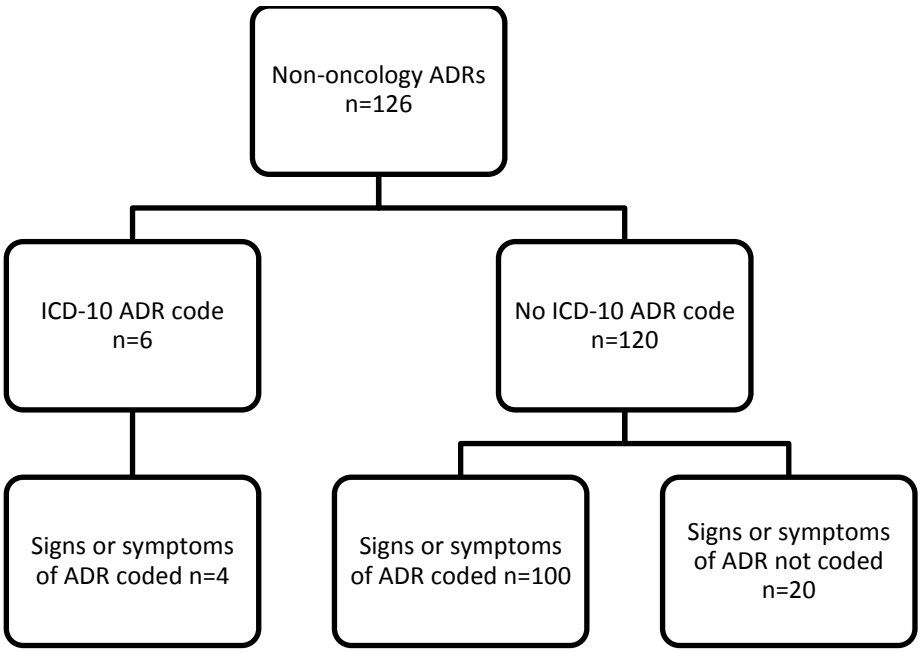


Figure 4.2 Summary of results for oncology ADRs

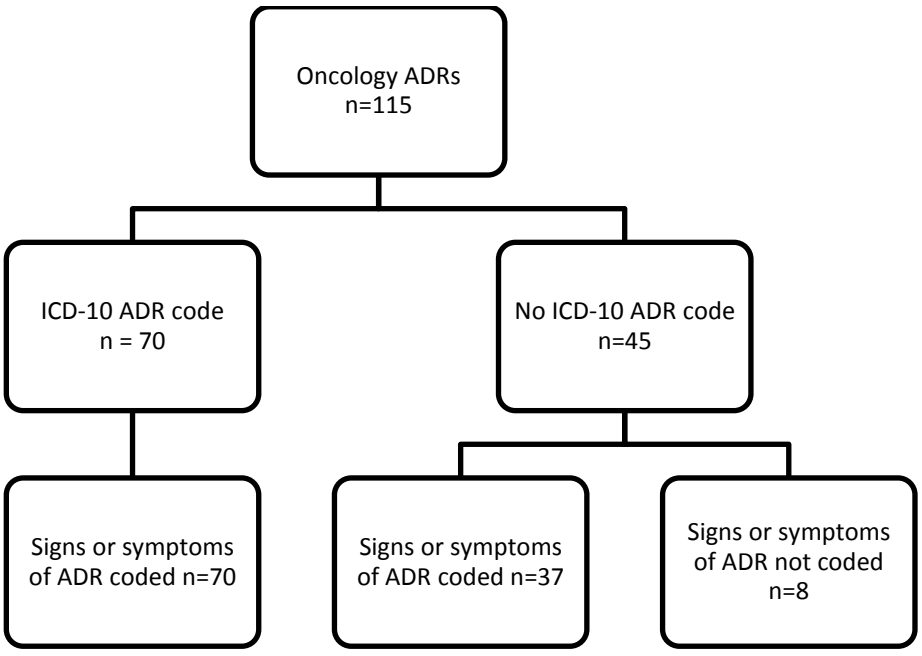


Table 4.4 Non-oncology ADR only acknowledged by signs and symptoms coded using ICD-10, ordered by reaction frequency (n=100)

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Post-tonsillectomy bleed	T81.0 Haemorrhage and haematoma complicating a procedure NEC K92.0 haematemesis H95.8 other post procedural disorders of ear and mastoid process	27
Immunosuppression	Z94.8 Other transplanted organ and tissue status Z94.4 Liver transplant status B00.9 Herpes viral infection, unspecified A41.9 Septicaemia, unspecified Z94.2 Lung transplant status Z94.0 Kidney Transplant status R50.9 Fever, unspecified N39.0 Urinary tract infection, site not specified M72.58 Fasciitis nec, other head neck ribs skull trunk vertebral column L30.9 Dermatitis unspecified J02.9 Acute pharyngitis, unspecified B96.8 Other specific bacterial agents as cause of disease	18

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Immunosuppression (continued)	B02.9 Zoster without complication B01.9 Varicella without complication A40.9 streptococcal septicaemia, unspecified	
Rash	R23.3 Spontaneous ecchymoses R21.X Rash and other nonspecific skin eruption D69.0 Allergic purpura L03.1 Cellulitis of other parts of limb	6
Hypoglycaemia	E16.2 Hypoglycaemia, unspecified	6
Constipation	R32.X Unspecified urinary incontinence R10.4 Other and unspecified abdominal pain K62.5 Haemorrhage of anus and rectum K59.0 Constipation	4

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Seizure	R56.8 Other and unspecified convulsions R56.0 Febrile convulsions G41.9 Status epilepticus	3
Respiratory depression	R09.2 Respiratory arrest R06.0 Dyspnoea E85.2 Non-invasive ventilation	3
Haematemesis	K29.7 gastritis, unspecified K29.0 Acute haemorrhagic gastritis	2
Fever, seizure	R56.0 Febrile convulsions	2
Fever	R50.9 Fever, unspecified	2
Diarrhoea	K52.9 Noninfective gastroenteritis and colitis, unspecified A08.4 Viral intestinal infection, unspecified	2

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Wheeze, increased work of breathing	B34.9 Wheezing	1
Vomiting, diarrhoea, difficulty in breathing	K52.9 Noninfective gastroenteritis and colitis, unspecified	1
Vomiting, abdominal pain	R21.X Rash and other nonspecific skin eruption R11.X nausea and vomiting	1
Thrombocytopenia	D69.3 Idiopathic thrombocytopenic purpura	1
Seizure, respiratory depression	R56.0 Febrile convulsions	1
Renal dysfunction	N28.9 Disorder of kidney and ureter, unspecified	1
Rash, irritability, fever	B34.9 viral infection, unspecified	1

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Rash, fever, lethargy	R50.9 Fever, unspecified R23.3 Spontaneous ecchymoses	1
Pyrexia, vomiting	R50.9 Fever, unspecified, R11.X nausea and vomiting	1
Pyrexia, irritability	J06.9 Acute upper respiratory infection, unspecified	1
Post-operative bleeding	T81.0 Haemorrhage and haematoma complicating a procedure NEC	1
Limb swelling	L03.1 Cellulitis of other parts of limb	1
Kawasaki disease	M30.3 Mucocutaneous lymph node syndrome	1
Irritability	R68.1 nonspecific symptoms peculiar to infancy	1
Intestinal obstruction	J56.0 Paralytic ileus	1

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Intermenstrual bleed	N92.0 Excessive and frequent menstruation with regular cycle	1
Impaired healing	T81.3 Disruption of operation wound, not elsewhere classified	1
Ileus	K56.7 Ileus unspecified	1
Hypertension	I10.X Essential (primary) hypertension	1
Hyperglycaemia	E13.8 Other specified diabetes mellitus with unspecified comps	1
Headache	G93.2 Benign intracranial hypertension	1
Diarrhoea, vomiting	K21.9 gastro-oesophageal reflux disease without oesophagitis K90.4 malabsorption due to intolerance, not elsewhere classified	1
Cyanosis/pallor	R23.0 Cyanosis	1

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Apnoea	J98.8 Other specified respiratory disorders	1
Adrenal suppression	E27.4 Other and unspecified adrenocortical insufficiency	1

Table 4.5 Oncology ADRs only acknowledged by signs and symptoms coded using ICD-10, ordered by reaction frequency (n=37)

Reaction	ICD-10 code for signs and or symptoms	Number of reactions
Immunosuppression	R50.9 fever, unspecified	5
	Z94.2 Lung transplant status	
	J22.X Unspecified acute lower respiratory infection	
	K61.0 Anal abscess	
	B08.1 Molluscum contagiosum	
	J22.X Unspecified acute lower respiratory infection	
	Z94.9 other transplanted organ and tissue status	
	J06.9 Acute upper respiratory infection, unspecified	
Constipation	R10.4 Other and unspecified abdominal pain.	3
	R11.X Nausea and vomiting	
	K59.0 Constipation	
Neutropenia	X90.3 Neutropenia drugs band 1	3
	R50.9 Fever, unspecified	
	D70.X Aranulocytosis	

Thrombocytopenia, neutropenia	R50.9 Fever, unspecified R04.0 Epistaxis	3
Anaemia, thrombocytopenia, neutropenia	R50.9 Fever, unspecified D70.X Agranulocytosis	2
Immunosuppression, deranged LFTs	J22.X Unspecified acute lower respiratory infection	2
Neutropenia, immunosuppression	A08.0 Rotaviral enteritis D70.X Agranulocytosis R50.9 fever, unspecified	2
Vomiting	R11.X Nausea and vomiting	2
Abdominal pain	R10.4 Other and unspecified abdominal pain	1
Diarrhoea, immunosuppression	B34.9 viral infection, unspecified R21.X rash and other nonspecific skin eruption R50.9 Fever, unspecified	1

Haematuria, thrombocytopenia, anaemia	R31.X Unspecified haematuria	1
Headache	R51.X Headache	1
Headache, thrombocytopenia, neutropenia, anaemia, diarrhoea, vomiting	D70.X Agranulocytosis R50.9 fever, unspecified	1
Immunosuppression, low lymphocyte count	B02.9 Zoster without complication B01.9 varicella without complication	1
Immunosuppression, anaemia	R30.0 Dysuria	1
Leukencepalopathy	R11.X Nausea and vomiting G81.9 Hemiplegia unspecified R29.8 Other specific signs involving nervous/musculoskeletal systems	1
Mucositis, neutropenia, anaemia, thrombocytopenia	D70.X agranulocytosis R50.9 fever, unspecified K12.1 Other forms of stomatitis	1

Neutropenia, gastritis	K29.7 Gastritis, unspecified	1
Neutropenia, thrombocytopenia, anaemia, immunosuppression	K13.7 Other and unspecified lesion of oral mucosa	1
Thrombocytopenia	D69.6 Thrombocytopenia, unspecified	1
Thrombocytopenia, anaemia, deranged LFTs, vomiting, nausea, diarrhoea	K52.9 Noninfective gastroenteritis and colitis, unspecified	1
Thrombocytopenia, immunosuppression, neutropenia	D70.X Agranulocytosis R50.9 fever, unspecified	1
Vomiting, neutropenia, immunosuppression, diarrhoea, thrombocytopenia, deranged LFTs	D70.X Agranulocytosis	1

4.3.3 ADRs coded using ICD-10 – consideration of type, severity and causality

Considering oncology and non-oncology reactions together, coded ADRs were not more likely to be type A than type B reactions, difference in proportions 3%, CI -3.0%, 8.9%, p = 0.255. Coded ADRs were not more likely to be of severity 1,2 and 3 than those of severity 4 and 5, difference in proportions 6%, CI -0.1%, 11.9%, p = 0.069. Coded ADRs were more likely to be definite and probable ADRs than possible ADRs, difference in proportions 47%, CI (32.3%, 59.7%) p < 0.001 (Table 4.6).

Table 4.6 Comparison of type, severity and causality assessments for coded and uncoded ADRs

Assessment	Score	ADRs coded (n = 76)	ADRs not coded (n = 165)	p –value (difference in proportions)
Type	**A**	74	155	0.255
	B	2	10	
Severity	**1,2,3**	74	150	0.069
	4,5	2	15	
Causality	**Definite & Probable**	75	87	<0.001
	Possible	1	78	

4.4 Discussion

We have demonstrated that the majority of ADRs detected in prospective cohort study at a paediatric tertiary care centre would not have been identified if the study had relied on ICD-10 codes as a single means of detection. This is due to deficiencies in how ADRs were recorded in the case notes and in how they were recorded in the clinical coding system.

We attempted to validate the use of ICD codes in the detection of ADRs by reviewing the ICD codes in the records of patients who have been identified as having had a suspected ADR in the course of a pharmacovigilance study. The results of our study demonstrate that ADRs are not consistently coded using ICD ADR codes, 4.8% non-oncology ADRs were coded. However, oncology ADRs were coded with much greater accuracy (61%). In a similar, albeit retrospective, study of the medical records of 530 adult patients in a Slovenian hospital, 30 ADRs leading to admission were identified of which 30 were documented by a physician but only 1 (3.3%) had an ICD-10 code which identified it as an ADR. This was a case of drug-induced liver disease secondary to an antifungal agent. Three of the 30 ADRs identified were secondary to antineoplastic agents (Brvar et al., 2009). A prospective study of drug-related problems leading to emergency department visits in Finland included 7113 visits of which 167 were classified as certainly or probably drug-related, and of these, 102 were ADRs. Only 2% of the ADR-related visits were coded as 'drug-related' using ICD but the authors do not report the details of these cases. Seven of the 102 ADR-related visits were oncology patients and were secondary to antineoplastic agents (Juntti-Patinen et al., 2006). A further prospective study of ADEs detected in the emergency department determined that 221 of 1574 (14%) of attendances were due to an ADE. However, only 15 of these 221 (6.8%) ADEs had an ICD-10 diagnostic code which indicated a causal relationship between the presentation and a medication (Hohl et al., 2012).

There are several reasons why ADRs identified in this prospective study may not have been correctly coded. The ADRs were identified based on a definition chosen for the specific purpose of studying ADRs prospectively. It is possible that the individuals involved in coding the events, that is clinicians and clinical coders, may not agree with, or be aware of this definition. For example, defining post-tonsillectomy haemorrhage as an ADR may meet with opposition because, at present, the contribution of dexamethasone and non-steroidal anti-inflammatory drugs to this event is not yet established (Geva and Brigger, 2011, Lewis et al., 2013). It is interesting to note that ADRs which were classified as definite or probable

in this study were more likely to have been coded using an appropriate ICD-10 ADR code. This suggests that whether or not an event is recorded and subsequently coded may rely on the ease of its detection and the assessment of its causality by the clinician. Finally (and crucially), if an ADR is not identified and recorded by the clinician it cannot be coded correctly.

In this study, there was a far greater proportion of oncology ADRs than non-oncology ADRs coded using ICD-10 ADR codes. The two main reasons for this are – a) the oncology unit was using a structured admission proforma for unplanned admissions presenting with febrile neutropenia (one of our most common ADRs) and b) there were specifically trained coding staff assigned to the oncology unit who had the opportunity to become familiar with the diagnoses and complications inclusive of ADRs in oncology patients and how to code them. Other specialties have structured admission proformas but these are mainly for planned admissions (e.g. neurosurgery) and they are thus unlikely to be used in the context of an ADR-related admission. Other specialities also have specifically trained coding staff (e.g. cardiology) but ADR recording in the case notes is less likely to be consistent because a specific proforma does not exist. A study of ADRs in a Canadian paediatric hospital which used ICD codes to estimate ADR incidence over a period of 21 years showed that the incidence increased throughout the study. They concluded that the reason for this apparent increase in incidence reflected the fact that the more complete coding of episodes of care had been prioritised in their hospital (Huet et al., 2011). This finding suggests that changes in organisational priorities can improve the recording of ADRs as part of hospital administrative data which in turn improves the utility of those data for pharmacovigilance.

The ICD-10 sign and symptom codes for each reaction were recorded to facilitate an exploration of whether any of these codes were commonly being used for ADR cases and if so, could these provide an additional means of ADR detection. Considering the two most common ADRs which were not coded using ICD-10 ADR codes, tables 4.3 and 4.4 show that the codes used to describe immunosuppression were diverse and table 4.4 shows that post-tonsillectomy haemorrhage is consistently recorded. However, this consistency must be balanced against the fact that the causes of post-tonsillectomy haemorrhage are multi-factorial and cannot be attributed to peri-operative medicine use alone (Windfuhr, Chen and Remmert, 2005, Lowe et al., 2007) The diversity of codes used to describe immunosuppression limits their usefulness in the identification of ADRs. Therefore, the only

codes which would have been specific enough for the reliable detection of a proportion of the ADRs in our study were the ICD-10 ADR codes.

4.5 Conclusion

The use of ICD-10 codes to identify ADRs in a paediatric tertiary care centre is not currently a reliable method of pharmacovigilance due to deficiencies in how ADRs are recorded in the case notes and how they are recorded in the clinical coding system. This finding is consistent with similar studies carried out in adult centres.

The use of ICD-10 codes to identify ADRs could be made more reliable if deficiencies in case note recording and coding systems for ADRs are addressed through changes to current practice, complemented by relevant training. Since the most useful codes available to us in this context relate either to 'adverse effects in therapeutic use' for specific medicine classes or are prefixed 'drug induced' they will not be specific to ADRs but will encompass ADRs.

Training of clinicians should focus on the consolidation of existing knowledge in relation to the identification of suspected drug-related problems (inclusive of ADRs), assessment of causality and an improved awareness of the potential utility of the clinical coding system in the context of pharmacovigilance. It may be possible to provide, or revise existing, admission and discharge proformas with specific sections which ask for details of drug-related problems identified by the clinician at the point of admission and during the hospital stay. Training of clinical coders should focus on the consolidation of existing knowledge of codes for 'adverse effects in therapeutic use' for specific medicine classes or those prefixed 'drug induced'. Coders should understand the potential utility of these codes in the context of pharmacovigilance and they should be updated on the introduction of any existing or revised proformas which document drug-related problems at the points of admission and discharge. Any changes made should be monitored through audit which would focus on the frequency and accuracy of the use of codes for 'adverse effects in therapeutic use' for specific medicine classes or those prefixed 'drug induced'.

5 Dexamethasone and post-tonsillectomy haemorrhage risk in children – a systematic review and meta-analysis

5.1 Introduction

Chapter 2 of this thesis describes a study of ADRs identified at the point of admission to hospital. 26 cases of post-tonsillectomy haemorrhage were identified and highlighted as ADRs to non-steroidal anti-inflammatory drugs (NSAIDs) and/or dexamethasone (Gallagher R.M. et al., 2012). The link between the use of NSAIDs and dexamethasone and post-tonsillectomy haemorrhage risk in children warrants further investigation. If a link exists, it may be possible to avoid some post-tonsillectomy haemorrhages by rationalising the use of anti-emetics and analgesia. Since there are a large number of studies of the use of these medicines in children undergoing tonsillectomy, albeit that they focus on benefit rather than harm, a systematic review was designed to investigate the link between their use and the risk of haemorrhage.

Children who undergo tonsillectomy or adenotonsillectomy are at risk of experiencing complications. These include post-operative nausea and vomiting (PONV) and post-operative haemorrhage. In studies where intra-operative anti-emetics were not administered, post-tonsillectomy nausea and vomiting rates as high as 70% have been reported (Ferrari and Donlon, 1992). Post-tonsillectomy haemorrhage rates range from 0.1 to 8.1% (Randall and Hoffer, 1998).

The Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) guideline on the prevention of post-operative vomiting (POV) recommends the use of dexamethasone (0.15mg/kg in combination with ondansetron 0.05mg/kg) to minimise the risk of POV in children undergoing tonsillectomy (The Association of Paediatric Anaesthetists of Great Britain & Ireland, 2009). A Cochrane review of dexamethasone use in tonsillectomy supports this recommendation: children receiving a single intraoperative dose of dexamethasone at a dose between 0.15 and 1mg/kg were half as likely to vomit within 24 hours of their operation (Steward, Grisel and Meinzen-Derr, 2011).

Although there is evidence of the efficacy of dexamethasone in the context of tonsillectomy, evidence of its safety is less well established. Czarnetzki et al. (2008) showed that post-operative haemorrhage rates were increased by 6.5 fold (95% CI 1.69, 16.3) with

intraoperative dexamethasone use in children undergoing tonsillectomy (a single dose of 0.05, 0.15, or 0.5 mg/kg). Three recent meta-analyses have also addressed this issue: (a) using 14 randomised controlled trials (RCTs) of adults and children who underwent tonsillectomy, no difference in bleeding rates were demonstrated between dexamethasone and comparator arms (RR 1.02 95% CI 0.65, 1.61, p=0.92) (Geva and Brigger, 2011); (b) using 12 paediatric studies that reported data on haemorrhage rates (Shargorodsky, Hartnick and Lee, 2012), again no significant difference in post-operative bleeding was identified in patients receiving single-dose dexamethasone versus placebo (OR 1.07 95% CI 0.58, 1.98, p=0.82); and (c) using data from 29 RCTs of adult and paediatric tonsillectomy patients (Plante et al., 2012), a pooled effects estimate again revealed no significant difference in post-operative haemorrhage rate in patients who had received dexamethasone versus those who had not (OR 0.96 95% CI 0.66, 1.40, p=0.83).

Although three previous systematic reviews have already been undertaken, including one which focussed on paediatric studies, this study was undertaken because there are limitations to the use of standard systematic review methodology in the evaluation of adverse event outcomes. This is particularly true of rare adverse events such as post-tonsillectomy haemorrhage because haemorrhage rate data derived from small RCTs of dexamethasone may not be generalizable, particularly if adverse event reporting was sub-optimal. It has been recommended that systematic reviews of rare adverse effects should include non-randomised studies (NRS) which may cover a broader population than RCTs and in which the adverse event may be the primary outcome (Loke, Golder and Vandenbroucke, 2011, Chou and Helfand, 2005). Furthermore, an assessment of adverse event monitoring and reporting can provide an indication of the reliability of the reported adverse event rate. It is possible that haemorrhage rate data for dexamethasone used in this context may be unpublished (publication bias) or that it may have been selectively unreported due to undesirable outcome results (outcome reporting bias)(Kirkham et al., 2010).

This chapter describes a systematic review which aimed to determine whether the use of dexamethasone with or without NSAIDs in paediatric tonsillectomy affects the rate of post-tonsillectomy haemorrhage in children. In order to address some of the limitations of standard systematic review methodology in the evaluation of a rare adverse event outcome, this study considers both RCTs and NRS and furthermore assesses the methodological quality of haemorrhage rate recording and reporting.

5.2 Methods

5.2.1 Search strategy

The databases and tertiary sources used in this review are listed in Table 5.1. Searches were carried out in November 2011. Search strategies were developed specifically for each database and tertiary source, they are presented in Appendices 7 (database search strategies) & 8 (restricted interface search strategies). The reference lists of previous systematic reviews, identified during the search, were also examined for additional references. Following the selection of studies via this process, forward and backward citation tracking was undertaken for each study if it was indexed in the Scopus database. Contact was made with experts to identify other potentially relevant published and unpublished studies. Although contact with the pharmaceutical industry to obtain adverse event data may be considered when investigating rare adverse events, we did not carry this out. The use of dexamethasone is not specifically licensed for use in paediatric tonsillectomy so it was thought unlikely that the manufacturers would hold relevant data on the use of their product in this narrow context.

5.2.2 Study eligibility

Randomised controlled trials (RCTs) and quasi-randomised controlled trials (q-RCTs) that considered dexamethasone (except by peri-tonsillar infiltration) or, dexamethasone in combination with NSAIDs, in the context of paediatric tonsillectomy or adenotonsillectomy[xv] in the immediate peri-operative period were included. For the purposes of this study, the immediate peri-operative period was defined as: within the 24 hours before the procedure, during the procedure or in the 24 hours which followed the procedure. This review considered only children up to the age of 18 years; studies that included both adults and children were also considered and, if possible, only the data for the children were used. If data for children and adults could not be separated, the study was excluded. Studies were only considered for inclusion if they were published in English.

[xv] for the remainder of this chapter, the term tonsillectomy will be used to encompass both tonsillectomy and adenotonsillectomy

Table 5.1 Databases and tertiary sources searched

Agency for Health & Research Quality http://www.ahrq.gov/
BioSciences Information Service of Biological Abstracts (BIOSIS) Citation Index via webofknowledge.com
British Nursing Index (BNI) via www.library.nhs.uk
British Library Direct http://direct.bl.uk/bld/Home.do
Cumulative Index to Nursing and Allied Health Literature (CINAHL®) via ebscohost.com
Cochrane Library, The http://www.thecochranelibrary.com/view/0/index.html
Current Controlled trials http://www.controlled-trials.com/
Clinical Trials http://clinicaltrials.gov
Database of Abstracts of Reviews of Effectiveness (DARE) http://www.crd.york.ac.uk/CMS2Web
Excerpta Medica database (EMBASE™) via www.library.nhs.uk
Faculty of 1000 http://f1000.com/
Iowa Drug Information Service (IDIS) via http://www.uiowa.edu/idis
Medical Literature Analysis and Retrieval System Online (MEDLINE®) via ovid.com
Medscape http://www.medscape.com/
Science Citation Index via ebscohost.com
Scirus http://www.scirus.com/
Scopus via ebscohost.com
Toxicology Information Online (TOXLINE®) – US National Library of Medicine via proquest.com
TRIP database http://www.tripdatabase.com/
UK Clinical Research Network Portfolio Database http://public.ukcrn.org.uk/search/
US Food & Drug Administration http://www.fda.gov/

5.2.3 Types of outcome measure

The main outcome of interest extracted from each study was haemorrhage rate. The definition of haemorrhage included any bleeding which required a change in post-operative management, for example re-operation, blood transfusion, prolonged hospital stay, re-admission or contact with a healthcare provider, for example an accident and emergency department (AED) or a general practitioner. In some studies, where some participants may have experienced more than one haemorrhage, we recorded the number of haemorrhages rather than the number of patients who experienced a haemorrhage. This is because we considered recurrent bleeding to be a clinically important outcome in post-operative patients.

5.2.4 Study selection

5.2.4.1 Inspection of citations

After duplicate citations were removed, all titles and abstracts were independently reviewed by two reviewers with reference to the inclusion/exclusion criteria (Appendix 9), and a decision was made about whether to retrieve the full report of the study. The number of titles/abstracts identified, selected and rejected was recorded.

5.2.4.2 Inspection of retrieved reports

Once the full reports were retrieved, they were inspected for relevance to the review and the inclusion and exclusion criteria were applied. Studies not meeting the pre-determined criteria were excluded. If there was any disagreement about whether to include any of the studies, a third reviewer assessed them and, together with the other reviewers made a consensus decision about whether to include or exclude. A record was made of the number of full reports retrieved and the number excluded.

For quality assurance purposes, 5% of studies excluded at title and abstract stage were re-reviewed by the original reviewers for inclusion and five studies excluded at the full article stage were re-reviewed by a third reviewer.

5.2.5 Data collection

A formal data extraction form was designed, piloted on a small selection of studies and adjusted as necessary (Appendices 10 & 11). For each study, information regarding methods, participants, comparison groups, interventions and outcomes was tabulated. Where they were recorded or provided by the author, the following data were extracted for each randomised study:

1. Study characteristics: number of participants, number of participants in each intervention group, year completed, setting, inclusion criteria, definition of post-operative haemorrhage, and length of follow-up.

2. Participant characteristics: age, sex, underlying disease, indication for surgery.

3. Interventions: number of intervention groups, intervention details: peri- operative medicines inclusive of dose, surgical technique.

4. Outcomes reported: post-operative haemorrhage rate.

5. Additional data relating to haemorrhage: severity, timing (i.e. need for intervention, primary or secondary).

Where they were recorded or provided by the author, the following data were extracted for each non-randomised study:

1. Study characteristics: number of participants, number of participants in each intervention group, year completed, setting, inclusion criteria, definition of post-operative haemorrhage, and length of follow-up.

2. Participant characteristics: age, sex, underlying disease, indication for surgery.

3. Characteristics of surgery: surgical technique, peri-operative medicines inclusive of dose.

4. Characteristics of peri-operative care: medicines

5. Data relating to haemorrhage: number of haemorrhages, severity, timing (i.e. need for intervention, primary or secondary), risk factors identified.

5.2.6 Quality assessment

For RCTs which compared dexamethasone with another intervention and reported haemorrhage rate or for which haemorrhage rate data were obtained from the author(s), the methodological quality was assessed using the Cochrane Collaboration's domain based evaluation tool for assessing risk of bias (Higgins and Green, 2009). The overall risk of bias was summarised for each study as follows: low risk of bias if low risk of bias for all key domains, unclear risk of bias if unclear risk of bias for one or more key domains and high risk if high risk of bias for one or more key domains. The methodological quality of haemorrhage rate recording and reporting was assessed for both randomised and non-randomised studies using selected elements of the McMaster Quality Assessment Scale of Harms for primary studies (the McHarm Scale) http://hiru.mcmaster.ca/epc/mcharm.pdf. The elements used were selected based on an evaluation of their relevance to our research question and they aimed to evaluate: the quality and appropriateness of study design and reporting, the applicability of the study findings to the population and measures taken to reduce bias (Appendix 12) (Downs and Black, 1998).

Both data collection and quality assessment of studies were undertaken by one reviewer, with three randomised and three non-randomised studies assessed by a second reviewer to check for consistency.

5.2.7 Statistical analysis and synthesis

Statistical analyses were performed using RevMan (version 5.1 software). As haemorrhage rate data are dichotomous, the data were analysed by calculating the Peto odds ratio for each randomised study and for non-randomised studies odds ratios (OR) were calculated with corresponding 95% confidence intervals (CIs). For each study, we only included data for participants who were not excluded following randomisation and for whom follow-up was complete.

5.2.7.1 Meta-analysis

We aimed to conduct two meta-analyses. For randomised controlled trials, dexamethasone alone was compared with any other intervention used in paediatric tonsillectomy. For non-randomised studies, dexamethasone alone was compared with any other intervention used in paediatric tonsillectomy. Publication bias for trials included in the meta-analysis was assessed by visual inspection of a funnel plot. All study authors were contacted where possible for missing outcome data.

5.2.7.2 Heterogeneity and subgroups

A chi-squared test for statistical heterogeneity was undertaken, and the I^2 statistic was calculated. Where the necessary data were available, the following subgroup analysis was also planned:

- A comparison of primary and secondary haemorrhage rates
- A comparison of studies in which some participants received NSAIDs in addition to dexamethasone with those in which no participants received NSAIDs

5.2.7.3 Studies not suitable for inclusion in a meta-analysis

Randomised controlled trials in which all patients received dexamethasone:

- Report the haemorrhage rate for each arm of the trial

Non-randomised studies in which all patients received dexamethasone:

- Report the haemorrhage rate for each study

5.3 Results

5.3.1 Search results

The database searches undertaken in November 2011 identified 3419 abstracts for screening after duplicate records were removed. After review of abstracts, 139 full text articles were reviewed. Of these, 52 unique studies (37 RCTs and 15 NRS) fulfilled the inclusion criteria (Figure 5.1).

Forward and backward citation tracking for all the eligible articles in the database search, plus the reference sections of 15 review articles identified in our database search, identified 962 potentially relevant citations not identified in our initial searches. After review of abstracts, 880 articles were excluded, leaving 82 full articles to be reviewed. Of these, ten additional articles (3 RCTs and 7 NRS) met the inclusion criteria (Figure 5.2). One article reported a RCT already identified in another article picked up by our database search. In total, 61 studies were included in this review (39 RCTs and 22 NRS).

Figure 5.1 Database Search Flow Diagram

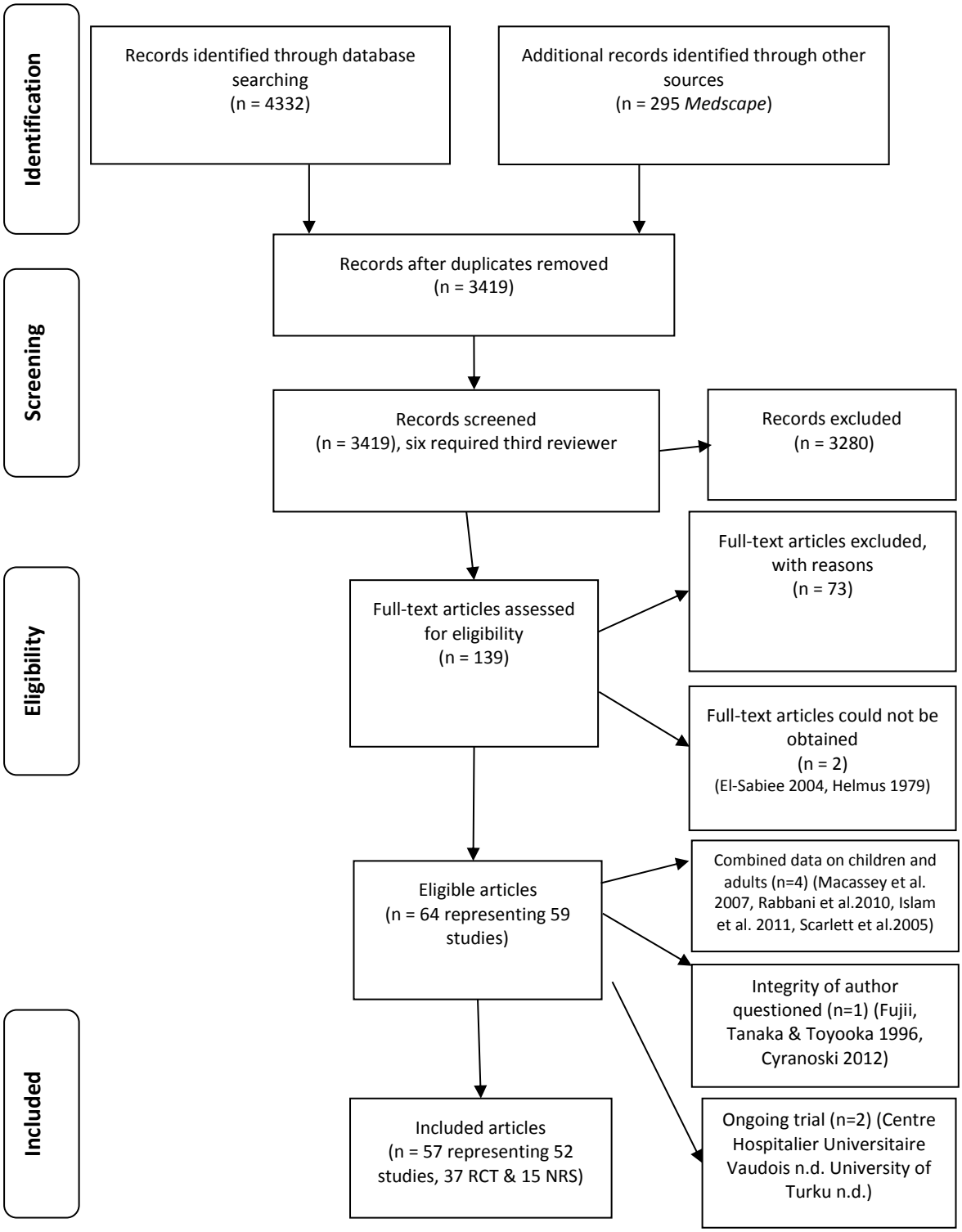
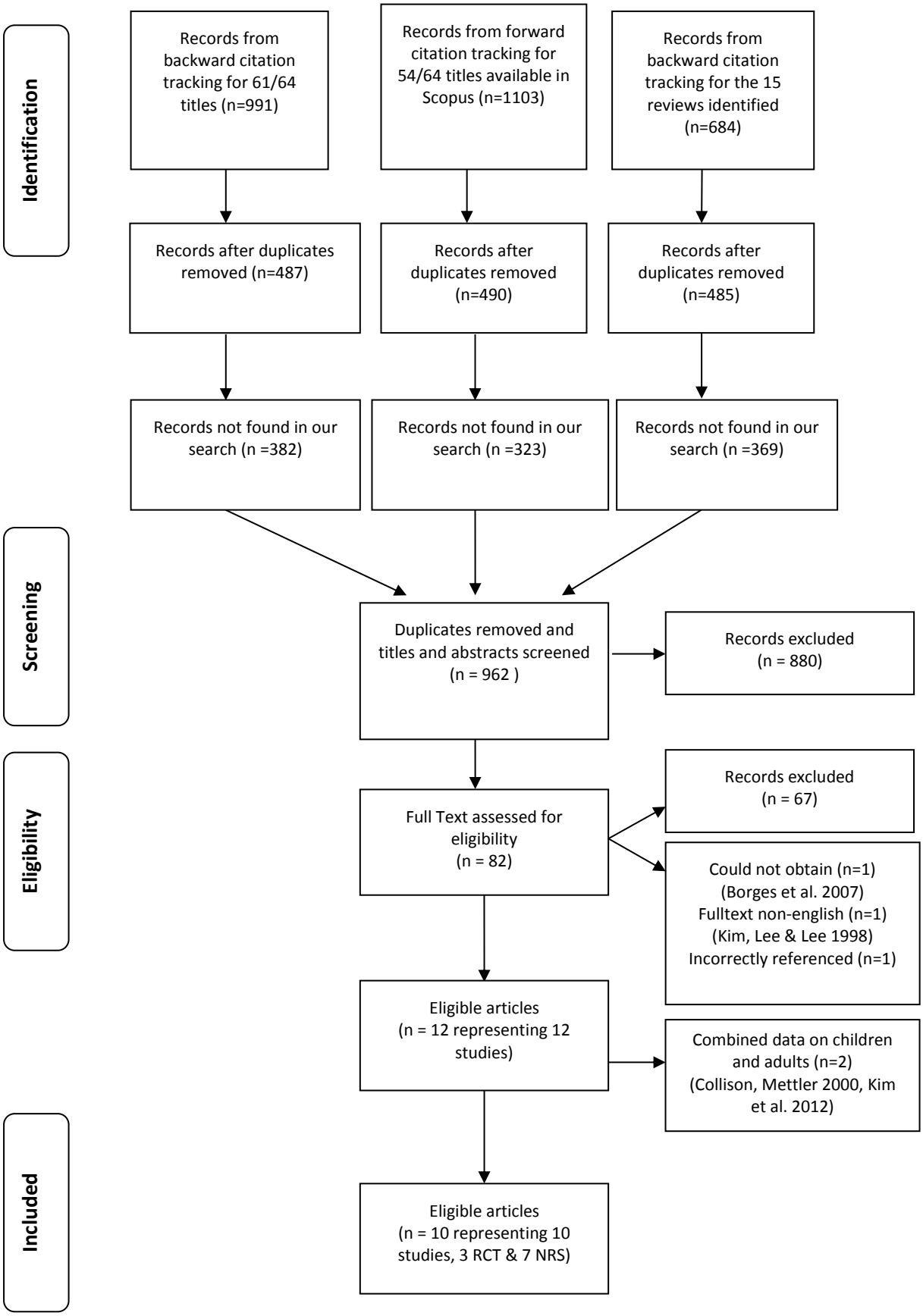


Figure 5.2 Citation Tracking Flow Diagram



5.3.2 Included studies

Of the 39 RCTs, 32 compared dexamethasone with another intervention (Catlin and Grimes, 1991, Volk et al., 1993, Ohlms, Wilder and Weston, 1995, April et al., 1996, Splinter and Roberts, 1996, Tom et al., 1996, Splinter and Roberts, 1997, Pappas et al., 1998, Splinter et al., 1998, Vosdoganis and Baines, 1999, Holt et al., 2000, Nawasreh, Fraihat and Maaita, 2000, Kyrou et al., 2001, Aouad et al., 2001, Giannoni, White and Enneking, 2002, Elhakim et al., 2003, Celiker et al., 2004, Hanasono et al., 2004, Samarkandi et al., 2004, Gunter et al., 2006, Malde, Sonawane and Jagtap, 2005, Kaan et al., 2006, Mohammad et al., 2006, Al-Shehri, 2007, Fazel et al., 2007, Alajmi et al., 2008, Czarnetzki et al., 2008, Bhattacharya et al., 2009, Karaman et al., 2009, Khani et al., 2009, Mohamed, Ibraheem and Abdelraheem, 2009, Gallagher T.Q. et al., 2012), of these, 17 studies involving 1973 participants did not report haemorrhage rate (Splinter and Roberts, 1996, Tom et al., 1996, Splinter and Roberts, 1997, Splinter et al., 1998, Vosdoganis and Baines, 1999, Kyrou et al., 2001, Aouad et al., 2001, Elhakim et al., 2003, Celiker et al., 2004, Samarkandi et al., 2004, Gunter et al., 2006, Al-Shehri, 2007, Fazel et al., 2007, Bhattacharya et al., 2009, Karaman et al., 2009, Khani et al., 2009, Mohamed, Ibraheem and Abdelraheem, 2009). In the remaining seven randomised studies, all participants received dexamethasone (Splinter et al., 1999, Sukhani et al., 2002, O'Flaherty and Lin, 2003, Derkay et al., 2006, Kim et al., 2007, Erdem et al., 2008, Rawlinson et al., 2011) and of these four did not report haemorrhage rate (588 participants) (Splinter et al., 1999, Sukhani et al., 2002, Kim et al., 2007, Erdem et al., 2008).

Nine of the 22 NRS compared dexamethasone with another intervention (Shikowitz and Jocono, 1996, Conley and Ellison, 1999, Lalakea, Marquez-Biggs and Messner, 1999, Werle et al., 2003, Edler et al., 2007, Liechti et al., 2007, Bennett and Emery, 2008, Shakeel et al., 2010, Windfuhr et al., 2011). Of these, six studies involving 688 participants did not report haemorrhage rate (Shikowitz and Jocono, 1996, Lalakea, Marquez-Biggs and Messner, 1999, Werle et al., 2003, Edler et al., 2007, Liechti et al., 2007, Bennett and Emery, 2008). In the remaining 13 (Gallagher R.M. et al., 2012, Thiesen et al., 2013, Postma and Folsom, 2002, Stewart, Baines and Dalton, 2002, Betts et al., 2003, Bent et al., 2004, Ewah, Robb and Raw, 2006, Kalantar, Takehana and Shapiro, 2006, Brigger, Cunningham and Hartnick, 2010, Rashid et al., 2010, Ahmed et al., 2011, Hanss et al., 2011, Robb and Ewah, 2011), all participants received dexamethasone and of these two did not report haemorrhage rate (258 participants) (Betts et al., 2003, Rashid et al., 2010).

5.3.2.1 Randomised studies which compared dexamethasone with another intervention & reported haemorrhage rate

These 15 studies involving 1693 participants are summarised in Table 5.2 (Catlin and Grimes, 1991, Volk et al., 1993, Ohlms, Wilder and Weston, 1995, April et al., 1996, Pappas et al., 1998, Holt et al., 2000, Nawasreh, Fraihat and Maaita, 2000, Giannoni, White and Enneking, 2002, Hanasono et al., 2004, Malde, Sonawane and Jagtap, 2005, Kaan et al., 2006, Mohammad et al., 2006, Alajmi et al., 2008, Czarnetzki et al., 2008, Gallagher T.Q. et al., 2012). They were all published between 1991 and 2012; the length of follow up ranged from 24 hours to 16 days and all of the studies compared dexamethasone with placebo. Seven of the studies used sharp dissection to remove the tonsils (Catlin and Grimes, 1991, Ohlms, Wilder and Weston, 1995, Holt et al., 2000, Malde, Sonawane and Jagtap, 2005, Kaan et al., 2006, Mohammad et al., 2006, Alajmi et al., 2008), three used more than one method, (Volk et al., 1993, Hanasono et al., 2004, Czarnetzki et al., 2008) while the remainder used electrodissection (April et al., 1996, Pappas et al., 1998, Nawasreh, Fraihat and Maaita, 2000, Giannoni, White and Enneking, 2002, Gallagher T.Q. et al., 2012). The dose of peri-operative dexamethasone ranged from 0.05mg/kg to 1mg/kg; in one study all patients received 10mg rather than a weight-based dose (Volk et al., 1993). At least some of the participants in four of the studies received NSAIDs (Giannoni, White and Enneking, 2002, Mohammad et al., 2006, Alajmi et al., 2008, Czarnetzki et al., 2008). The primary outcome in the majority of studies was post-operative nausea and vomiting and/or post-operative pain. Haemorrhage rate and severity was the primary outcome in one study (Gallagher T.Q. et al., 2012). Four studies pre-defined haemorrhage (April et al., 1996, Nawasreh, Fraihat and Maaita, 2000, Czarnetzki et al., 2008, Gallagher T.Q. et al., 2012) and seven reported additional information about the haemorrhages they detected (Table 5.3) (Catlin and Grimes, 1991, Volk et al., 1993, Ohlms, Wilder and Weston, 1995, April et al., 1996, Hanasono et al., 2004, Czarnetzki et al., 2008, Gallagher T.Q. et al., 2012). The risk of bias assessment using the Cochrane risk of bias tool was completed for these studies (Table 5.4): 12 had a high overall risk of bias (Catlin and Grimes, 1991, Volk et al., 1993, Pappas et al., 1998, Holt et al., 2000, Nawasreh, Fraihat and Maaita, 2000, Giannoni, White and Enneking, 2002, Hanasono et al., 2004, Malde, Sonawane and Jagtap, 2005, Mohammad et al., 2006, Alajmi et al., 2008, Czarnetzki et al., 2008, Gallagher T.Q. et al., 2012), and the remainder had an unclear overall risk of bias (Ohlms, Wilder and Weston, 1995, April et al., 1996, Kaan et al., 2006). The results of the McHarm scale assessment were as follows: only one of these studies pre-defined haemorrhage (Gallagher T.Q. et al., 2012), four actively

collected data on haemorrhage rate (Hanasono et al., 2004, Alajmi et al., 2008, Czarnetzki et al., 2008, Gallagher T.Q. et al., 2012), two passively collected data on haemorrhage rate (Pappas et al., 1998, Czarnetzki et al., 2008) and one used a standard check-list for haemorrhage rate data collection (Gallagher T.Q.et al., 2012). It was unclear whether there was a possibility of selective outcome reporting bias for five of these studies (April et al., 1996, Pappas et al., 1998, Nawasreh, Fraihat and Maaita, 2000, Hanasono et al., 2004, Kaan et al., 2006).

The overall haemorrhage rate for participants who received placebo ranged from 0% to 8.6% and the overall haemorrhage rate for participants who received dexamethasone ranged from 0% to 15.6%. The pooled estimate of haemorrhage rate for children who received dexamethasone was 6.2%. Of the 15 studies that reported data on haemorrhage rate, there was a non-significant increase in risk of haemorrhage for the dexamethasone intervention group (Peto odds ratio 1.41, 95% CI 0.89, 2.25, p = 0.15) (Figure 5.3).

14 out of 15 studies reporting data on haemorrhage separated the data into primary and secondary haemorrhage rates. For primary haemorrhage, only seven events were observed in the dexamethasone group and three on placebo; the pooled estimate demonstrated a non-significant increase in haemorrhage rate (Peto odds ratio 1.42, 95% CI 0.38, 5.36, p=0.61; Figure 5.4). For secondary haemorrhage, the pooled estimate again suggested that there was a non-significant increase in risk of haemorrhage for the dexamethasone intervention group (Peto odds ratio 1.42, 95% CI 0.86, 2.35, p = 0.17; Figure 5.4). In the four studies in which some patients also received NSAIDs, the pooled estimate indicated that there was a non-significant increase in risk of haemorrhage for the dexamethasone intervention group (Peto odds ratio 1.56, 95% CI 0.69, 3.51, p=0.28). For the eight studies in which no patients received NSAIDs, again there was a non-significant increase in risk of haemorrhage in the dexamethasone group (Peto odds ratio 1.32, 95% CI 0.73, 2.37, p=0.36) (Figure 5.5). A funnel plot of the studies included in the meta-analysis shows no evidence of publication bias (Figure 5.6).

Table 5.2 Description of randomised studies which compared dexamethasone with another intervention and reported haemorrhage rate[xvi]

Study	No. of participants	No. of participants in analysis	Length of follow up	Primary outcome(s)	Interventions	Participants per intervention group		Dissection Technique	Haemostasis Technique	Dexamethasone Dose	Peri-operative NSAID
						Dex	Other				
Catlin 1991	29	25	7 days	Length of stay, intravenous fluid requirement, pain, nausea, emesis, fever, post-op analgesia, complications, appetite.	Dexamethasone vs. Placebo	10	15	Adenoidectomy by curette, excision of tonsils by sharp and blunt dissection and snare	Electrocautery	8mg / square metre	None
Volk 1993	50	49	7-10 days	Fever, mouth odour, oral intake, pain, activity, weight loss, trismus and analgesic usage	Dexamethasone vs. Placebo	25	24	Combination of blunt and sharp dissection	Suction cautery	10mg	None

[xvi] Key to abbreviations used in tables Dex = dexamethasone, NSAID = non-steroidal anti-inflammatory drug, POD = post-operative day, PONV = post-operative nausea and vomiting, PR = per rectum

Study	No. of participants	No. of participants in analysis	Length of follow up	Primary outcome(s)	Interventions	Participants per intervention group		Dissection Technique	Haemostasis Technique	Dexamethasone Dose	Peri-operative NSAID
						Dex	Other				
Ohlms 1995	69	69	7 days	Pain scores	Dexamethasone vs. Placebo	34	35	Sharp dissection - snare technique, adenoid removed using curettes if indicated	Using packs, electro-cautery if persistent bleeding	0.5mg/kg (max 12mg)	None
April 1996	80	80	24 hours	Post-operative oral intake, pain, vomiting, temperature and complications	Dexamethasone vs. Placebo	41	39	Electro-dissection	Suction cautery	1mg/kg (max 16mg)	None
Pappas 1998	130	128	24hours from discharge	Post-operative nausea and vomiting	Dexamethasone vs. Placebo	63	65	Electro-dissection	Not reported	1mg/kg (max 25mg)	None

Study	No. of participants	No. of participants in analysis	Length of follow up	Primary outcome(s)	Interventions	Participants per intervention group		Dissection Technique	Haemostasis Technique	Dexamethasone Dose	Peri-operative NSAID
						Dex	Other				
Nawasreh 2000	120	120	24 hours	Temperature, vomiting, oral intake	Dexamethasone vs. Placebo	62	58	Electrocautery dissection, enlarged adenoid removed by shaving + curette	Not reported	1mg/kg (max 16mg)	Not reported
Holt 2000	132	125	6 days	Post- operative nausea and vomiting	Dexamethasone + tropisetron vs.tropisetron	66	59	Sharp dissection	Suture ligation	0.5mg/kg (max 8mg)	None
Giannoni 2002	50	50	10 days	Post-operative pain assessment	Dexamethasone vs. Placebo	25	25	Electrocautery	Not reported	1mg/kg (max 16mg)	Single pre-operative dose ibuprofen 15mg/kg
Hanasono 2004	222	222	3 days	Oral intake, pain scores, vomiting	Dexamethasone vs. Placebo	106	113	Electro-cautery OR sharp wire snare tran-section	Electrocautery OR directed cautery	1mg/kg	None

Study	No. of participants	No. of participants in analysis	Length of follow up	Primary outcome(s)	Interventions	Participants per intervention group		Dissection Technique	Haemostasis Technique	Dexamethasone Dose	Peri-operative NSAID
						Dex	Other				
Malde 2005	90	78	7 days	Post-operative pain and post-operative nausea and vomiting	Dexamethasone vs. Placebo	39	39	Sharp dissection snare technique	Ligation using ties, packs or sutured	0.15mg/kg	None
Kaan 2006	62	62	6 hours	Early oral intake, pain and vomiting	Dexamethasone vs. Placebo	32	30	Sharp dissection	Suture ligation	0.5mg/kg (max 16mg)	None
Mohammad 2006	50	50	24 hours	Vomiting, trismus, pain, fever, time to first solid intake, primary haemorrhage	Dexamethasone vs. Placebo	25	25	Sharp dissection snare technique	Electro-cautery OR ligation with silk	1mg/kg (max. 12mg)	Diclofenac IV if required
Czarnetzki 2008	215	207	10 days	Prevention of post-operative nausea and vomiting at 24 hours	Dexamethasone vs. Placebo	154	53	Cold steel, electro-cautery	Gauze compression, electrocautery	0.05-0.5mg/kg	Yes – some patients

Study	No. of participants	No. of participants in analysis	Length of follow up	Primary outcome(s)	Interventions	Participants per intervention group		Dissection Technique	Haemostasis Technique	Dexamethasone Dose	Peri-operative NSAID
						Dex	Other				
Alajmi 2008	80	80	16 days	Post-op pain, nausea, vomiting and oedema	Dexamethasone vs. Placebo	42	38	Sharp dissection	Packs or sutures, electrocautery if persistent bleed	1mg/kg	Profinal (ibuprofen) 5mg/kg PO if required
Gallagher T.Q. 2012	314	305	14 days	Rate and severity of post-tonsillectomy haemorrhage	Dexamethasone vs. Placebo	154	151	Mono-polar electrocautery and a spatula-tip	Suction cautery	0.5mg/kg (max 20mg)	None

Table 5.3 Details of haemorrhages in randomised studies which compared dexamethasone with another intervention

Study	Definition of haemorrhage	Participants per intervention group		Post-operative haemorrhage rate						Severity of Haemorrhage		Contact with author
				Primary		Secondary		Total				
		Dex	Other	Dex	Other	Dex	Other	Dex	Other	Dex	Other	
Catlin 1991	None	10	15	0	0	2	1	2	1	2x day 5, neither required treatment	1x day 6, did not require treatment	None
Volk 1993	None	25	24	0	0	2	1	2	1	Minor – controlled in the operating room	Minor – controlled in the operating room	Author confirmed that these were delayed bleeds

Study	Definition of haemorrhage	Participants per intervention group		Post-operative haemorrhage rate						Severity of Haemorrhage		Contact with author
				Primary		Secondary		Total				
		Dex	Other	Dex	Other	Dex	Other	Dex	Other	Dex	Other	
Ohlms 1995	None	34	35	0	0	3	0	3	0	Day 3 – cauterized in emergency department Day 10 – observed for 24 hours Day 12 – cauterized in theatre	-	None
April 1996	Primary < 24 hours, Secondary 2-14 days	41	39	0	0	1	1	1	1	Treated with suction and silver nitrate but not admitted	Day 7, admitted and required observation and intravenous fluids	Author provided data on NSAID use
Pappas 1998	None	63	65	0	0	0	0	0	0	-	-	Author provided data on bleeds

Study	Definition of haemorrhage	Participants per intervention group		Post-operative haemorrhage rate						Severity of Haemorrhage		Contact with author
				Primary		Secondary		Total				
		Dex	Other	Dex	Other	Dex	Other	Dex	Other	Dex	Other	
Nawasreh 2000	Primary <24 hours. Secondary post-operative day 2-14	62	58	0	0	2	2	2	2	No details	No details	Author provided data on timing of bleeds
Holt 2000	None	66	59	-	-	-	-	1	2	No details	No details	Author could not provide data on timing of bleeds by intervention
Giannoni 2002	None	25	25	0	0	1	1	1	1	No details	No details	None
Hanasono 2004	None	106	113	0	0	1	1	1	1	Day 3 requiring re-admission	Day 1 requiring re-admission	None
Malde 2005	None	39	39	0	0	0	1	0	1	-	Day 4	None
Kaan 2006	None	32	30	0	0	0	0	0	0	-	-	Author provided data on bleeds
Mohammad 2006	None	25	25	0	1	0	0	0	1	No details	No details	None

Study	Definition of haemorrhage	Participants per intervention group		Post-operative haemorrhage rate						Severity of Haemorrhage		Contact with author
				Primary		Secondary		Total				
		Dex	Other	Dex	Other	Dex	Other	Dex	Other	Dex	Other	
Czarnetzki 2008	Category 1 - 3[xvii]	154	53	5	0	19	2	24[xviii]	2	7x category 1 8x category 2 9x category 3	1x category 1 1x category 2	None
Alajmi 2008	None	42	38	0	0	0	3	0	3	-	All readmitted	None
Gallagher T.Q. 2012	Severity levels I-III[xix]	154	151	2	2	15	11	17	13	11x level I 3x level II 3x level III	7x level I 5x level II 1x level III	None

[xvii] **Category 1** - history of bleeding leading to readmission but without evidence of bleeding at re-admission. **Category 2** - readmission due to bleeding with evidence if bleeding at medical examination but no need for reoperation. **Category 3** - emergency reoperation due to bleeding.

[xviii] count of bleeds, there were 22 patients affected by 26 bleeds

[xix] **Level I** - All children who reported to have any history of postoperative haemorrhage, whether or not there was clinical evidence. **Level II** - All children who required inpatient admission for post-operative haemorrhage regardless of the need for operative intervention. This level excludes children undergoing evaluation in the emergency department for reported postoperative haemorrhage who had no evidence of clot formation or haemorrhage and were deemed safe discharge. **Level III** - All children who required return to the operating department for control of postoperative bleeding.

Table 5.4 Risk of bias for randomised studies which compare dexamethasone to another intervention and reported haemorrhage rate

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Catlin 1991	High	Unclear – 'double – blind randomisation system' – no details given	Unclear – see previous comment	Unclear – see previous comment	Unclear – not described	High - 29 patients recruited but 4 lost to follow up, unclear which intervention group these 4 were in.	High - reporting of pain and nausea and vomiting rates is incomplete	Low - none
Volk 1993	High	Unclear - not described	Unclear - not described	Unclear – can't tell if both study drugs looked the same	Unclear - not described	High - had problems with compliance with the post-operative questionnaire - so only got complete follow up for 19/25 dexamethasone and 16/24 placebo	Low - all outcomes reported for the patients followed up	Low - none
Ohlms 1995	Unclear	Unclear - not described	Unclear -not described	Low - medication prepared in pharmacy and administered in a double blind fashion	Low - see previous comment	Low - outcomes reported for all participants	Low -all outcomes reported for all patients	Unclear - although haemorrhage rate reported, looks like only detected if patients presented.

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
April 1996	Unclear	Low - table of random numbers distributed in blocks of six according to diagnosis	Low - patients weight and diagnosis list was sent to pharmacy and a syringe was prepared based on the random number	Low - numbered otherwise unmarked syringe containing colourless dexamethasone or saline	Low -parents undertook observations - they did not know which intervention the child had received	Low - outcomes reported for all participants	Unclear -reporting incomplete about pain medication requirements and pain rating	Low - none
Pappas 1998	High	Low - computer generated table	Unclear - not described	Unclear - states administered in a randomized double blind fashion - study drugs were prepared by pharmacy but don't know if they looked identical	Unclear - not described	Low - 2 had to be excluded – both were from the dexamethasone group	High - do not report compliance with analgesic regime at home	Unclear – relied on all parents completing diary adequately and reporting accurately

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Nawasreh 2000	High	Unclear -patients were divided into two groups	High - first group received dexamethasone, second group received placebo	High – see previous comment	Unclear - not described	Low - outcomes reported for all participants	Unclear - reporting incomplete about pain medication requirements	Unclear - follow up beyond discharge for adverse events seems to have only been if patients presented with a problem
Holt 2000	High	Low- random number generation tables	Low- packed in pharmacy and numbered according to randomisation	Low- two ampoules per study arm (saline instead of dexamethasone in one group)	Low- anaesthetist took no part in outcome assessment, this was undertaken by nursing staff who did not know which patients had received which intervention	Low- 132 enrolled - 7 excluded: 3x received propofol, 4x tonsillectomy cancelled.	High- followed up on day 6 - no report of haemorrhage rate despite this being reported for patients in the pre-discharge period	High-5 patients could not be contacted so no 6 day follow up data available for them - 3 x tropisetron, 2x tropisetron + dex

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Giannoni 2002	High	Low - random number generator (Excel)	Low -study drug was supplied as syringes of a liquid, identical in colour and volume but designated by a letter	Low - see previous comment	Low –all physicians, nurses, patients, parents and others caring for the subjects were blinded to the assignment until the conclusion of the study.	High - 3 patients, all from the dex group had data collection on the day of surgery but did not complete the evaluation period - 1 required steroid injection for asthma exacerbation on Day 2 and 2 could not be contacted after Day 2 so data for these 3 patients was excluded from analysis from day 1-10	Low - all endpoints are reported on	Low -none

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Hanasono 2004	High	Unclear - random number list - does not describe how it was generated	Unclear - study medication was supplied in a blinded manner and medication records were maintained in pharmacy until the end of the study	Unclear – see previous comment	Unclear – see previous comment	High – outcome measures for pain, emesis and oral intake only reported for 173 of 219 participants	Low – all outcomes are reported on	High - Only followed up for 3 days so would not observe haemorrhage occurring after that. Patients were only asked about post-op problems leading to unplanned office or emergency department visit on POD 3, minor bleeds might not have been reported.

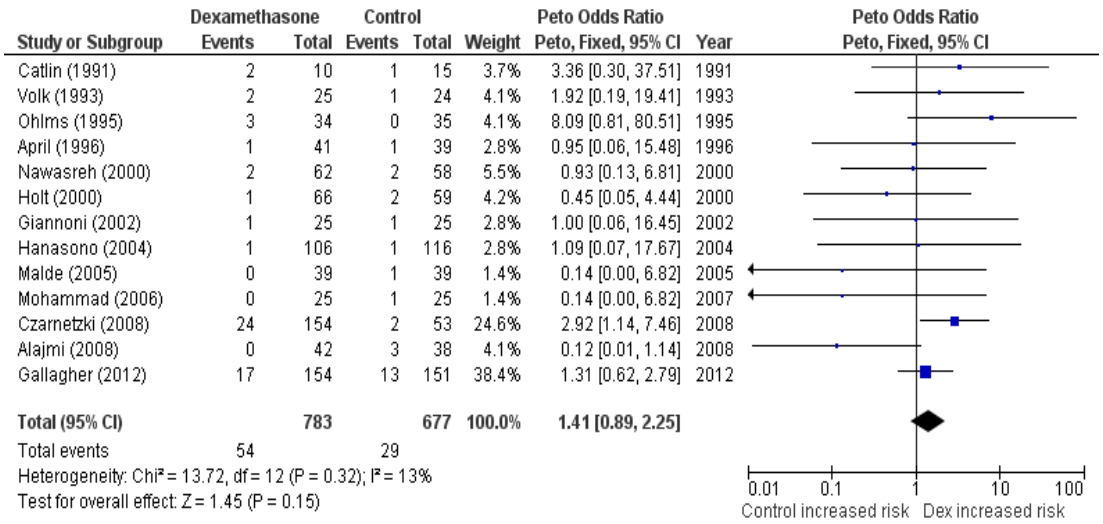
Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Malde 2005	High	Low - computer generated random number table	Unclear - not described	Unclear - not described	Low – undertaken by second anaesthetist who was unaware which drug had been administered	High- follow up details were not available for six patients of each group - does not specify from which point, assume means post-discharge follow-up	Low - all outcomes reported on	Low - none
Kaan 2006	Unclear	Low - randomizer.org was used	Unclear - not described	Unclear - all procedures were performed in a double-blind fashion - no details of how	Unclear - independent' observer - no details of how or whether they were blinded	Low - outcomes reported for all participants	Low – all outcomes are reported on	Unclear - instructed to return if bleeding, 2+ vomiting or inadequate oral intake - might have decided not to return so wouldn't have picked up these adverse events

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Mohammad 2006	High	Unclear - not described	Unclear - not described	Unclear - not described	Unclear - not described	Unclear - method of scoring pain is not well described	High - patients observed for 24 hours and discharged the day after surgery but study reports outcome data for secondary haemorrhage, oral intake at 36 & 72 hours, note the statement about contacting people by phone only if they had the facility	Low - none

Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Czarnetzki 2008	High	Unclear - randomization was done in blocks of 40 children (10 per group) - study medications were produced and randomized	Unclear - see previous comment	Low - indistinguishable syringes	Low - anaesthetist did not know what had been given so could not tell nurses / surgeons / parents what had been given	Low - patients lost to follow up or excluded because did not meet inclusion criteria are described	Low - all endpoints are reported on albeit with limited detail for some	High - Questionnaire at home was not completed for 23 children - so do not know if had NSAIDs, minor bleed or PONV that has not been recorded. There could be partial completion of some of the returned questionnaires. Early termination of this trial may have exaggerated harm.

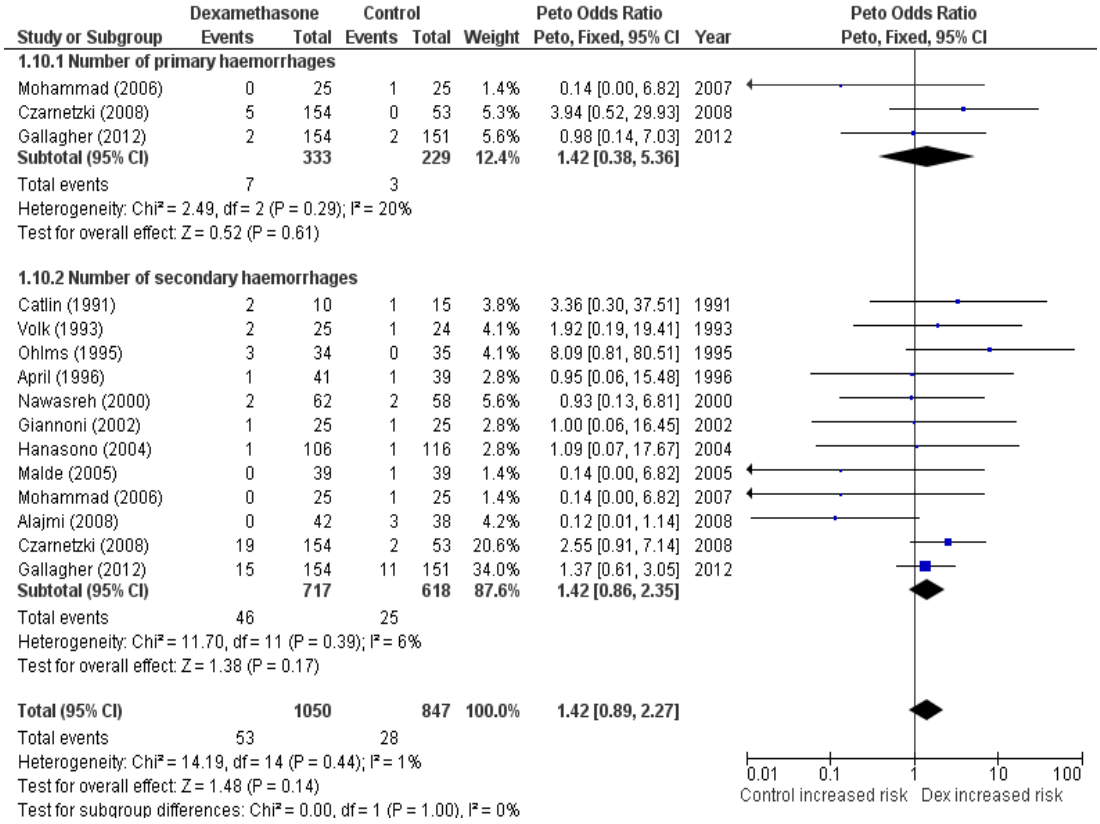
Study	Summary assessment of risk of bias	How was allocation sequence generated?	How was allocation sequence concealed?	What measures were taken to blind participants and personnel?	What measures were taken to blind outcome assessors?	Is the outcome data complete? Did the authors report exclusion and attrition and give reasons for these?	Is there a possibility of selective outcome reporting?	Are there any other potential sources of bias?
Alajmi 2008	High	Unclear - first two patients were given dexamethasone and the rest were given saline - in the next operating theatre this was reversed	Unclear - not described	Unclear -states that participants were blinded	Unclear - some personnel knew who had which intervention, don't know who did observations	Low - outcomes reported for all participants	High - outcomes not reported for each follow-up visit, haemorrhage only reported in the context of readmission - authors state that no re-admission signified no complication but do not report what was recorded at POD 7, POD 10 & POD 16 follow ups	Low -none
Gallagher T.Q. 2012	High	Low - random number generator	Low - carried out by hospital pharmacy	Low- identical packaging of dex and placebo	Low - anaesthetist, surgeon, patients, guardians, data collectors were blinded	Low - 9 excluded, 3 received additional post-op steroid, 6 lost to follow up but clear which intervention groups these 9 were in	High – data on secondary outcomes not fully reported	Unclear - strict instructions to return with bleeding - but might have gone elsewhere or not attended if only minor

Figure 5.3 Haemorrhage rates for randomised studies which compared dexamethasone with another intervention[xx]



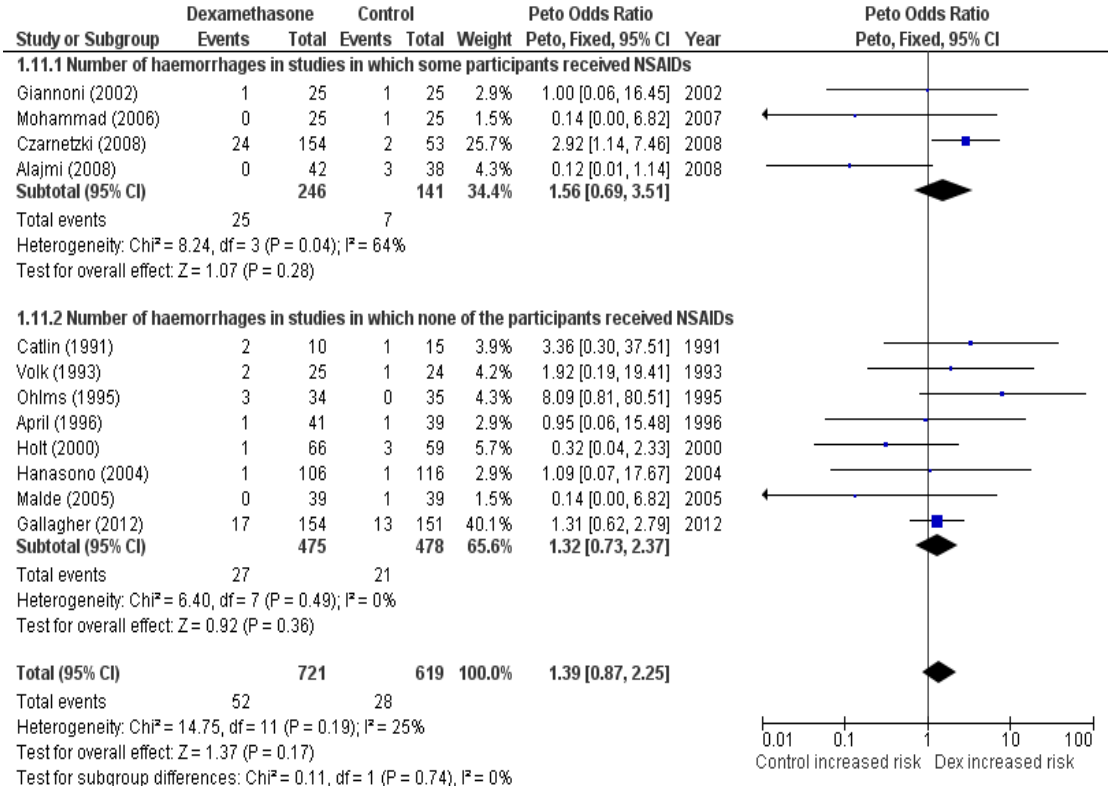
[xx] The following reported zero haemorrhages in both intervention groups: Pappas (1998) dexamethasone (0/63) control (0/65), Kaan (2006) dexamethasone (0/32) control (0/30)

Figure 5.4 Sub-group analysis – Primary & Secondary Haemorrhage Rates[xxi]



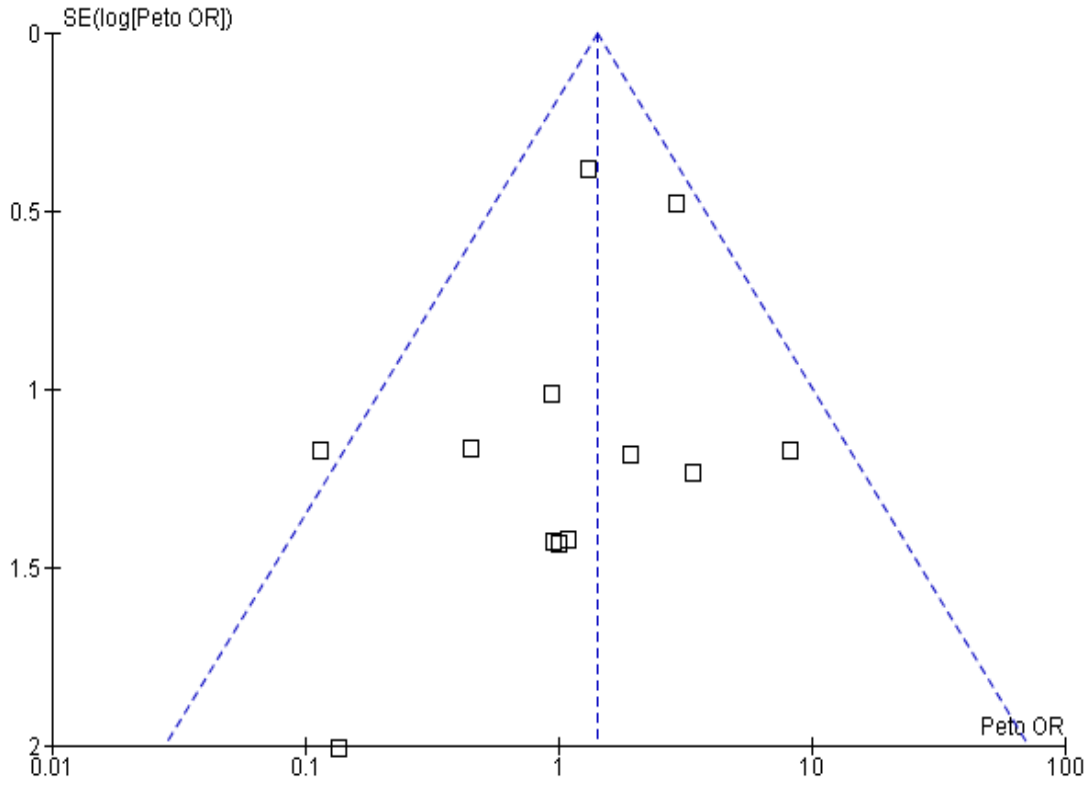
[xxi] Holt (2000) reported only overall haemorrhage rate. The following reported zero primary haemorrhages in both intervention groups: Volk (1993), Ohlms (1995), April (1996 , Pappas (1998), Nawasreh (2000), Giannoni (2002), Hanasono (2004), Malde (2005), Kaan (2006), Catlin (2006), Alajmi (2008). The following reported zero secondary haemorrhages in both intervention groups: Pappas (1998), Kaan (2006)

Figure 5.5 Sub-group analysis – Haemorrhage rates with NSAID use[xxii]



[xxii] The following reported zero haemorrhages in both intervention groups: Pappas (1998), Kaan (2006)
For the following it was unclear whether NSAIDs had been administered: Nawasreh (2000)

Figure 5.6 Funnel Plot



5.3.2.2 Randomised studies in which all participants received dexamethasone and reported haemorrhage rate

These three studies involved 249 participants and were published between 2003 and 2011 (O'Flaherty and Lin, 2003, Derkay et al., 2006, Rawlinson et al., 2011). Rawlinson et al. (2011) followed patients up for 14 days, Derkay et al. (2006) for four hours and O'Flaherty & Lin (2003) followed up patients for 24 hours. The primary outcome in all three studies was post-operative pain and/or post-operative nausea and vomiting. In Rawlinson's study, study all patients received dexamethasone 0.4mg/kg and the electrocautery and microdebrider dissection techniques were compared; no patients received NSAIDs (Rawlinson et al., 2011). Derkay et al. (2006) administered dexamethasone 0.1mg/kg to all participants and tonsillectomy was undertaken by cold steel dissection. In their study which compared magnesium and ketamine use, O'Flaherty & Lin (2003) administered 0.2mg/kg dexamethasone to all participants, but did not report the tonsillectomy technique(s) used and their reporting of early post-operative haemorrhages was ambiguous (Table 5.5). Only one study pre-defined haemorrhage (Derkay et al., 2006). Another actively collected haemorrhage rate data as well as specifying the timing and frequency of haemorrhage rate data collection (O'Flaherty and Lin, 2003). The haemorrhage rates in two of these studies ranged from 0% to 2% (Derkay et al., 2006, Rawlinson et al., 2011). The rate was unclear in one of these studies (O'Flaherty and Lin, 2003).

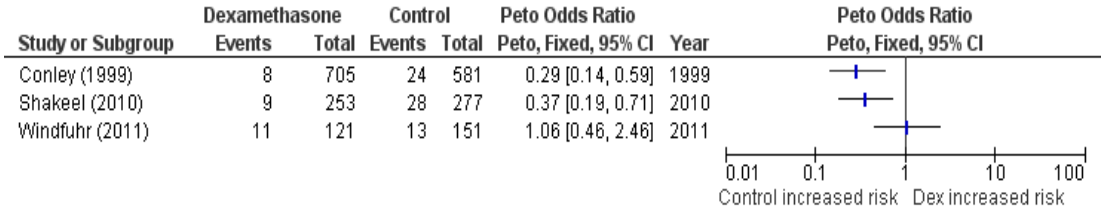
Table 5.5 Randomised studies in which all participants received dexamethasone and in which haemorrhage rate was reported

Study	No. of participants	Length of follow up	Primary outcome(s)	Interventions	Dissection Technique	Haemostasis Technique	Dex Dose	Peri-operative NSAID	Post-operative haemorrhage rate			Contact with authors
									Primary	Secondary	Total	
O'Flaherty 2003	10 Ketamine/Placebo	24 hours	Post-operative pain	All had dex	Not reported	Not reported	0.2 mg/kg	1 patient had ibuprofen	Unclear	0	-	None
	11 Magnesium/Placebo							none	Unclear	1	-	
	9 Ketamine/Magnesium							1 patient had ibuprofen	Unclear	1	-	
	7 Placebo/Placebo							none	Unclear	1	-	
Derkay 2006	150	14 days	Post-operative pain	All had dex	Electrocautery	Suction electrocautery	0.4 mg/kg (max 20mg)	Not reported	Not reported	Not reported	3	None
Rawlinson 2011	32	4 hours	PONV and pain	All had dex + ondansetron	Cold steel	Bipolar diathermy	0.1 mg/kg	Ibuprofen 5mg/kg	0	0	0	None
	30							Diclofenac 1-2mg/kg IV	0	0	0	

5.3.2.3 Non-randomised studies which compared dexamethasone with another intervention and reported haemorrhage rate

There were 2088 participants in these three studies published between 1999 and 2011(Conley and Ellison, 1999, Shakeel et al., 2010, Windfuhr et al., 2011). They were all retrospective case note reviews and two of them retrieved two week follow up data (Conley and Ellison, 1999, Shakeel et al., 2010). In one of the studies, a single method of tonsil dissection was employed (Windfuhr et al., 2011), while in the other studies there were several methods recorded (Conley and Ellison, 1999, Shakeel et al., 2010). In the retrospective chart review conducted by Conley & Ellison (1999), patients who received dexamethasone were operated on using a standard surgical technique – cold-knife dissection and snare and haemostasis was achieved using tonsillar packs dipped in bismuth subgallate-phenylephrine hydrochloride mixture followed by suction electrocautery and a three minute observation period. However, patients who did not receive dexamethasone were operated on using either cold-knife dissection, snare and suction electrocautery or electrocautery dissection; tonsillar packs were not used in any of these patients**.** The dexamethasone doses administered in these three studies ranged from 0.04mg/kg to 0.62mg/kg. The report of one study specifies that dexamethasone was administered or withheld according to the anaesthetist's preference (Windfuhr et al., 2011). NSAIDs were administered to some of the participants in one study (Table 5.6) (Shakeel et al., 2010). The primary outcome was haemorrhage rate for all of these studies. Two of these studies pre-defined haemorrhage and all reported their haemorrhages in detail, providing information on the need for and types of re-intervention (Table 5.7) (Conley and Ellison, 1999, Windfuhr et al., 2011). All of these studies pre-defined haemorrhage but none actively collected data on haemorrhage rate. None of these studies used a standard checklist for haemorrhage rate data collection and for all of them it was unclear whether there was a possibility of selective outcome reporting bias. The haemorrhage rates for participants who did and did not receive dexamethasone ranged from 1.1% to 8.3% and 3.8% to 9.7%, respectively (Figure 5.7).

Figure 5.7 Haemorrhage rates in non-randomised studies



5.3.2.4 Non-randomised studies in which all participants received dexamethasone & reported haemorrhage rate

These 11 studies included 6200 participants, and were published between 2002 and 2011 (Gallagher R.M. et al., 2012, Thiesen et al., 2013, Postma and Folsom, 2002, Stewart, Baines and Dalton, 2002, Bent et al., 2004, Ewah, Robb and Raw, 2006, Kalantar, Takehana and Shapiro, 2006, Brigger, Cunningham and Hartnick, 2010, Ahmed et al., 2011, Hanss et al., 2011, Robb and Ewah, 2011). They comprise five retrospective chart reviews (Postma and Folsom, 2002, Bent et al., 2004, Kalantar, Takehana and Shapiro, 2006, Brigger, Cunningham and Hartnick, 2010, Hanss et al., 2011), three prospective observational studies (Gallagher R.M. et al., 2012, Thiesen et al., 2013, Ewah, Robb and Raw, 2006), two audits (Stewart, Baines and Dalton, 2002, Robb and Ewah, 2011) and a retrospective analysis of data from an RCT (Ahmed et al., 2011). The period of follow-up in these studies ranged from six hours to 30 days and seven reported the technique used to remove the tonsils (Postma and Folsom, 2002, Stewart, Baines and Dalton, 2002, Bent et al., 2004, Ewah, Robb and Raw, 2006, Brigger, Cunningham and Hartnick, 2010, Hanss et al., 2011, Robb and Ewah, 2011). The primary outcome was haemorrhage rate in two of these studies (Brigger, Cunningham and Hartnick, 2010, Ahmed et al., 2011), while most of the remaining studies examined post-operative pain and vomiting. Dexamethasone doses ranged from 0.06mg/kg to 1.5mg/kg and NSAID use was reported in four of the studies (Gallagher R.M. et al., 2012, Thiesen et al., 2013, Ewah, Robb and Raw, 2006, Robb and Ewah, 2011). Two of the studies pre-defined haemorrhage (Postma and Folsom, 2002, Brigger, Cunningham and Hartnick, 2010), one undertook passive haemorrhage rate data collection (Brigger, Cunningham and Hartnick, 2010), the timing and frequency of haemorrhage rate data collection was specified by two authors (Stewart, Baines and Dalton, 2002, Hanss et al., 2011) and there was a possibility of selective outcome reporting in two studies (Thiesen et al., 2013, Kalantar, Takehana and Shapiro, 2006). The haemorrhage rate in these 11 studies ranged from 0.4% to 5.7%.

Table 5.6 Description of non-randomised studies which compared dexamethasone with another intervention and reported haemorrhage rate

Study	No. of participants	Design	Primary outcome(s)	Interventions	Participants per intervention group		Dissection Technique	Haemostasis Technique	Dex Dose	Peri-operative NSAID
					Dex	Other				
Conley 1999	1286	Retrospective casenote review	Incidence of post-tonsillectomy haemorrhage	Group 1 Dexamethasone, Group 2 no dexamethasone	705	581	Cold -knife dissection + snare or electro-cautery dissection	Group 1 - tonsillar packs dipped in bismuth subgallate +/- electro-cautery Group 2 - suction electro-cautery	0.5mg/kg (max 10mg)	None
Shakeel 2010	530	Retrospective casenote review	Incidence of secondary post-tonsillectomy bleeding	Dexamethasone OR no dexamethasone	253	277	Cold steel, bipolar diathermy, harmonic scalpel, coblation, monopolar diathermy	Not reported	Various – recorded as <0.1mg/kg and >0.1mg/kg	Post-operative ibuprofen
Windfuhr 2011	272	Retrospective casenote review	Rates of post-operative nausea, vomiting and bleeding	Dexamethasone OR no dexamethasone	121	151	Cold - dissection with scissors, raspatory, removing the inferior pole with a snare	Suture ligation and bipolar cautery where required	0.04-0.62mg/kg	None

Table 5.7 Details of haemorrhages reported in non-randomised studies which compared dexamethasone with another intervention

Study	Definition of haemorrhage	No. of participants	Participants per intervention group		Post-operative haemorrhage rate						Severity of haemorrhage		Contact with authors
					Primary		Secondary		Total				
			Dex	Other	Dex	Other	Dex	Other	Dex	Other	Dex	Other	
Conley 1999	Category 1-5[xxiii]	1286	705	581	0	6	8	16	8	24	2x delayed major 5x delayed minor 1x delayed minor that occurred at home	5x major primary 1x minor primary 11x major delayed 5x minor delayed 2x occurred at home	Author provided data on NSAIDs
Shakeel 2010	None	530	253	277	0	0	9	28	9	28	6x evidence on examination 1x required re-operation	9x evidence on re-examination 5x required re-operation	Author provided data on dexamethasone dose, NSAID administration and timing and severity of bleeds.
Windfuhr 2011	Primary <24 hours, Secondary >24 hours	272	121	151	3	4	8	9	11[xxiv]	13[xxv]	3x day of surgery 1 x days 2, 5, 7 2x day 32x day 8 1x day 10 7 required surgical intervention	4x day of surgery 3x day 1 1 x days 3,5,6,7,9,12 10 required surgical intervention	None

[xxiii] 1.no bleeding 2. immediate major (<24 hours requiring re-operation) 3. immediate minor (<24 hours requiring admission) 4. delayed major (>24 hours requiring re-operation) 5. delayed minor (>24 hours, not requiring admission)
[xxiv] Count of bleeds, 9 participants experienced 1 haemorrhage, 1 participant experienced 2 secondary haemorrhages
[xxv] Count of bleeds, 11 participants experienced 1 haemorrhage, 1 participant experienced 2 secondary haemorrhages

5.4 Discussion

5.4.1 Summary of findings

Data from the 15 RCTs included in our meta-analysis and the three NRS in which dexamethasone was compared with another intervention, indicate that the overall risk of post-tonsillectomy haemorrhage in children is not significantly increased by the peri-operative use of dexamethasone.

5.4.2 Limitations of included studies

The overall risk of bias was high or unclear for all of the included RCTs. Amongst both the randomised and non-randomised studies there was clinical heterogeneity. Some of the elements of study design that have an impact on haemorrhage risk are: dissection technique, haemostasis technique (Lowe et al., 2007), patient age, gender and the indication for surgery (Windfuhr, Chen and Remmert, 2005, Brigger, Cunningham and Hartnick, 2010) and the peri-operative use of NSAIDs (Lewis et al., 2013). Our evaluation of haemorrhage rate data collection and reporting indicates that this was inadequately reported in the majority of studies. Many studies did not follow up patients beyond the point at which primary outcomes would be measured. Studies which relied on re-admission as a method of haemorrhage detection may have missed minor self-limiting bleeds or bleeds attended to at other healthcare facilities. Studies which used patient and parent questionnaires to detect bleeding episodes may have missed haemorrhages due to questionnaires being incomplete or unreturned. Very few studies described active surveillance for adverse outcomes, for example a telephone call or face-to-face contact whereby participants were specifically asked about any haemorrhages experienced.

5.4.3 Comparison with results of previous studies

In our meta-analysis of 15 RCTs, the pooled estimate risk ratio for haemorrhage in patients who received dexamethasone was 1.41 (95% CI 0.89, 2.25, p=0.15; I^2= 13%). The interpretation of this finding conforms to that of three previous meta-analyses of randomised studies although the difference in the summary statistic reflects differences in study identification and inclusion. Geva et al. (2011) calculated a relative risk of haemorrhage of 1.02 (95% CI 0.65-1.61, p=0.92) for adult and paediatric patients in their meta-analysis who received dexamethasone. The haemorrhage rate amongst those who received dexamethasone was 5.9%. Their analysis included 14 studies, nine of which were also included in this analysis; of the five that were not included in this analysis, three

included adult participants only, one was in Hebrew and for one we were not able to obtain sufficient detail from the author about the participants who experienced a haemorrhage. A meta-analysis of studies involving only children calculated an odds ratio of haemorrhage for children who had received dexamethasone compared with those who did not (OR=1.07; 95%CI 0.58, 1.98, p=0.82) (Shargorodsky, Hartnick and Lee, 2012). Their analysis included 12 studies of which 10 were the same as those in this review. The two studies we did not include were those where haemorrhage rate data could not be obtained from the authors. The haemorrhage rate for children who received dexamethasone in this study was 6.2%. Finally, the most recent meta-analysis calculated an odds ratio of 0.96 (95% CI 0.66, 1.40, I^2 = 0%) (Plante et al., 2012). This review included 29 studies of systemic steroid use in tonsillectomy and haemorrhage rate in adults and children. The haemorrhage rate for patients who received systemic steroids was 4.6%. We included 13 of these 29 plus an additional study they did not identify (Pappas et al., 1998) and another where the results were published more recently (Gallagher T.Q. et al., 2012). Of the 16 studies, we did not include: five were not in English, six involved adults only, for three data on haemorrhage rate could not be obtained, one reported combined data on adults and children and in one the intervention was prednisolone rather than dexamethasone.

5.4.4 Data not included in previous reviews

This study included two RCTs not included by previous systematic reviews. One of these studies was identified in both the EMBASE and MEDLINE. Although it did not report haemorrhage rate, we obtained the necessary data from the author (Pappas et al., 1998). The results of the second randomised study by Gallagher T.Q. et al. (2012) were published after the previous reviews. This was the only randomised study included here which had the rate and severity of post-tonsillectomy haemorrhage as its primary outcome measure. The study was a non-inferiority study (1-sided test). Non-inferiority was tested for haemorrhage events in each of three groups (level I-III, see footnote to Table 5.3 for definitions) rather than grouping all haemorrhage events together. The hypothesis was that dexamethasone would not increase haemorrhage rate by more than 5% (rather than that there would be no difference between the two groups). Non-inferiority was not shown for level I bleeding events but it was demonstrated for both level II and level II bleeding events. Unsurprisingly, the assessments of risk of bias and methodological quality show that the risk of bias for this study is generally low and overall the methodology for haemorrhage rate detection and reporting was the most robust. Consequently, the haemorrhage rate in this study (9.6%) is at the upper end of the range for the randomised studies included in

this review. The overall relative risk of haemorrhage with dexamethasone administration was calculated in this study and a non-significant increase in risk was found: 1.32 (95% CI 0.58-3.07, p = 0.5653). The categorisation of haemorrhages by severity level was one strength of this study; this was undertaken by only six of the randomised studies included in the meta-analysis. When haemorrhages are categorised in such a way the results become useful to clinicians and policy-makers. In T.Q. Gallagher's study, although there were a total of 30 haemorrhages, 18 did not require any change in post-operative care and only four required re-operation.

The evaluation of haemorrhage rate data from NRS was not conducted in previous reviews. Evaluation of three studies provided conflicting results. The data for two of these studies indicated that patients in the control group were more likely to experience a haemorrhage than patients who received dexamethasone (Conley and Ellison, 1999, Shakeel et al., 2010). In one of these studies, there were too many differences in the way the two intervention groups were managed to draw any meaningful conclusions about the effects of dexamethasone administration on haemorrhage risk (Conley and Ellison, 1999). In a third study, there was no difference between the intervention groups but dexamethasone had been administered according to anaesthetist preference (no further details available), and it is therefore possible that patients with an increased risk of haemorrhage were not administered dexamethasone (Windfuhr et al., 2011). All three studies were retrospective chart reviews using hospital records. Although they report haemorrhage rates which correspond to those quoted in the literature (Randall and Hoffer, 1998), there is some evidence that retrospective chart review underestimates haemorrhage rate (Doshi et al., 2008).

5.5 Conclusion

This study did not find any evidence that dexamethasone significantly increases the risk of post-tonsillectomy haemorrhage. However the degree of imprecision of the odds ratio in the pooled estimate (upper bounds of the 95% CI was 2.25) prevents us from ruling out a clinically relevant doubling in risk. There were insufficient data to determine any additional impact of NSAID use, an issue which needs further investigation given the recent moves away from use of codeine in children after tonsillectomy. In the studies included here, inadequacies in haemorrhage rate detection and reporting were identified. Further large studies (both randomised and observational) are needed to provide evidence about the safety of dexamethasone ± NSAIDs in paediatric tonsillectomy. These need to have

haemorrhage rate as their primary outcome with pre-defined levels of severity. Robust methodologies need to be developed with strategies to prospectively and actively capture data on haemorrhage outcomes for all participants over an adequate follow up period. The findings of four ongoing trials will provide additional data on outcomes for the use of dexamethasone (Centre Hospitalier Universitaire Vaudois, University of Turku) and ibuprofen (Massachusetts Eye and Ear Infirmary, Cumberland Pharmaceuticals) in paediatric tonsillectomy.

6 Development of a risk score for post-operative vomiting in children

6.1 Introduction

In chapter 3 of this thesis, the impact of off-label and unlicensed prescribing on ADR risk in inpatients was explored in a case-control study nested within a prospective cohort. Medicines administered in theatre were not included in the analyses because, in the prospective cohort study, they had only been recorded if they had been implicated in an ADR. In the multivariate analysis, exposure to GA was a significant predictor of ADR risk (HR 5.30, 95% CI 4.42, 6.35 p<0.001). In the prospective cohort study, nausea and/or vomiting following GA was the most common reaction type (Thiesen et al., 2013). In view of the significant impact of GA on ADR risk and of PONV on the ADR rate, a more detailed assessment of these cases was undertaken.

Post-operative nausea and vomiting (PONV) are significant causes of morbidity in paediatric surgical patients. Post-operative vomiting (POV) rather than PONV rates tend to be reported in paediatric studies because very young children may not be able to report nausea. The overall incidence of POV in children is 9-42%, although severe or intractable POV is far less common (Rose and Watcha, 1999, Kovac, 2007). The reported incidence of POV in some surgery types is higher, for example up to 80% in strabismus surgery, 70% in tonsillectomy and 66% following craniotomy (Kovac, 2007).

It is important that we are able to predict the likelihood of POV. Prediction provides us with opportunity for prevention either by the administration of prophylactic anti-emetics or the modification of other aspects of peri-operative care.

The POst-operative VOmiting in Children (POVOC) score was developed as a simplified model to assess POV risk in children undergoing surgery, since pre-existing tools had been developed for use in adults and had limited application in children (Eberhart et al., 2004). Its development utilised data from 1401 children aged 0-14 years. Individuals who had received intra-operative anti-emetics were excluded (n=88), as were those who were lost to follow up, or had incomplete records (n=56). Data from the remaining 1257 children were analysed, 657 cases to develop the score and 600 to validate it. The final score contained the following four risk factors:

1. strabismus surgery
2. age > 3 years
3. duration of surgery >30 minutes; and
4. history of POV in the child or history of PONV in the father, mother or siblings

The UK national guideline (The Association of Paediatric Anaesthetists of Great Britain & Ireland, 2009) on the prevention of POV places risk factors for POV into three categories:

1. patient-related e.g. age > 3years, history of POV
2. surgery-related e.g. duration of the procedure and type of surgery; and
3. anaesthetic-related e.g. technique, anaesthetic agents

They specify that there is an increased risk with adenotonsillectomy and strabismus surgery and that volatile anaesthetic, opioids and anticholinesterase agents may increase the risk of POV.

The aim of the study described in this chapter was to explore in more detail the POV cases detected in the prospective cohort study and to use a case-control design to develop a risk score for POV in children. The additional data in this study were collected and analysed by JRB, with advice from the ADRIC statistics team.

6.2 Methods

6.2.1 Study design

In order to identify risk factors for POV, it was necessary to compare the characteristics of patients from the prospective cohort study who experienced POV with those who did not. POV was defined as that which started within 24hrs after a general anaesthetic. The analysis in chapter 3 included only probable and definite ADRs because these were deemed to have a low probability of the underlying disease being responsible for the reaction. Possible ADRs were included in this study of POV risk factors because we wanted to explore more than just drug-related risk factors. Due to resource constraints, it was not possible to include all patients who did not experience POV as controls. Therefore, a nested case-control design was chosen; all possible, probable and definite POV cases were included and they were matched 1:1 to controls who had not experienced POV. This study used data derived from a larger study which used routinely collected clinical data in an anonymised format, the Chair of Liverpool Paediatric LREC informed us that this study did not require individual patient consent or review by an Ethics Committee.

6.2.2 Identification of cases

Cases were patients from the prospective cohort study who experienced POV which, following causality assessment using the LCAT (Gallagher et al., 2011) was deemed to be possible, probable or definite. The inclusion and exclusion criteria for the prospective cohort study are described in chapter 3 of the thesis. POV was defined in the prospective cohort study protocol as that which started within 24hrs after general anaesthetic and when the patient was back on the ward, it was recorded in the study database as 'procedural vomiting'.

There were 367 possible, probable or definite cases of POV in the prospective cohort study. We included only the first episode of POV in each individual. After subsequent episodes of POV in the same individual were excluded, 356 cases remained in this study.

6.2.3 Identification of controls

Controls were first admissions who met the inclusion criteria for the prospective cohort study and who underwent a surgical procedure within the time frame of the study but did not go directly to PICU after theatre and were not suspected of experiencing POV. The

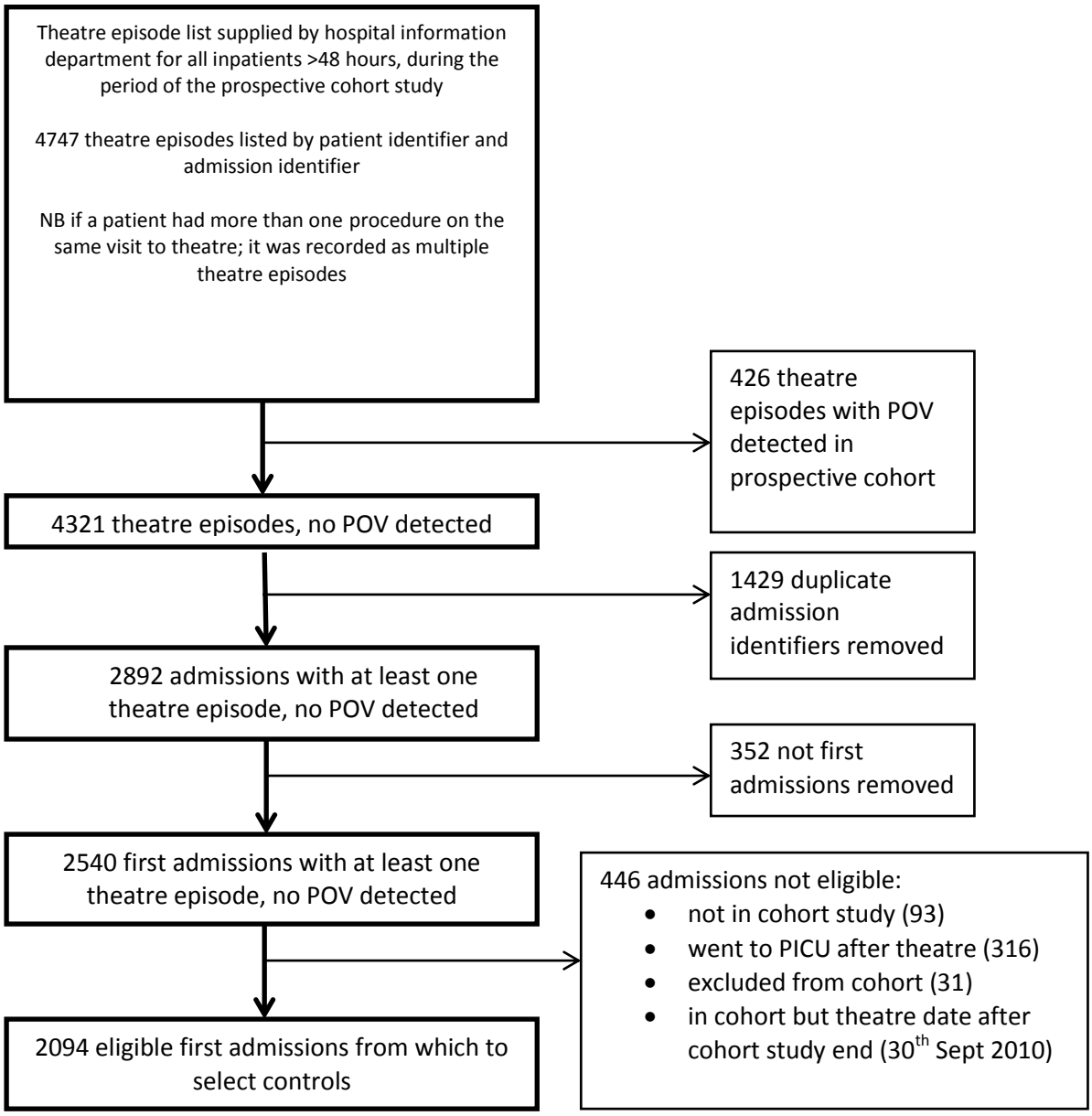
procedure for identifying potential controls is shown in Figure 6.1. Controls were selected at random from the list of patient numbers, ordered lowest to highest.

If a patient who a) experienced POV which started in theatre recovery or b) was not identified in the prospective cohort, was identified amongst the controls, they were included as a case and a new control was selected.

6.2.4 Selection of predictors

The selection of candidate predictors for inclusion was based on the risk factors proposed in UK (The Association of Paediatric Anaesthetists of Great Britain & Ireland, 2009) and US (Gan et al., 2003) guidelines and was discussed with clinical experts. The data available in patient records were examined and the practicalities and relative merits of collecting each item in terms of predictive value were discussed with a clinical expert. The following predictors were identified: specialty, age, gender, history of POV, pre-operative state, procedure type, duration of anaesthesia, pre-medication, induction agent, maintenance agent, intra-operative analgesia, intra-operative anti-emetics, other intra-operative medicines, intra-operative fluids, post-operative opioids, post-operative epidural, post-operative non-steroidal anti-inflammatory drugs (NSAIDs), other post-operative medicines and intra- or post-operative hypotension. The following items were also included: patient identifier, patient weight and details of the POV episode (Table 6.1).

Figure 6.1 Procedure for identifying controls



6.2.5 Data collection

Data for each case and each control were obtained from the prospective cohort study database if it was available, with additional data obtained from the patients' electronic theatre record and case notes. Table 6.1 indicates which data were collected, and from which sources, for both cases and controls. Definitions of intra-operative and post-operative hypotension (Table 6.2, (Haque and Zaritsky, 2007)) were recommended by a clinical expert to inform a pragmatic approach for data collection, since there is no consensus definition of intra-operative hypotension in children (Nafiu et al., 2009).

6.2.6 Refinement of predictors

After data collection but before analysis was undertaken, the list of predictors was reassessed and amended. This was undertaken in conjunction with a clinical expert taking into account the clinical questions we might seek to address such as the differences in the likelihood of POV with different anti-emetic agents. It also took into account the observations about data availability and quality made during data collection and the need to simplify predictors to facilitate analysis (Table 6.3). This process resulted in the inclusion of 28 predictors in the exploratory analysis (Table 6.8).

Table 6.1 Dataset items and sources

Item	Details recorded	Source for cases	Source for controls
Unit Number (patient identifier)	-	Study database	List of controls
Specialty	Hospital record abbreviation e.g. NEUS	Electronic theatre record	Electronic theatre record
ADRID (POV case identifier)	-	Study database	Not applicable
Weight (kg)	-	Study database	Study database
POV Duration (days)	-	Study database	Casenotes
Total vomits recorded	-	Study database/ casenotes	Casenotes
Post-operative anti-emetics	Name, dose, frequency, duration	Study database/ casenotes	Study database/ casenotes
Age on admission	-	Study database	Study database
Gender	-	Study database	Study database
Previous GA?	Yes or No	Study database/casenotes/electronic record	Casenotes/electronic record
History of POV	Yes or No, year of previous GA (if any)	Study database/casenotes/electronic record	Casenotes/electronic record
Pre-operative state	co-operative/upset/other	Casenotes	Casenotes
Procedure	Name of procedure	Electronic record	Electronic record
Duration of anaesthesia	Minutes between anaesthesia started and into recovery	Electronic record	Electronic record
Details of Premedication	Name, dose	Study database/casenotes	Study database/casenotes
Induction anaesthesia	Name, dose if intravenous	Study database/casenotes	Casenotes
Maintenance anaesthesia	Name, dose if intravenous	Study database/casenotes	Casenotes
Intra-operative analgesia	Name, dose	Study database/casenotes	Casenotes

Item	Details recorded	Source for cases	Source for controls
Intra-operative fluids	Type, rate	Casenotes	Casenotes
Intra-operative anti-emetics	Name, dose	Study database/casenotes	Casenotes
Other intra-operative medicines	Name, dose	Study database/casenotes	Casenotes
Post-operative opioids	Name, dose, frequency, duration	Study database/casenotes	Study database/casenotes
Post-operative epidural	Name, dose, frequency, duration	Study database/casenotes	Study database/casenotes
Post-operative NSAIDs	Name, dose, frequency, duration	Study database/casenotes	Study database/casenotes
Other post-operative medicines	Name, dose, frequency, duration	Study database/casenotes	Study database/casenotes
Intra-operative hypotension [xxvi]	Yes or no, details if yes	Casenotes	Casenotes
Post-operative hypotension [xxvii]	Yes or no, details if yes	Casenotes	Casenotes

Table 6.2 Pediatric Advanced Life Support (PALS) definition of hypotension (Haque and Zaritsky, 2007)

Age group	Definition of hypotension (mmHg)
0 days–1 wk.	<60
1 week–1 mo.	<60
1 mo.–1 yr.	<70
>1–5 yrs.	70 + 2 x yrs.
6–12 yrs.	70 + 2 x yrs. (up to 10 yrs.)
	<90 (>10 yrs.)
13–18 yrs.	<90

[xxvi] defined by us as four consecutive systolic BP readings (over 15 minutes) below the lower limits by age defined in the Pediatric Advanced Life Support (PALS) guidelines (Haque and Zaritsky, 2007), table 6.2

[xxvii] defined by us as any systolic reading below the lower limits by age defined in the PALS guidelines (Haque and Zaritsky, 2007) in the first 24 hours post-op, see table 6.2

Table 6.3 Refinement of predictors before analysis

Item	Details recorded	Refinement	Data Type
Specialty	Hospital record abbreviation e.g. NEUS	24 abbreviations combined to 8[xxviii]: 1. ANAES 2. BURN PLAS 3. CAD CARD CSUR 4. CRANIO NEUS OSUR 5. ENT EYE 6. HAEM HO ONC 7. PAES NEO PAED GASTRO RENAL RESP UROP NEPH 8. ORTH SPIN	Categorical

[xxviii] Key to specialty groups: 1. ANAES = anaesthetics, 2. BURN = burns PLAS =plastic surgery, 3. CAD, CARD = cardiology CSUR = cardiac surgery, 4. CRANIO = craniofacial surgery, NEUS = neurosurgery, OSUR = oral surgery, 5. ENT = ear, nose and throat, EYE = ophthalmology, 6. HAEM = haematology, HO = haematology/oncology, ONC = oncology, 7. PAES = paediatric surgery, NEO = neonatal, PAED = general paediatrics, GASTRO = gastroenterology, RENAL = nephrology, RESP = respiratory medicine, UROP = paediatric urology, NEPH = nephrology, 8. ORTH = orthopaedics, SPIN = spinal surgery.

Item	Details recorded	Refinement	Data Type
Age on admission	-	Age in years	Continuous
Gender	-	Male/Female	Categorical
Previous GA?	Yes or No	-	Categorical
History of POV	Yes or No, year of previous GA (if any)	Only record if previous GA (Yes/No)	Categorical
Pre-operative state	co-operative/upset/other	Excluded due to inconsistent reporting	-
Procedure	Name of procedure	Excluded due to large number of different procedures recorded	-
Duration of anaesthesia	Minutes between anaesthesia started and into recovery	Time in minutes	Continuous
Details of Premedication	Name, dose	Indicate whether exposed or not (Yes/No) Drugs in this category: Midazolam/Ketamine	Categorical

Item	Details recorded	Refinement	Data Type
Induction anaesthesia	Name, dose if intravenous	Indicate which agent type (inhaled/intravenous/both) Drugs in this category: Sevoflurane, desflurane, nitrous oxide, isoflurane, propofol, thiopental	Categorical
Maintenance anaesthesia	Name, dose if intravenous	Indicate which agent type (inhaled/intravenous/both) Drugs in this category: Sevoflurane, desflurane, nitrous oxide, isoflurane, propofol, thiopental	Categorical
Intra-operative analgesia	Name, dose	Indicate whether exposed or not (Yes/No) Drugs in this category: Morphine, fentanyl, ketamine, remifentanil, clonidine	Categorical
Intra-operative fluids	Type, rate	Indicate rate mL/kg/hr.	Continuous

Item	Details recorded	Refinement	Data Type
Intra-operative anti-emetics	Name, dose	Indicate whether exposed or not (Yes/No) and to which drug(s), each drug becomes a separate predictor: Ondansetron (Yes/No) Dexamethasone (Yes/No) Droperidol (Yes/No) Cyclizine (Yes/No)	Categorical
Other intra-operative medicines	Name, dose	Indicate whether exposed or not (Yes/No) and to which drug(s), each drug becomes a separate predictor: Reversal (Yes/No) Tranexamic acid (Yes/No)	Categorical
Post-operative opioids	Name, dose, frequency, duration	Indicate whether exposed or not (Yes/No) and to which drug(s), each drug becomes a separate predictor: Morphine infusion (Yes/No) Fentanyl infusion (Yes/No) Enteral opioids (Yes/No)	Categorical

Item	Details recorded	Refinement	Data Type
Post-operative epidural	Name, dose, frequency, duration	Indicate whether exposed or not (Yes/No) and to which drug(s), each drug becomes a separate predictor: Fentanyl + Levobupivicaine Epidural (Yes/No) Clonidine + Levobupivicaine Epidural (Yes/No) Levobupivicaine Epidural (Yes/No)	Categorical
Post-operative NSAIDs	Name, dose, frequency, duration	Indicate whether exposed or not (Yes/No) Drugs in this category: diclofenac, ibuprofen	Categorical
Other post-operative medicines	Name, dose, frequency, duration	Indicate whether exposed or not (Yes/No) and to which drug(s), each drug becomes a separate predictor: Clonidine (Yes/No) Ketamine (Yes/No)	Categorical
Intra-operative hypotension[xxvi]	Yes or no, details if yes	Yes/No	Categorical
Post-operative hypotension[xxvii]	Yes or no, details if yes	Yes/No	Categorical

6.2.7 Data Analysis

A univariate analysis was performed to compare differences in POV risk factors for cases and controls. Categorical outcomes were compared between groups using the chi-square statistic. For continuous variables, the median and interquartile ranges were reported for each group and, since the distribution was found to be non-parametric for all continuous variables, these were compared using the Mann-Whitney U test. Differences were considered significant at the 5% level ($p < 0.05$). Checks were made for correlations between the continuous outcome variables using the Spearman's ρ test for non-parametric data. A correlation was considered significant at the 5% level ($p < 0.05$), with significant correlations of magnitude >0.8 being highlighted.

A logistic regression model was used to assess the influence of independent variables (risk factors) on the likelihood of POV. Both forward and backward selection procedures were undertaken. The final models from each process were compared and selection of variables for inclusion in the final model was undertaken. Differences were considered significant at the 5% level ($p < 0.05$) and, where appropriate, all results were presented with 95% confidence intervals. To evaluate competing models, the Nagelkerke R Square statistic was used to assess the proportion of variation in the outcome variable explained by the model.

The final model was assessed for goodness-of-fit using the Hosmer-Lemeshow statistic. In this case, a p-value of >0.1 suggests that the model is a good fit to the data. Outliers were identified by plotting the standardised and normalised residuals against patient ID. Influential observations were identified by plotting Cook's distance, Leverage and Delta of Beta against patient ID. A classification table, a classification plot and receiver operating characteristic (ROC) curve were produced to evaluate how well the model discriminated between outcomes. The following rules for interpreting the area under the ROC curve (AUC) were applied (Hosmer and Lemeshow, 2000):

0.5	discrimination no better than chance
$0.7 \leq AUC < 0.8$	acceptable discrimination
$0.8 \leq AUC < 0.9$	excellent discrimination
$AUC \geq 0.9$	outstanding discrimination

The aim was to include, in the final risk score, those variables with the greatest predictive value considered in the context of the practical clinical application of the tool. The final score was evaluated by assessing its distribution amongst patients who experienced POV against those who did not.

A post-hoc analysis was undertaken as part of the evaluation of the risk score. The median score and inter-quartile range (IQR) was reported for each of each of four groups:

1. Administered antiemetic and experienced POV (antiemetic + POV)
2. Administered antiemetic and did not experience POV (antiemetic + no POV)
3. Not administered antiemetic and experienced POV (no antiemetic + POV)
4. Not administered antiemetic and did not experience POV (no antiemetic + no POV)

The difference between the median scores was tested using a Kruskal-Wallis test and the difference between the median scores of pairs of these groups was tested using a Mann-Whitney U test.

A second post-hoc analysis was undertaken to explore intra-operative anti-emetic use in the study population. The median ondansetron and dexamethasone doses (and IQR) were reported for both of the groups:

1. Administered antiemetic and experienced POV (antiemetic + POV)
2. Administered antiemetic and did not experience POV (antiemetic + no POV)

The difference between median doses was tested using a Mann-Whitney U test.

6.3 Results

6.3.1 Patients included in the analysis

During case note review of the 356 randomly selected controls, 29 were identified as suspected POV cases. Therefore these controls became cases and an additional 29 controls were randomly selected.

The 29 additional cases had not been identified in the prospective cohort study for the following reasons:

- overlooked (21 cases)
- started in theatre (4 cases)
- identified but case notes not available for full assessment of case during the study (3 cases)
- recorded as 'vomiting' rather than procedural vomiting (1 case)

Subsequently the causality of these cases was assessed independently by a research nurse, a research pharmacist and a paediatric anaesthetist using the LCAT (Gallagher et al., 2011). If there was disagreement about causality, the cases were referred to a pharmacologist whose assessment was taken as definitive. One case was classified as unlikely, 14 cases were classified as possible and 14 as probable. Therefore the final number of cases was 384 and the final number of controls was 385.

Data were retrieved for 374 of 384 cases (97.4%) and 349 of 385 controls (90.6%). The reasons for missing data were as follows:

- case notes not found (6 cases, 26 controls)
- anaesthetic chart not filed (4 cases, 7 controls)
- notes scanned into electronic storage but anaesthetic charts missing (3 controls)

All patients for whom data were retrieved were included in the analysis.

6.3.2 Univariate analysis

The results of this analysis are summarised in Tables 6.4, 6.5 and 6.6. There were no significant correlations of magnitude >0.8 found between the continuous outcome variables age, duration of anaesthetic and rate of intra-operative fluids.

Patient-related variables are summarised in Table 6.4. Gender did not predict POV risk, but increasing age and a positive history of POV did. The median age of patients who experienced POV was significantly greater than that of those who did not ($p < 0.001$). Patients with a positive history of POV were significantly more likely to experience POV than those without ($p = 0.006$). Intra-operative hypotension increased the likelihood of POV ($p < 0.001$). Post-operative hypotension did not significantly increase the likelihood of POV. However, it is important to note that a record of post-operative blood pressure measurements was found for less than half of the participants.

Table 6.4 Results of univariate analysis, patient-related variables

Categorical Variable	All	No POV n (%)	POV n (%)	Difference (95%CI)	p-value [xxix]
Gender (n=723)		**n=349**	**n=374**		
Male	403	204 (58.5%)	199 (53.2%)	-5.2%	0.156
Female	320	145 (41.5%)	175 (46.8%)	(-12.5%, 2.0%)	
History of POV (n=278)		***n=89***	***n=189***		
Yes	77	15 (16.9%)	62 (32.8%)	16%	0.006
No	201	74 (83.1%)	127 (67.2%)	(5.7%, 26.2%)	
Intra-operative hypotension (n=701)		***n=328***	***n=373***		
Yes	269	102 (31.1%)	167 (44.8%)	13.7%	<0.001
No	432	226 (68.9%)	206 (55.2%)	(6.6%, 20.8%)	
Post-operative hypotension (n=324)		***n=113***	***n=211***		
Yes	32	9 (8.0%)	23 (10.9%)	2.9%	0.399
No	292	104 (92.0%)	188 (89.1%)	(-3.6%, 9.5%)	

Continuous Variable	n	No POV (median, IQR)	POV (median, IQR)	p-value[xxx]
Age (years)	723	4.0 (1.0 – 11.0)	8.0 (3.0 – 13.0)	<0.001

[xxix] Chi-square statistic
[xxx] Mann-Whitney U test

Table 6.5 shows that surgery-related variables and membership of some specialty groups had a significant impact on POV risk ($p < 0.001$). The greatest differences were seen in the craniofacial surgery category 4 (more patients experienced POV than did not) and the general surgery category 7 (fewer patients experienced POV than did not). Some of the specialty groups contained very few patients. Duration of anaesthetic was a significant predictor of POV risk, the median duration significantly longer in patients who experienced POV ($p < 0.001$). The rate of intraoperative fluid infusion did not have a significant impact on POV risk.

Table 6.5 Results of univariate analysis, surgery-related variables

Categorical Variable	All	No POV n (%)	POV n (%)	Difference (95%CI)	p-value[xxxi]
Specialty Group (n = 723)		***n=349***	***n=374***		
Anaesthetics	4	4 (1.1%)	0	1.1% (0.0%, 2.3%)	
Burns, plastic surgery	48	26 (7.4%)	22 (5.9%)	1.6% (-2.1%, 5.2%)	
Cardiology, cardiac surgery	22	10 (2.9%)	12 (3.2%)	-0.3% (-2.8%, 2.2%)	
Craniofacial, neuro- and oral surgery	159	50 (14.3%)	109 (29.1%)	-14.8% (-20.7%, -8.9%)	<0.001
Ear, nose and throat, opthalmology	42	23 (6.6%)	19 (5.1%)	1.5% (-1.9%, 4.9%)	
Haematology/oncology	12	9 (2.6%)	3 (0.8%)	1.8% (-0.1%, 3.7%)	
Paediatric and neonatal surgery, paediatrics, gastroenterology, nephrology, respiratory medicine, urology, nephrology,	259	152 (43.6%)	107 (28.6%)	14.9% (8.0%, 21.9%)	
Orthopaedics and spinal surgery	177	75 (21.5%)	102 (27.3%)	-5.8% (-12.0%, 0.5%)	

Continuous Variable	n	No POV (median, IQR)	POV (median, IQR)	p-value[xxxii]
Duration of anaesthesia (minutes)	723	95 (55.0 – 163.5)	140 (95.0 – 226.3)	<0.001
Intraoperative fluid rate (mL/kg/hour)	723	6.0 (0.0 – 10.0)	6.0 (2.0 – 9.0)	0.349

[xxxi] Chi-square statistic
[xxxii] Mann-Whitney U test

Finally, drug related risk variables are summarised in Table 6.6. Use of the following drugs was associated with increased POV risk:

1. Pre-operative drugs
    a. Pre-medication (midazolam or ketamine)
2. Intra-operative drugs
    a. Combination of intravenous and inhaled agents for induction
    b. Analgesia
    c. Tranexamic acid
    d. Anti-emetic
    e. Ondansetron
    f. Dexamethasone
3. Post-operative drugs
    a. Morphine infusion
    b. Fentanyl infusion
    c. Ketamine infusion
    d. Fentanyl + levobupivicaine epidural
    e. Levobupivicaine epidural
    f. Enteral opioid
    g. NSAID

The drugs most strongly associated with POV risk ($p < 0.001$) were intra-operative anti-emetics, intra-operative analgesia, post-operative morphine and fentanyl, oral opioids and NSAIDs.

Intra-operative anti-emetics were analysed together in a single category and also separately as ondansetron, dexamethasone, cyclizine and droperidol. Some patients received more than one anti-emetic and in the majority of patients that was ondansetron and/or dexamethasone.

Intra-operative analgesia was defined as one or more of: morphine, fentanyl, remifentanil, ketamine or clonidine. Table 6.7 provides additional detail about how frequently each of these analgesic agents was administered. The most frequently used intra-operative analgesics were opioids and 45.5% of cases and 30.1% of controls received two or more intra-operative analgesics.

Table 6.6 Results of univariate analysis, drug-related variables

Categorical Variable	All	No POV n (%)	POV n (%)	Difference (95%CI)	p-value[xxxiii]
Premedication (n=723)		***n=349***	***n=374***		
Yes	115	42 (12.0%)	73 (19.5%)	7.5% (2.2%, 12.8%)	0.006
No	608	307 (88.0%)	301 (80.5%)		
Induction agent (n=716)		***n=342***	***n=374***		
Inhaled	290	148 (43.3%)	142 (38.0%)	5.3% (-1.9%, 12.5%)	0.007
Intravenous	372	179 (52.3%)	193 (51.6%)	0.7% (-6.6%, 8.1%)	
Both	54	15 (4.4%)	39 (10.4%)	-6.0% (-9.8%, -2.3%)	
Maintenance agent (n=703)		***n=331***	***n=374***		
Inhaled	650	312 (94.3%)	338 (90.4%)	4.5% (0.6%, 8.3%)	0.264
Intravenous	29	9 (2.7%)	20 (5.3%)	-2.6% (-5.5%, 0.3%)	
Both	24	8 (2.4%)	16 (1.9%)	-1.8% (-4.5%, 0.8%)	
Intra-op analgesia (n=723)		***n=349***	***n=374***		
Yes	471	183 (52.3%)	288 (77.0%)	24.6% (17.8%, 31.3%)	<0.001
No	252	166 (47.6%)	86 (23.0%)		
Intra-op tranexamic acid (n=723)		***n=349***	***n=374***		
Yes	26	5 (1.4%)	21 (5.6%)	4.2% (1.5%, 6.8%)	0.003
No	697	344 (94.4%)	353 (98.6%)		
Reversal (n=723)		***n=349***	***n=374***		
Yes	81	46 (13.2%)	35 (9.4%)	-3.8% (-8.4%, 0.8%)	0.103
No	642	303 (86.8%)	339 (90.6%)		
Intra-op anti-emetic (n=723)		***n=349***	***n=374***		
Yes	401	155 (44.4%)	246 (65.8%)	21.4% (14.3%, 28.5%)	<0.001
No	322	194 (55.6%)	128 (34.2%)		
Intra-op ondansetron (n=723)		***n=349***	***n=374***		
Yes	303	110 (31.5%)	193 (51.6%)	20.1% (13.1%, 27.1%)	<0.001
No	420	239 (68.5%)	181 (48.4%)		
Intra-op droperidol (n=723)		***n=349***	***n=374***		
Yes	7	1 (0.3%)	6 (1.6%)	1.3% (-0.1%, 2.7%)	0.071
No	716	348 (98.4%)	368 (99.7%)		
Intra-op dexamethasone (n=723)		***n=349***	***n=374***		
Yes	231	93 (26.6%)	138 (36.9%)	10.3% (3.5%, 17.0%)	0.003
No	492	256 (73.4%)	236 (63.1%)		
Intra-op cyclizine (n=723)		***n=349***	***n=374***		
Yes	3	2 (0.6%)	1 (0.3%)	-0.3% (-1.3%, 0.6%)	0.523
No	720	347 (99.4%)	373 (99.7%)		
Post-op morphine infusion (n=723)		***n=349***	***n=374***		
Yes	187	64 (18.3%)	123 (32.9%)	14.5% (8.3%, 20.8%)	<0.001
No	536	285 (81.7%)	251 (67.1%)		
Post-op fentanyl infusion (n=723)		***n=349***	***n=374***		
Yes	79	17 (4.9%)	62 (16.6%)	11.7% (7.3%, 16.1%)	<0.001
No	644	332 (95.1%)	312 (83.4%)		
Post-op clonidine infusion (n=723)		***n=349***	***n=374***		
Yes	1	1 (0.3%)	0	-0.3% (-0.8%, 0.3%)	0.300
No	722	348 (99.7%)	374 (100%)		
Post-op ketamine infusion (n=723)		***n=349***	***n=374***		
Yes	46	13 (3.7%)	33 (8.8%)	5.1% (1.6%, 8.6%)	0.005
No	677	336 (96.3%)	341 (91.2%)		
Post-op enteral opioids (n=723)		***n=349***	***n=374***		
Yes	509	202 (57.9%)	307 (82.1%)	24.2% (17.7%, 30.7%)	<0.001
No	214	147 (42.1%)	67 (17.9%)		
Post-op fentanyl + levobupivicaine epidural (n=723)		***n=349***	***n=374***		
Yes	70	24 (6.9%)	46 (12.3%)	5.4% (1.2%, 9.7%)	0.014
No	653	325 (93.1%)	328 (87.7%)		
Post-op clonidine + levobupivicaine epidural (n=723)		***n=349***	***n=374***		
Yes	21	11 (3.2%)	10 (2.7%)	-0.5% (-2.9%, 2.0%)	0.702
No	702	338 (96.8%)	364 (97.3%)		
Post-op levobupivicaine epidural (n=723)		***n=349***	***n=374***		
Yes	30	9 (2.6%)	21 (5.6%)	3.0% (0.2%, 5.9%)	0.041
No	693	340 (97.4%)	353 (94.4%)		
Post-op NSAID (n=723)		***n=349***	***n=374***		
Yes	495	198 (56.7%)	297 (79.4%)	22.7% (16.1%, 29.3%)	<0.001
No	228	151 (43.3%)	77 (20.6%)		

[xxxiii] Chi-square statistic

Table 6.7 Frequency of use for individual intra-operative analgesics

Drug	Frequency		
	Cases (% of total)	Controls (% of total)	Total (% of total)
Morphine	189 (43.8%)	112 (46.1%)	**301 (44.6%)**
Fentanyl	75 (17.4%)	49 (20.2%)	**124 (18.4%)**
Ketamine	35 (8.1%)	29 (11.9%)	**64 (9.5%)**
Remifentanil	132 (30.6%)	52 (21.4%)	**184 (27.3%)**
Clonidine	1 (0.2%)	1(0.4%)	**2 (0.3%)**
Total	**432**	**243**	**675**

6.3.3 Selection of variables for multivariate analysis

The results of the univariate analysis were reviewed in order to select variables for inclusion in the multivariate modelling. This was undertaken with expert clinical and statistical advice. In general, we aimed to include all significant predictors. The decision about each individual variable and a rationale are provided in Table 6.8. This process resulted in the inclusion of 11 predictors in the multivariate modelling process.

Table 6.8 Selection of variables for multivariate analysis

Variable	Significant impact demonstrated in univariate analysis?	Decision about inclusion in multivariate analysis	Rationale
Specialty Group	Yes	Include but combine some outcomes to reduce number from 8 to 6: 1. OTHER (ANAES CAD CARD CSUR HAEM HO ONC) 2. BURN PLAS 3. CRANIO NEUS OSUR 4. ENT EYE 5. PAES NEO PAED GASTRO RENAL RESP UROP NEPH 6. ORTH SPIN	Very few patients in some categories
Gender	No	Include	Would expect to see gender in a risk prediction model
History of POV	Yes	Exclude	Not recorded for all patients, dependent on previous exposure to anaesthetic
Premedication	Yes	Include	-
Induction agent	Yes	Exclude	Use of a combination of inhaled and intravenous is the significant predictor but it was used in relatively few patients
Maintenance agent	No	Exclude	-
Intra-operative analgesia	Yes	Include	-
Intra-operative tranexamic acid	Yes	Exclude	Used in relatively few patients
Reversal	No	Exclude	-
Intra-operative anti-emetic	Yes	Include	-
Intra-operative ondansetron	Yes	Exclude - use variable 'intra-operative antiemetic' only	Droperidol and cyclizine used in very few patients, some patients received two or more anti-emetics
Intra-operative droperidol	No		
Intra-operative dexamethasone	Yes		
Intra-operative cyclizine	No		
Post-operative morphine infusion	Yes	Combine with post-operative enteral opioid - name variable 'post-operative opioid'	Reduce number of variables
Post-operative fentanyl infusion)	Yes		
Post-operative clonidine infusion	No	Exclude	-
Post-operative ketamine infusion	No	Exclude	-
Post-operative enteral opioids	Yes	Combine with post-operative morphine and fentanyl infusion - name variable 'post-operative opioid'	Reduce number of variables
Fentanyl + levobupivicaine epidural	Yes	Combine - name variable 'post-operative epidural'	Reduce number of variables
Clonidine + levobupivicaine epidural	No		
Levobupivicaine epidural	Yes		
Post-operative NSAID	Yes	Include	-
Intra-operative hypotension	Yes	Include	-
Post-operative hypotension	No	Exclude	-
Age (years)	Yes	Include	-
Duration of anaesthesia (minutes)	Yes	Include	-
Intraoperative fluid rate (mL/kg/hour)	No	Exclude	-

6.3.4 Multivariate analysis

Forward and backward stepwise selection took six steps and the following six predictors appeared in the model at the final step: age, duration of anaesthetic, premedication, intra-operative analgesia, post-operative NSAID and intra-operative hypotension (Table 6.9).

Table 6.9 Results of forward and backward stepwise selection

Variable[xxxiv]	Estimated odds ratio	95% CI	p-value
Age	1.045	1.013, 1.079	0.006
Duration of anaesthesia	1.003	1.001, 1.005	<0.001
Pre-medication(1)	1.627	1.043, 2.538	0.032
Intra-operative analgesia(1)	2.006	1.413, 2.847	<0.001
Post-operative NSAID(1)	1.930	1.342, 2.776	<0.001
Intra-operative hypotension(0,1)	9.454	1.192, 74.993	0.034

[xxxiv] Coding for categorical variables:

Variable	Outcomes	Parameter coding 1	Parameter coding 2
Pre-medication	Yes No	1 0	-
Intra-operative analgesia	Yes No	1 0	-
Post-operative opioid	Yes No	1 0	-
Post-operative NSAID	Yes No	1 0	-
Intra-operative hypotension	Yes No Unrecorded	0 1 0	1 0 0

The variables selected for the model were those which were selected by both stepwise methods: age, duration of anaesthesia, pre-medication, intra-operative analgesia and post-operative NSAID. The duration of anaesthesia was a significant predictor of POV risk, however the magnitude of the estimated odds ratio for this variable was small. The interpretation of the odds ratio is that for every additional minute of anaesthesia, the risk of POV increases by 0.3%. Intra-operative hypotension was excluded because of the imprecision in the estimate.

The Nagelkerke R Square value for the model was 0.196. The p-value for the Hosmer-Lemeshow statistic was 0.040. Therefore the model was not a good fit to the data. In order to achieve a better fit, 'premedication' was removed because it was the least significant predictor in the model (p=0.030) and was only administered to 115/723 (15.9%) of participants (Table 6.6). For the revised model, the Nagelkerke R Square value was 0.188 and the goodness-of-fit of the model improved (p=0.523).

Finally, the variable post-operative NSAID was removed from the model. We assume that POV risk would be assessed pre-operatively or in the immediate post-operative period, and thus the administration of NSAIDs may not be predictable at this time. A NSAID may be prescribed by the anaesthetist but never administered or, it may be written up in the days that follow the operation.

The variables entered into the final model (Table 6.10) were:

1. age
2. duration of anaesthesia
3. intra-operative analgesia

The Nagelkerke R Square value for the final model was 0.164 and the model was a good fit to the data (p = 0.489). No outliers were identified. Four influential observations were identified and the participants were removed temporarily from the dataset. The remaining data (719 participants) were used to produce a new model but this had little impact on the parameter estimates, and therefore these four participants were returned to the dataset.

The risk score is the equation of the final model:

Score = 0.061 (age in years) + 0.004 (duration of anaesthetic) + 0.798 (intraoperative analgesia)

Table 6.10 Final model – predictors of post-operative vomiting in children

Variable	Estimated odds ratio exp(B)	Standard error	p-value	95% CI for estimated odds ratio
Age	1.063	0.015	<0.001	1.032, 1.095
Duration of anaesthesia	1.004	0.001	<0.001	1.002, 1.006
Intraoperative analgesia (1)[xxxv]	2.222	0.173	<0.001	1.584, 3.117
Constant	0.227	0.192	<0.001	-

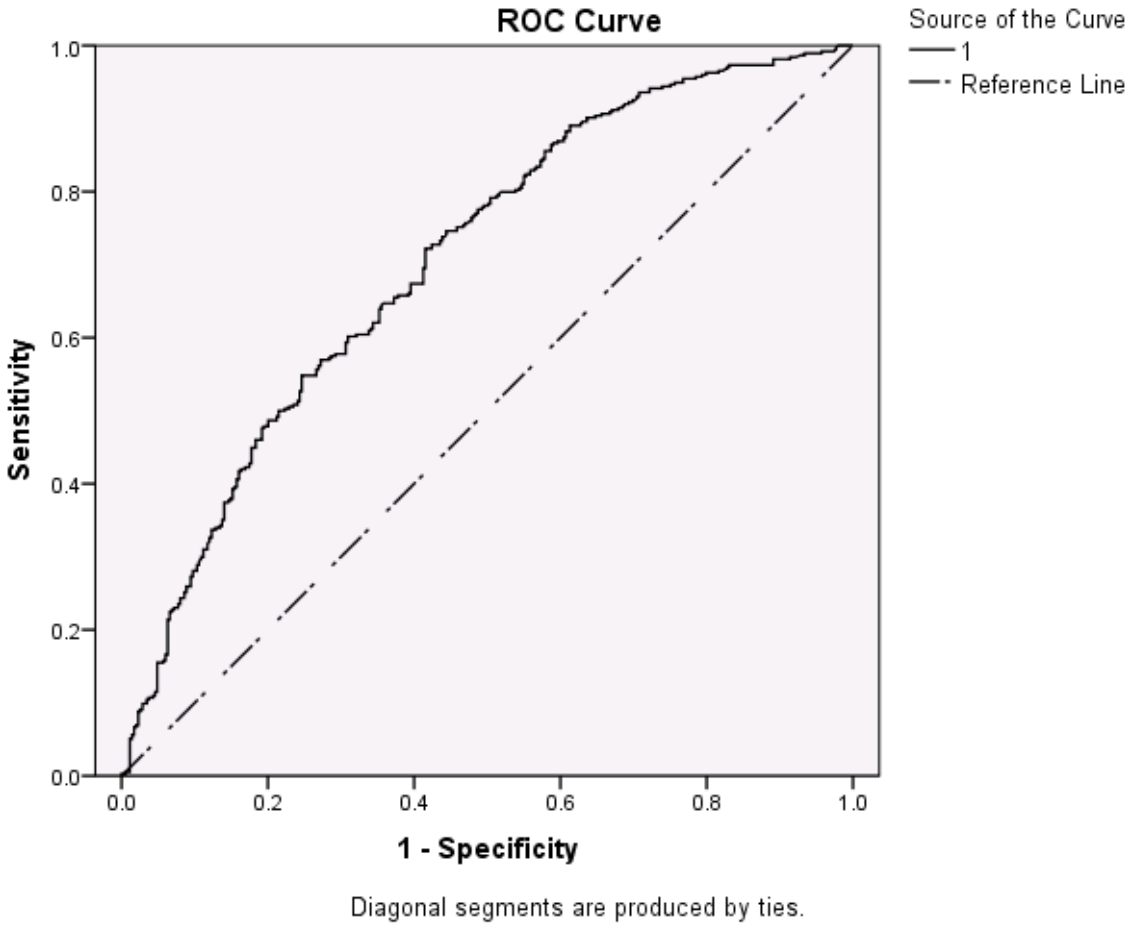
[xxxv] Coding for categorical variable:

Variable	Outcomes	Parameter coding 1	Parameter coding 2
Intra-operative analgesia	Yes	1	-
	No	0	

6.3.5 Evaluation of risk score

The risk score was evaluated by determining how well it predicted a) the occurrence of POV (sensitivity) and b) the non-occurrence of POV (specificity). With a cut value of 0.5, sensitivity was 67.4% and specificity was 60.2%. The area under the ROC curve for the score was 0.706 which demonstrated acceptable discrimination between outcomes (Figure 6.2).

Figure 6.2 ROC Curve for the risk score

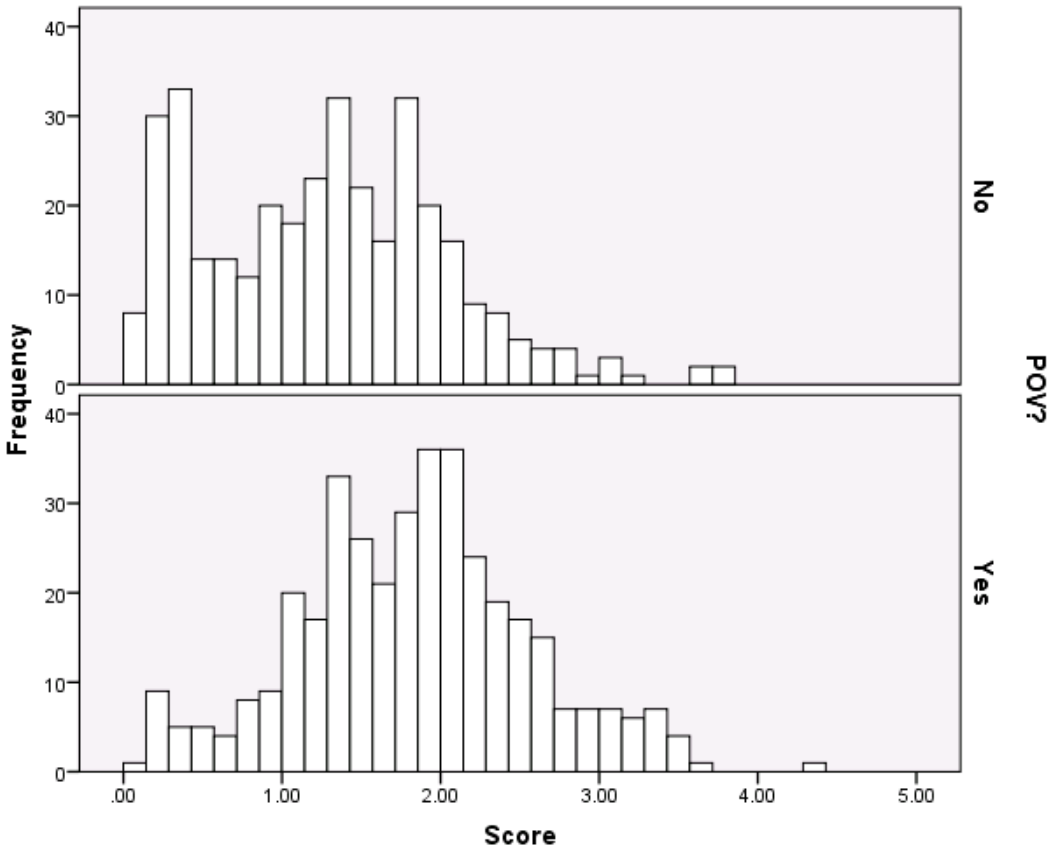


Area under the curve	Standard error	Asymptotic significance[xxxvi]	Asymptotic 95% CI
0.706	0.019	<0.001	0.668, 0.743

[xxxvi] null hypothesis = area is 0.5

The frequency of each score was plotted as two histograms, one for cases and one for controls (Figure 6.3). It was difficult to identify a score above which patients were at 'high risk'.

Figure 6.3 Comparison of risk score frequency for cases and controls



6.3.6 Comparison of risk scores in participants who received anti-emetic and those who did not

Evaluation of the model was complicated by the fact that anti-emetic was administered to some of the participants, in accordance with local and/or national guidelines and the clinical judgement of the anaesthetist. Therefore those who received intra-operative anti-emetic were already predicted to be at high risk of POV. In order to explore this in more detail, we compared the median risk score for patients in each of four groups:

1. Administered antiemetic and experienced POV (antiemetic + POV)
2. Administered antiemetic and did not experience POV (antiemetic + no POV)
3. Not administered antiemetic and experienced POV (no antiemetic + POV)
4. Not administered antiemetic and did not experience POV (no antiemetic + no POV)

A Kruskal-Wallis test demonstrated a significant difference between the median scores for the four groups ($p<0.001$), (Table 6.11). A pair-wise comparison of the groups (Mann-Whitney U test) demonstrated that the difference in score was significant for all pairs (Table 6.12). Patients who received antiemetic and experienced POV had the highest median score.

Table 6.11 Comparison of median scores[xxxvii]

	POV	**Median score (IQR)**	**No POV**	**Median score (IQR)**
Anti-emetic	246	2.01 (1.69, 2.44)	155	1.65 (1.29, 2.01)
No anti-emetic	128	1.38 (1.00, 1.79)	194	0.94 (0.36, 1.39)

[xxxvii] Score = 0.061 (age in years) + 0.004 (duration of anaesthetic) + 0.798 (intraoperative analgesia)

Table 6.12 Pairwise comparison of median scores[xxxviii]

	Antiemetic + POV	Antiemetic + no POV	No antiemetic + POV	No antiemetic + no POV
Antiemetic + POV				
Antiemetic + no POV	<0.001[xxxix]			
No antiemetic + POV	<0.001[xxxix]	0.002[xxxix]		
No antiemetic + no POV	<0.001[xxxix]	<0.001[xxxix]	<0.001[xxxix]	

[xxxviii] Score = 0.061 (age in years) + 0.004 (duration of anaesthetic) + 0.798 (intraoperative analgesia)
[xxxix] Mann-Whitney U test

6.3.7 Comparison of anti-emetic dose between cases and controls

Since prophylactic anti-emetic use was effective in 155 participants (antiemetic + no POV) but ineffective in 246 patients (antiemetic + POV), we compared the doses of ondansetron and dexamethasone used in these two groups. The aim was to identify whether differences in dosing could account for differences in efficacy. Droperidol was administered to 6 cases and 1 control and cyclizine was administered to 1 case and 2 controls, these participants were not included in this analysis. There was no significant difference in the median ondansetron and dexamethasone doses between the case and control groups (Table 6.13). The exception was the dose of dexamethasone when used in combination with ondansetron (p = 0.028) where the median dose received by cases was greater than that received by controls.

Table 6.13 Comparison of anti-emetic doses between cases (n=239) and controls (n=152)

Antiemetic(s)	POV or no POV	Number of patients	Number of patients with dose recorded	Median dose (IQR) mg/kg	
Ondansetron alone	POV	106	101	0.94 (0.08 - 0.11)	
	No POV	59	58	0.96 (0.08 – 0.10)	
				p-value[xl] 0.824	
				Ondansetron	**Dexamethasone**
Ondansetron with dexamethasone	POV	83	83	0.10 (0.09 – 0.13)	0.13 (0.10 – 0.18)
	No POV	50	48	0.1021 (0.09 – 0.12)	0.1021 (0.87 – 0.14)
				p-value[xl]0.990	**p-value**[xl]0.028
Dexamethasone alone	POV	50	50	0.12 (0.10 – 0.18)	
	No POV	43	43	0.13 (0.10 – 0.17)	
				p-value[xl] 0.844	

[xl] Mann-Whitney U test

6.4 Discussion

A risk score for POV in children was developed using a dataset derived from a large observational cohort study of paediatric admissions (Thiesen et al., 2013). During the development of the risk score, 21 additional cases of POV (5.5% of all cases) were identified, these had been overlooked in the cohort study. This highlights that ADRs were overlooked in the studies described in Chapters 2 and 3, however checks were undertaken to minimise this. For example, in the admissions study, three senior investigators independently assessed 4.8% reports of admissions deemed not to have had an ADR, they concluded that none had been wrongly classified (Gallagher R.M. et al., 2012).

The following variables were included in our risk score:

1. age
2. duration of anaesthesia
3. administration of an intra-operative analgesia

The use of intra-operative anti-emetics was a positive predictor of POV risk (albeit non-significant). Patients were administered anti-emetics at the discretion of the anaesthetist and therefore we would expect patients at high risk to have received an anti-emetic. However, this observation indicates that anti-emetics were not always effective (see 6.4.3). The ability of the model to discriminate between outcomes was acceptable but it was not possible to say at which point on the scoring scale patients became ‘high risk’. This is unsurprising in a population which was heterogeneous in terms of both the characteristics of individuals and in terms of how they were surgically and medically managed.

6.4.1 Comparison with previous studies

Any comparison of this work with previous studies must take into account differences in the patients included, the setting and the variables selected for evaluation. Here the results of one previous paediatric risk score development study are compared to the present study.

The design of the study by Eberhart et al. (2004) differed from this study in several ways. Notably, in Eberhart's study, children who receive intra-operative anti-emetic were excluded from the analysis. Furthermore, the cardiac, craniofacial, neuro- and oral surgery patients included in this study were absent from Eberhart's study, whereas the large proportion of ENT and ophthalmology patients in their study was not observed here. The differences between the two studies are summarised in Table 6.14.

Table 6.14 Comparison of the designs of the present study and the study by Eberhart et al. (2004)

Item	Present study	Eberhart et al. (2004)
Data collection	Prospective + retrospective	Prospective
Duration	12 months	22 months
Number of sites	1	4
Age of participants	0-16 years	0-14 years
Number of participants	769	1401
Number of participants included in analysis	723	1257
Reasons for exclusion from analysis	Retrospective data could not be retrieved	Lost to follow up Incomplete dataset Received intra-operative anti-emetic
Surgery types	Specialty Group [xxviii](n = 723) Anaesthetics (0.6%) Burns, plastic surgery (6.6%) Cardiology, cardiac surgery (3.0%) Craniofacial, neuro- and oral surgery 22.0%) Ear, nose and throat, opthalmology (5.8%) Haematology/oncology (1.7%) Paediatric and neonatal surgery, paediatrics, gastroenterology, nephrology, respiratory medicine, urology, nephrology (35.8%) Orthopaedics and spinal surgery (24.5%)	Surgery type (n = 1375) ENT (33.6%) Ophthalmological (12.9%) Urological (21.5%) Abdominal (11.6%) Orthopaedic (4.9%) Dental (5.2%) Diagnostic (3.1%) Plastic (4.8%) Miscellaneous (2.4%)

In the development of the POVOC score, Eberhart et al. (2004) selected variables for their exploratory analysis and subsequent logistic regression modelling which differed from this study. The additional variables included in their score development were: height, history of POV in the child, history of PONV in the father, mother or siblings, duration of surgery and type of airway device. Rather than grouping children into categories by specialty, they grouped them by type of surgery.

Eberhart et al. (2004) used stepwise forward and backward logistic regression analysis for variable selection in accordance with the approach in this study. They also calculated Nagelkerke's R Square value for their model. This value demonstrated that their model explained 27.1% of the variation in the outcome variable compared to 19.6% in this study. The R Square value is most useful for the assessment of linear regression models therefore a high R Square value would not be expected for a logistic regression model. The R Square value is not a measure of goodness-of-fit for the model although this is implied by Eberhart et al. (2004). A more useful measure of goodness-of-fit is the Hosmer-Lemeshow statistic which was calculated for the present model and demonstrated that it was a good fit to the data. The area under the ROC curve for Eberhart's model was 0.72 (95% CI 0.68, 0.77) which demonstrated only similar discrimination between outcomes to the model developed here (AUC 0.71, 95% CI 0.67, 0.74).

Variables excluded by Eberhart et al. (2004) following an explorative backward logistic regression analysis were:

- Administration of local or regional anaesthesia
- Intra-operative opioid administration
- Post-operative opioid administration
- Female gender
- Surface surgery

Not all of these variables were analysed in our study but intraoperative analgesia (mainly opioids), post-operative opioid and gender were included. Our analysis resulted in the exclusion of the variables post-operative opioid administration and gender but the inclusion of intra-operative analgesia.

In concordance with the present score, the final POVOC score included age as a predictor of POV, using a categorical variable (age ≥3 years). It also included duration of surgery as a categorical variable (duration >30 minutes) which is analogous to duration of anaesthesia. In contrast with the present score, Eberhart did not include administration of intra-operative analgesia but did include the following additional predictors:

- strabismus surgery
- a history of POV in the child or PONV in the father, mother or siblings

Strabismus surgery was not identified as a predictor in this study because a) specialty group was included rather than procedure type, and b) there were only three patients who underwent ophthalmological surgery in this study. A history of POV was not included as a predictor because it could only be ascertained for 38.5% of participants. A history of PONV in family members was not included because it is not routinely recorded at this centre.

The POVOC score has been externally validated by its developers in a study of 524 patients (Kranke et al., 2007). The risk factor strabismus surgery was not included because it is not relevant to all paediatric surgery settings. The area under the curve for the ROC curve in the validation study was 0.72 (95% CI 0.68, 0.77), sensitivity was 76% and specificity was 60%.

6.4.2 Study limitations

A limitation of this study was its retrospective design, the selection of variables was dictated by the routine availability of outcome data in the patient records and the collection of data relied on the accuracy and completeness of those records. For example, the use of reversal was recorded in relatively few patients (n=81) but this apparent low frequency of use is thought to be due to the absence of a written record.

In terms of risk score development, this work has limitations common to all risk score development studies. There is no definitive approach to score development but some general principles should be adhered to: these include the use of high quality data and an adequate sample size (Royston et al., 2009). The limitations on data quality have been described above. The sample size was adequate for logistic regression analysis, and the number of controls was less than ten times the number of variables entered into the model (Peduzzi et al., 1996). The selection of predictors is of utmost importance and must be guided by both statistical and clinical considerations. In this study, this process was conducted with attention to these details but inevitably opinions will differ about the

clinical relevance of individual predictors and the appropriateness of combining variables. There are limitations of the Hosmer-Lemeshow test for goodness-of-fit and of the Nagelkerke R Square value to explain the variability of the data. However, both are reported here for comparison with previous studies and because these are both widely used measures in risk score evaluation.

A further limitation was that the same dataset was used to both develop and test the predictive validity of the score. A better test of the predictive validity of the score, and thus its clinical value, would be to conduct external validation on a different dataset. External validation may highlight deficiencies in the risk score which may have arisen as a result of the modelling methods used or the population chosen for score development. The original development may have omitted an important predictor or the population chosen for validation may have different characteristics than that used for development (Altman et al., 2009). Resources were not available to carry out an external validation of the risk score developed here.

The generalizability of the score may be limited by the study design. Only patients who stayed for longer than 48 hours were included and certain surgery types (e.g. day cases, ENT procedures) were almost entirely excluded. Cases of POV in patients who went to PICU in the immediate post-operative period were not detected. Complex cardiac surgery patients who routinely go to PICU in the immediate post-operative period were thus indirectly excluded from the study. The score was developed with the inclusion of patients who had received intra- and/or post-operative anti-emetics which complicated the interpretation of the findings.

6.4.3 Post-operative vomiting in patients who received anti-emetic

Since local and national guidelines recommend the use of anti-emetics in particular patients, it was inevitable that the dataset would contain patients who had received them. Ideally, the variable 'intra-operative anti-emetic' would have been included in the risk score. This would have allowed the prediction of the reduction in POV risk achieved by adding an anti-emetic for individual patients.

The administration of intra-operative anti-emetic to prevent POV was not effective in 61.3% of patients. Amongst patients who received anti-emetic, the median risk score for those who experienced POV was higher than that for those who did not; this suggests that baseline risk impacts the efficacy of the anti-emetic.

The doses of the most frequently used intra-operative anti-emetics were compared between the case and control groups. Patients receiving ondansetron alone and in combination with dexamethasone were evaluated. There was no difference in the median ondansetron dose between the case and control groups and the dose reflected local guideline recommendations – 0.1mg/kg ondansetron. Although the local guideline recommends the addition of 0.1-0.15mg/kg dexamethasone in children undergoing adenotonsillectomy or strabismus surgery, the use of this combination was common despite that fact that this study included only 17 (adeno) tonsillectomy patients and no strabismus surgery patients. The median dose of dexamethasone administered to cases, when used in combination with ondansetron, was greater than that received by controls. This counter-intuitive finding may reflect the administration of higher doses of dexamethasone to patients undergoing neurosurgery.

Interestingly, in the UK national guideline, ondansetron at a dose of 0.15mg/kg is recommended for children at an increased risk of POV which is different from that recommended in the local guideline (The Association of Paediatric Anaesthetists of Great Britain & Ireland, 2009). Dexamethasone 0.15mg/kg is also recommended in combination with ondansetron 0.05mg/kg for adenotonsillectomy and strabismus surgery. By contrast, the US guideline recommends ondansetron 0.05-0.1mg/kg (Gan et al., 2007).

In this study, a significant proportion of patients who received an anti-emetic in theatre subsequently experienced POV. It is clear from the variation seen in the three guidelines for that the optimum regime for the prevention of POV in children, including the doses to be used, has not been agreed. A consistent approach to deciding which patients are at high risk may reduce the incidence of POV but only if effective anti-emetic regimes at appropriate doses can be administered to those at high risk. The development of a generic tool is difficult because the heterogeneity in the surgical and medical management of patients results in a large number of variables, some of which become redundant for some patients. However, differences will be less within specialties and the possibility of specialty-specific tools could be explored.

One of the study limitations was the administration of post-operative anti-emetics. Neither local, UK nor US guidelines are prescriptive about when post-operative anti-emetics should be administered. Anti-emetics may be administered when a child complains of being nauseated or experiences retching or not until they vomit. A consistent approach to the

prevention of POV after the patient has returned to the ward may have the potential to reduce the number of children experiencing POV.

6.5 Conclusion

It was not possible to develop a robust risk score for POV in children using data derived from a large prospective cohort study, supplemented by retrospective chart review. One approach to developing a robust risk score may be to focus on individual specialties. There is evidence that the risk of POV is greater with some surgery types (Kovac, 2007) but whether this is attributable to the surgery itself or independent risk factors associated with that surgery is unknown. Evidence exists to support both hypotheses (Gan et al., 2007). A specialty-specific score may discriminate better between cases and controls, as less clinical heterogeneity within the population would be expected to result in fewer predictor variables.

The optimum prophylactic anti-emetic regime for children undergoing surgery has not been determined and this is reflected by discrepancies between the recommendations of various guidelines. The NNT for both ondansetron and dexamethasone indicate that none of recommended regimes will be effective for every child (Steward, Grisel and Meinzen-Derr, 2011, Tramer et al., 1997, Bolton et al., 2006). It is also important to highlight that even where efficacy has been well studied, adequate safety data may be lacking (see Chapter 5 of this thesis). A robust tool for the prediction of POV has limited value if safe and effective measures for its prevention are not available. Further clinical studies of established and novel anti-emetics are warranted.

Since not all children will benefit from prophylactic anti-emetics, it is important to consider how we can optimise the management of POV when it occurs. This may be in recovery, on a hospital ward or in the child's home. The evidence to support recommendations for the management of established POV is less than that for prevention. There is some evidence that the administration of anti-emetics in practice is inconsistent (Jolley, 2000) and nursing staff do not always feel confident about which anti-emetic to administer or when (Sussanne et al., 2010). It may be possible to reduce the incidence of POV by developing a tool for clinicians, patients and parents which informs their decision about whether or not to administer anti-emetic treatment. Such a tool could incorporate an assessment of the likelihood of vomiting in an individual patient based on risk factors and reported symptoms.

A guideline for the selection of a safe and effective treatment would need to be incorporated.

In summary, the findings of this study do not provide any additional information to assist the clinician to identify patients who are high risk of developing POV. Furthermore, even if one is able to identify patients who are at high risk, there are limits to how far anaesthetic practice can be modified whilst still retaining the benefits of treatment. Nevertheless, additional evidence to inform the optimum approach to the prediction, prevention and management of POV is required.

7 Discussion

7.1 Summary of findings

This thesis focuses on adverse drug reactions occurring in children either as a result of prescribing in the community or hospital. A major aspect covered, because of the concerns expressed over the years by paediatricians, is the role of unlicensed and off-label medicines. In the largest studies undertaken so far, the contribution of off-label and unlicensed medicines to ADR risk in children has been assessed, in both children admitted to hospital and inpatients. In both studies, off-label and unlicensed medicines were more likely to be implicated in an ADR. Medicines licensed in children but given to a child below the minimum age or weight were over three times more likely to be implicated in an ADR than authorised medicines. A significant number of ADRs could be attributed to more than one medicine and in many cases a combination of two or more authorised, off-label or unlicensed medicines was the cause of the ADR. The number of off-label or unlicensed medicines administered to an individual was a positive predictor of ADR risk in both studies. However, the number of authorised medicines also predicted the likelihood of an ADR occurring.

The thesis also looked at three other aspects relating to the occurrence and detection of ADRs in children. First, the validity of clinical codes as a tool for pharmacovigilance in paediatric admissions was evaluated. The data show that the usefulness of clinical coding is limited and sole reliance on this to detect ADRs would lead to a gross under-estimate. Secondly, post-tonsillectomy haemorrhage was detected in the admissions study described in Chapter 2 of this thesis. We contend that although many factors contribute to the likelihood of haemorrhage, the combination of dexamethasone (off-label) and NSAID may increase the likelihood. A systematic review was undertaken to test this hypothesis. The results demonstrate that, although a considerable number of studies of dexamethasone with or without NSAID in tonsillectomy have been conducted, methodologies for the detection and recording of haemorrhage rates could not be considered reliable enough to test the hypothesis. Finally, post-operative vomiting (POV) was evaluated in further detail as it was the most common ADR in the inpatient study described in Chapter 3 of this thesis. Many factors contribute to the likelihood of POV, including the use of anaesthetic agents and post-operative analgesics. The study aimed to develop a prognostic score to predict the likelihood of POV in children. However, due to the observational design of the study, the

analysis was confounded by the administration of intra- and post-operative anti-emetics to our participants. The analysis also showed that intra-operative anti-emetics have limited efficacy, and when POV does occur, the use of post-operative interventions needs to be improved.

7.2 Interpretation of Findings & Limitations

7.2.1 Off-label and unlicensed prescribing and ADR risk

The study findings about the positive association between off-label and unlicensed medicine use and ADR risk concur with those of previous studies (Neubert et al., 2004, Santos et al., 2008). A positive association between ADR risk and an increase in the number of medicines, regardless of category, was also identified. In terms of study design, an observational approach to both ADR identification and prescription data collection has limitations. ADR identification relied on the recording of signs and symptoms by the clinical team and the identification of the causal link by the research team. Prescription data collection relied on accurate prescription records being available. Furthermore, these did not always contain the information required to assign off-label or unlicensed status to a medicine course, such that 6.8% of medicine courses in the admissions study and 5.2% of medicine courses in the inpatient study could not be classified. There were also areas of paediatric care not included in this study in which off-label and unlicensed medicine use is common, including paediatric- and neonatal intensive care and paediatric psychiatry. Finally, the definitions used for the classification of off-label and unlicensed medicines were selected because they had been used in the majority of previous studies but their application may still be open to interpretation. For example, at the time of the study described in Chapter 3, only one parenteral morphine product was licensed for use in children. The product in use at our centre was only licensed in children 12 years or older and, because the study methodology considered the brand in use rather than the active pharmaceutical ingredient, this impacted on the number of off-label morphine courses.

A simplistic interpretation of why off-label and unlicensed medicines increase ADR risk is because there is a lack of evidence for their use and this poses a risk. Indeed, this is supported by our finding that medicines given to children below the minimum age or weight specified in the drug literature were the category most likely to be implicated in an ADR. Systemic exposure to these medicines may have been greater than required for

therapeutic effect because of a lack of pharmacokinetic data in children. Studies which address this knowledge deficit will inform a more tailor-made approach to dosing in children than historical approaches such as scaling down adult doses and with this will come improved safety and efficacy (Hawcutt and Smyth, 2008). Such studies now form part of the paediatric investigation plan (PIP) required for all new medicines under development in Europe (The European Parliament and the Council of the European Union, 2006). However, the data in the thesis show that off-label and unlicensed medicines were diverse in terms of the quality of evidence to support their use and the frequency with which they caused ADRs. This prompts the question 'would this off-label or unlicensed medicine have caused the ADR if it was authorised?'. If there is sparse evidence to support the use of an off-label or unlicensed medicine, the answer is 'possibly'. The authorisation process demands a minimum amount of data to be generated and these will guide the safe and appropriate use of the medicine but, the ADR may still occur. However, if there is already evidence to support the safe and appropriate prescribing of an off-label or unlicensed medicine, it is difficult to see how the authorisation of that use would make a difference to ADR risk. This is evidenced by the finding that the number of medicines prescribed per se was an important predictor of risk, irrespective of whether they were off-label or not. This finding also points towards another predictor of ADR risk which was not explored in this thesis: disease state. Since the children included in the two cohort studies were admitted to hospital or had been in hospital for longer than 48 hours, we can assume that they were acutely unwell and/or had recently undergone significant surgery. In these complex cases there was potential for the development of ADRs in children who were already physiologically compromised with the additional risk of drug-drug interactions when multiple medicines were being administered.

In this thesis, the evidence base for an example of off-label medicine use in children was examined: intraoperative dexamethasone as an anti-emetic in tonsillectomy. There is good evidence for the efficacy of dexamethasone in this setting, but the systematic review determined that the evidence base for safety was more difficult to demonstrate. The systematic collection, recording and reporting of adverse outcomes is a vital component in the development of a robust evidence base so that advice on the use of medicines can facilitate benefit-risk assessments. In conclusion, although off-label and unlicensed medicine use does not, by definition, fall within the terms of a marketing authorisation, this does not always equate to a lack of evidence.

Although for some medicines the existence of a marketing authorisation may not have a direct impact on whether the prescriber has evidence to support their decision, it has other important benefits. Evidence-based off-label medicine prescribing often necessitates the use of formulations which are not age-appropriate, and thus risk is introduced at the point of administration. There is some evidence that off-label and unlicensed medicines are more likely to be implicated in medication errors (Conroy, 2011) and that the use of non-age appropriate formulations leads to dose inaccuracy (Aguado-Lorenzo et al., 2013). There may be an evidence-base for the use of the active pharmaceutical ingredient (API) in an unlicensed special, but data on bioavailability and stability of the product itself may be sparse or vary depending on the manufacturer (Mulla et al., 2011). Several regulatory measures in Europe have been implemented with the intention of increasing the availability of evidence based, age-appropriate medicines on which robust formulation studies have been performed. New medicines in development must have a paediatric investigation plan (PIP), older medicines still under patent protection can be granted a 'paediatric extension' for the completion of studies in children and for off-patent products, and a paediatric use marketing authorisation (PUMA) can be granted which is associated with a ten-year period of data and market protection. In the UK, since the introduction of the regulation, 74% of PIP submissions have been for new medicinal products and 24% have been for existing products, whereas only 2% of submissions have been for PUMAs. Six new paediatric formulations have been authorised and 13 paediatric extensions have been granted (data correct as of May 2012) (Branch, 2012). Finally, the new pharmacovigilance regulation introduced in Europe in 2012 is intended to enhance the timely identification of safety issues for authorised medicines, another advantage of the authorisation process for medicines (The European Parliament and the Council of the European Union, 2010).

7.2.2 ICD-10 coding of ADRs

ADRs detected in the admissions study (Chapter 2) were not reliably recorded in the clinical coding process. Therefore it is concluded that the screening of ICD-10 codes is not a reliable method for detecting ADRs. Compared to all other ADR types, a significantly greater number of neutropenia cases were assigned an ICD-10 code. This was a result of the use of a structured admission proforma to document neutropenia on the oncology unit and the assignment of specifically trained coding staff to that unit. The adoption of this approach in other clinical specialties may increase the rate of ADRs being coded, and improve our ability

to determine the burden of ADRs in the whole NHS used hospital episode statistics, but this will of course still also rely on the accurate identification of ADRs by healthcare staff in their assessment of patients.

7.2.3 Dexamethasone and post-tonsillectomy haemorrhage risk in children

The systematic review demonstrated that an increased risk of post-tonsillectomy haemorrhage with dexamethasone use cannot be ruled out and that there are currently inadequate data available to assess the risk associated with use of dexamethasone in combination with NSAIDs. In terms of study selection for our systematic review, the systematic search strategy applied, the range of primary and secondary sources searched and the rigorous screening process have been described. Limitations arose from the exclusion of non-English language publications and the potential for errors in the study selection methodology. However the latter of course applies to any systematic review. The major limitation of the systematic review arises from the characteristics of the included studies. There was significant clinical heterogeneity between studies and differences between the quality of haemorrhage rate data collection and reporting. Despite these limitations, the meta-analysis findings are supported by those of other similar reviews. The finding emphasised here is that the data available are inadequate and further well designed studies are needed.

7.2.4 Development of a risk score for post-operative vomiting

A robust risk score for POV in children was not developed. The use of data from a prospective cohort in which participants were evaluated for POV risk and managed accordingly as part of routine clinical practice meant that the interpretation of the findings was complex. However, the risk factors for POV were investigated via a univariate analysis and an exploration of the evidence and guidelines was undertaken. The interpretation of the findings must be in the context of the limitations of the study design; it was a retrospective analysis which included patients who stayed for longer than 48 hours but not those who were in intensive care. The risk factors identified by the authors of a previous risk score development study were similar to those identified here and the predictive properties of their model were no better (Eberhart et al., 2004). In concordance with the study described here, they identified that clinical heterogeneity in terms of both

anaesthetic and surgical techniques even for the same procedure will limit the predictive ability of any tool. Even when POV can be predicted, the available preventative measures may not always be effective. Therefore some attention should be given to establishing evidence-based guideline for the effective management of established POV.

7.3 Implications for Research

Despite the implementation of the Paediatric Regulation in Europe, the use of off-label and unlicensed medicines in paediatric practice will continue to be necessary. Irrespective of this, ADRs remain a function of the number of medicines prescribed, and research should focus on optimising the use of all medicines in children. Identifying the right dose is a good starting point.

The existing evidence for the use of individual authorised, off-label and unlicensed medicines should be properly evaluated and consolidated. Gaps in the evidence can thus be identified. For some medicines a synthesis of existing data will provide adequate evidence to support the assessment of benefit-risk. For others more clinical studies will be required and key to these will be an emphasis on the collection of safety as well as efficacy data. Since many off-label and unlicensed medicines require manipulation before they can be administered, studies which generate evidence for safe practice are needed. A prospective study of off-label and unlicensed medicine use and medication error risk, inclusive of a root cause analysis of each error, would inform the development of interventions to reduce the risk of errors. Data from the studies described in this thesis can inform priorities for clinical research. Additional studies in areas not covered, for example in paediatric and neonatal intensive care and paediatric psychiatry should be conducted to provide data pertaining to ADR incidence and risk factors.

It may be possible to enhance the value of ICD-10 codes as one facet of a pharmacovigilance strategy. This could be achieved through specific training alongside specific tools (e.g. structured proformas) for both those who record ADRs in the clinical notes and those who carry out the coding. However, the more fundamental problem is a lack of awareness and understanding about ADRs amongst health care professionals (Hazell and Shakir, 2006). Research should focus on the development of strategies to improve the detection, assessment and reporting of ADRs by healthcare professionals.

There is a lack of conclusive evidence for the safety of dexamethasone and NSAIDs in tonsillectomy. Evidence could be provided via a large prospective study of haemorrhage rates in children who receive dexamethasone, dexamethasone plus NSAID or neither. Some ongoing randomised studies promise to provide some additional data on both dexamethasone and ibuprofen use (Centre Hospitalier Universitaire Vaudois, University of Turku, Massachusetts Eye and Ear Infirmary, Cumberland Pharmaceuticals).

Although there are evidence-based interventions for the prevention of POV in children, they are not effective in every patient and the incidence of POV remains high. The focus of future research should be to reduce the incidence of POV and to improve its management. The incidence of POV could be reduced by improving the accuracy with which high risk patients are identified and by designing tailored interventions for its prevention. The management of POV could be improved by the design of evidence-based interventions appropriate to the post-operative setting, be that in hospital or at home.

7.4 Conclusion

The use of off-label and unlicensed medicines in children is common and these medicines are frequently associated with ADRs. The number of medicines administered whether authorised, off-label or unlicensed is a significant predictor of ADR risk.

A requirement to authorise all medicines used in children would lead to changes in the way we use some medicines and reduce the potential for adverse effects. For other medicines, authorisation would not change the way we use them and adverse effects would be no less likely, however it would bring with it other advantages. A requirement to authorise all medicines before use in children is obviously not immediately practicable. The rational prescribing of medicines is an important measure in the reduction of ADR risk which can be applied to all medicine use. This should be supported by on-going medication review, with the active participation of patients and their families. The aim is to ensure that the minimum number of medicines is used safely and effectively for the minimum duration necessary.

There continues to be enormous scope to optimise the use of medicines, authorised or otherwise, in children and further well-designed research will contribute to improvements in how we use medicines.

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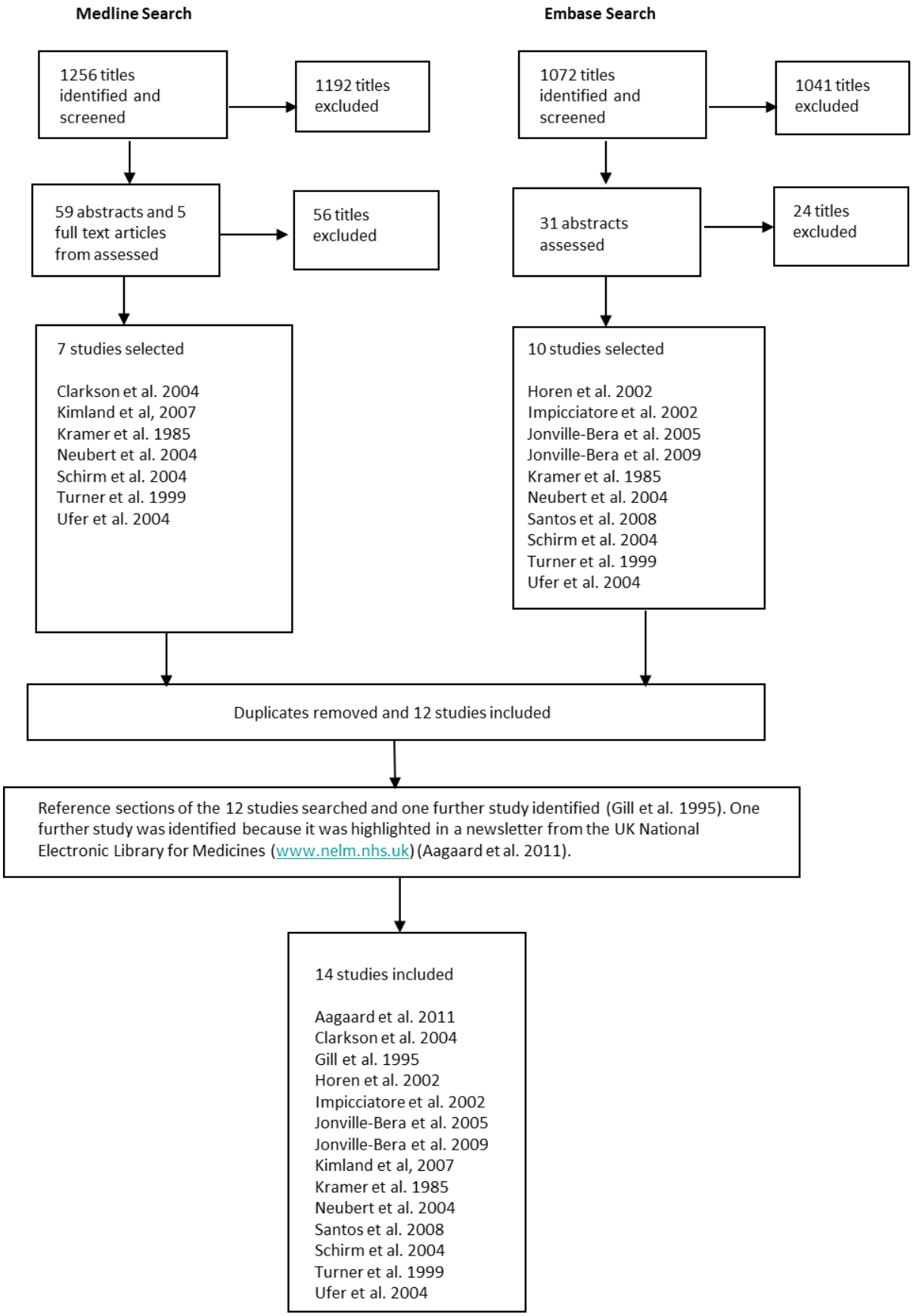
Appendix 1 Search strategy for narrative review



Appendix 2 Non-oncology ADRs which involved at least one off-label or unlicensed medicine course (n=48) greatest total number of medicines implicated first

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Constipation	3	Possibly Avoidable	Probable	3	Codeine Tablets Diclofenac Tablets	Ondansetron Oral Syrup	-

[xli] **Modified Hartwig scale (Hartwig, Siegel and Schneider, 1992)**

Severity level	Description
1	Required no change in treatment
2	Drug dosing or frequency changed
3	Required treatment, or drug administration discontinued
4	Result in patient transfer to higher level of care
5	Caused permanent harm to patient or significant haemodynamic instability
6	Directly or indirectly resulted in patient death

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Immunosuppression	4	Possibly Avoidable	Definite	3	Prednisolone Tablets	Infliximab Infusion	Tacrolimus Oral Liquid
Immunosuppression	3	Unavoidable	Definite	3	Prednisolone Tablets	Mycophenolate Mofetil Capsules	Tacrolimus Oral Liquid
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	3	Ibuprofen Oral Syrup	Dexamethasone Injection	Diclofenac Dispersible Tablets
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	3	Ibuprofen Oral Syrup	Dexamethasone Injection	Diclofenac Dispersible Tablets
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	3	Diclofenac Injection	Dexamethasone Injection Ibuprofen Oral Syrup	-

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	3	Ibuprofen Oral Syrup	Dexamethasone Injection	Diclofenac Dispersible Tablets
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	3	Ibuprofen Oral Syrup Diclofenac Suppositories	Dexamethasone Injection	-
Immunosuppression	3	Unavoidable	Possible	2	Prednisolone Tablets	-	Tacrolimus Oral Liquid
Constipation	3	Possibly Avoidable	Probable	2	-	-	Calcium Carbonate Oral Liquid Amlodipine Oral Liquid
Ileus	3	Possibly Avoidable	Probable	2	Codeine Tablets	Fentanyl Citrate Injection	-
Immunosuppression	3	Unavoidable	Possible	2	Methylprednisolone Injection	Methotrexate Tablets	-

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Immunosuppression	3	Unavoidable	Possible	2	Prednisolone Tablets	Tacrolimus Capsules	1
Immunosuppression	3	Unavoidable	Possible	2	Prednisolone Tablets	Mycophenolate Mofetil Capsules	-
Immunosuppression	4	Unavoidable	Probable	2	Prednisolone Tablets	Mycophenolate Mofetil Capsules	-
Immunosuppression	3	Unavoidable	Possible	2	Prednisolone Tablets	-	Tacrolimus Oral Liquid
Immunosuppression	4	Unavoidable	Probable	2	Prednisolone Tablets	-	Tacrolimus Oral Liquid
Immunosuppression	3	Unavoidable	Possible	2	Prednisolone Tablets	-	Tacrolimus Oral Liquid

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Immunosuppression	3	Unavoidable	Possible	2	Prednisolone Tablets	-	Tacrolimus Oral Liquid
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	-	Dexamethasone Injection	Diclofenac Dispersible Tablets
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	-	Dexamethasone Injection Ibuprofen Oral Syrup	
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	-	Dexamethasone Injection Ibuprofen Oral Syrup	-

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	-	Diclofenac Dispersible Tablets Ibuprofen Oral Syrup	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Tablets	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Post-Operative Bleeding	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Prednisolone Tablets	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	-	Dexamethasone Injection	Diclofenac Dispersible Tablets
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Ibuprofen Oral Syrup	Dexamethasone Injection	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	2	Diclofenac Injection	Ibuprofen Oral Syrup	-

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Respiratory Depression	4	Possibly Avoidable	Probable	2	Diazepam Rectal	-	Midazolam Buccal
Constipation	3	Unavoidable	Possible	1	-	Oxybutynin Oral Elixir	-
Constipation	3	Possibly Avoidable	Definite	1	-	Dihydrocodeine Tartrate Oral Solution	-
Candida	1	Unavoidable	Probable	1	-	Anakinra Injection	-
Deranged Renal Function	3	Definitely Avoidable	Probable	1	-	-	Captopril Oral Liquid
Headache	3	Unavoidable	Possible	1	-	Acetazolamide Tablet	-

Description Of ADR	Severity[xli]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-Label	Unlicensed
Hyperkalemia	2	Unavoidable	Probable	1	-	-	Spironolactone Oral Liquid
Immunosuppression	3	Unavoidable	Possible	1	-	Methotrexate Injection	-
Inter-Menstrual Bleed	3	Unavoidable	Probable	1	-	Desogestrel, Ethinylestradiol Tablet	-
Post-Tonsillectomy Bleed	3	Unavoidable	Possible	1	-	Ibuprofen Oral Syrup	-
Respiratory Depression	4	Possibly Avoidable	Probable	1	-	-	Midazolam Buccal
Wheeze And Increased Work Of Breathing	3	Unavoidable	Probable	1	-	Propanolol Oral Solution	-

Appendix 3 **Oncology ADRs which involved at least one off-label or unlicensed medicine course (n=93) greatest total number of medicines implicated first**

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed

[xlii] **Modified Hartwig scale (Hartwig, Siegel and Schneider, 1992)**

Severity level	Description
1	Required no change in treatment
2	Drug dosing or frequency changed
3	Required treatment, or drug administration discontinued
4	Result in patient transfer to higher level of care
5	Caused permanent harm to patient or significant haemodynamic instability
6	Directly or indirectly resulted in patient death

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression Neutropenia	3	Unavoidable	Definite	6	Vincristine Dexamethasone Tablets Teicoplanin	Doxorubicin	Methotrexate oral liquid Mercaptopurine oral liquid
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	5	Methotrexate injection Vincristine	Cyclophosphamide Cytarabine Doxorubicin	-
Immunosuppression Mucositis Neutropenia	3	Unavoidable	Probable	5	Vincristine	Cyclophosphamide Cytarabine Doxorubicin Methotrexate	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Dexamethasone liquid Vincristine	-	Mercaptopurine oral liquid Methotrexate oral liquid
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Probable	4	Vincristine Ifosfamide	Doxorubicin Etoposide	-
Anaemia Immunosuppression Nausea Neutropenia Thrombocytopenia Vomiting	3	Unavoidable	Definite	4	Prednisolone Tablets Vincristine	Cyclophosphamide Doxorubicin	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Ifosfamide Vincristine	Doxorubicin Etoposide	-
Anaemia Mucositis Neutropenia Thrombocytopenia	3	Unavoidable	Probable	4	Doxorubicin Vincristine	Cyclophosphamide Cisplatin	-
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Doxorubicin Vincristine Ifosfamide	Dactinomycin	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Probable	4	Vincristine	Cyclophosphamide Doxorubicin Dexamethasone injection	-
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Vincristine	Doxorubicin Etoposide Ifosfamide	-
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Vincristine Ifosfamide	Doxorubicin Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Deranged LFTs	1	Unavoidable	Definite	4	Teicoplanin	Doxorubicin	Methotrexate oral liquid Mercaptopurine oral liquid
Gastritis	3	Possibly Avoidable	Possible	4	Daunorubicin Dexamethasone liquid Vincristine	Cyclophosphamide	-
Immunosuppression	3	Unavoidable	Definite	4	Dexamethasone oral liquid Vincristine	-	Mercaptopurine oral liquid Methotrexate oral liquid

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Probable	4	Vincristine Ifosfamide	Dactinomycin Doxorubicin	-
Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Cytarabine Vincristine	Cyclophosphamide	Mercaptopurine oral liquid
Mucositis Neutropenia Thrombocytopenia	3	Unavoidable	Definite	4	Vincristine Ifosfamide	Dactinomycin Doxorubicin	-
Neutropenia	1	Unavoidable	Probable	4	Daunorubicin Dexamethasone liquid Vincristine	Cyclophosphamide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	Vincristine	Cyclophosphamide Doxorubicin	-
Anaemia Mucositis Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	-	Cyclophosphamide Etoposide Methotrexate injection	-
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	Cytarabine Methotrexate injection	Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Neutropenia	3	Unavoidable	Probable	3	Vincristine	Carboplatin Etoposide	-
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Probable	3	Cytarabine Daunorubicin	Etoposide	-
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	Vincristine	Etoposide Doxorubicin	-
Anaemia Mucositis Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	Cytarabine	Amsacrine Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Nausea Neutropenia Thrombocytopenia Vomiting	3	Unavoidable	Definite	3	Cytarabine Methotrexate injection	Etoposide	-
Anaemia Haematuria Thrombocytopenia	3	Unavoidable	Probable	3	Methotrexate injection Cytarabine	Cyclophosphamide	-
Back Pain	3	Unavoidable	Definite	3	Dexamethasone oral solution Vincristine	Doxorubicin	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Constipation	3	Unavoidable	Possible	3	Dihydrocodeine tablets Ifosfamide	Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Probable	3	Vincristine	Etoposide Doxorubicin	-
Immunosuppression	3	Possibly Avoidable	Probable	3	Prednisolone tablets Tacrolimus capsules	Mycophenolate Mofetil Capsules	-
Immunosuppression Neutropenia	5	Unavoidable	Definite	3	Dexamethasone oral solution Vincristine	Doxorubicin	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression Nausea Neutropenia Vomiting	3	Unavoidable	Definite	3	Ifosfamide	Dactinomycin Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	3	Dexamethasone oral solution Vincristine	Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	3	Dexamethasone oral liquid Vincristine	Doxorubicin	-
Immunosuppression	3	Unavoidable	Possible	3	Prednisolone Tablets Tacrolimus Capsules	Mycophenolate Mofetil Capsules	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression Neutropenia	3	Unavoidable	Definite	3	Vincristine	-	Mercaptopurine oral liquid Methotrexate oral liquid
Immunosuppression Neutropenia	3	Unavoidable	Definite	3	Vincristine	-	Mercaptopurine oral liquid Methotrexate oral liquid
Immunosuppression Neutropenia	3	Unavoidable	Definite	3	Vincristine	-	Mercaptopurine oral liquid Methotrexate oral liquid

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression	3	Unavoidable	Definite	3	Dexamethasone oral liquid	-	Mercaptopurine oral liquid Methotrexate oral liquid
Immunosuppression Neutropenia	3	Unavoidable	Definite	3	Vincristine	Doxorubicin Etoposide	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	Vincristine	Carboplatin Etoposide	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	3	Vincristine	Carboplatin Etoposide	-
Vomiting	3	Unavoidable	Definite	3	Vincristine	Carboplatin Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Deranged LFTs Diarrhoea Nausea Thrombocytopenia Vomiting	3	Unavoidable	Definite	2	-	Irinotecan Temozolomide capsules	-
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Probable	2	-	Carboplatin Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Diarrhoea Headache Neutropenia Thrombocytopenia Vomiting	3	Unavoidable	Definite	2	Cytarabine	Etoposide	-
Anaemia Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	Cytarabine	Doxorubicin	-
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Probable	2	-	Carboplatin Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Deranged Renal Function	3	Unavoidable	Probable	2	-	Doxorubicin Cisplatin	-
Anaemia Neutropenia	3	Unavoidable	Definite	2	Ifosfamide	Etoposide	-
Anaemia Mucositis Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Cytarabine Etoposide	-
Anaemia Neutropenia Thrombocytopenia	3	Possibly Avoidable	Definite	2	Vincristine	-	Pegasparaginase

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Neutropenia Immunosuppression	3	Unavoidable	Definite	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid
Constipation	3	Possibly Avoidable	Definite	2	Vincristine	Ondansetron tablets	-
Deranged LFTs	1	Unavoidable	Probable	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Deranged LFTs Diarrhoea Immunosuppression Neutropenia Thrombocytopenia Vomiting	3	Unavoidable	Definite	2	-	Ifosfamide Doxorubicin	-
Deranged LFTs Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	Vincristine	Doxorubicin	-
Diarrhoea	1	Unavoidable	Possible	2	Vincristine	Prednisolone tablets	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Diarrhoea Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Vincristine	Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Ifosfamide	Etoposide	-
Immunosuppression Neutropenia	3	Unavoidable	Probable	2	Ifosfamide	Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Ifosfamide	Doxorubicin	-
Immunosuppression	3	Unavoidable	Possible	2	Vincristine	Prednisolone tablets	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Ifosfamide	Doxorubicin	-
Immunosuppression Mucositis Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	Vincristine	Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Prednisolone tablets	Vinblastine	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Vincristine	Doxorubicin	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Immunosuppression Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	Ifosfamide	Doxorubicin	-
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	Vinblastine	-	Mercaptopurine oral liquid
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid
Immunosuppression Neutropenia	3	Unavoidable	Definite	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Carboplatin Etoposide	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Cyclophosphamide Doxorubicin	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	Cytarabine	Etoposide	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Doxorubicin Cisplatin	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Cyclophosphamide Doxorubicin	-

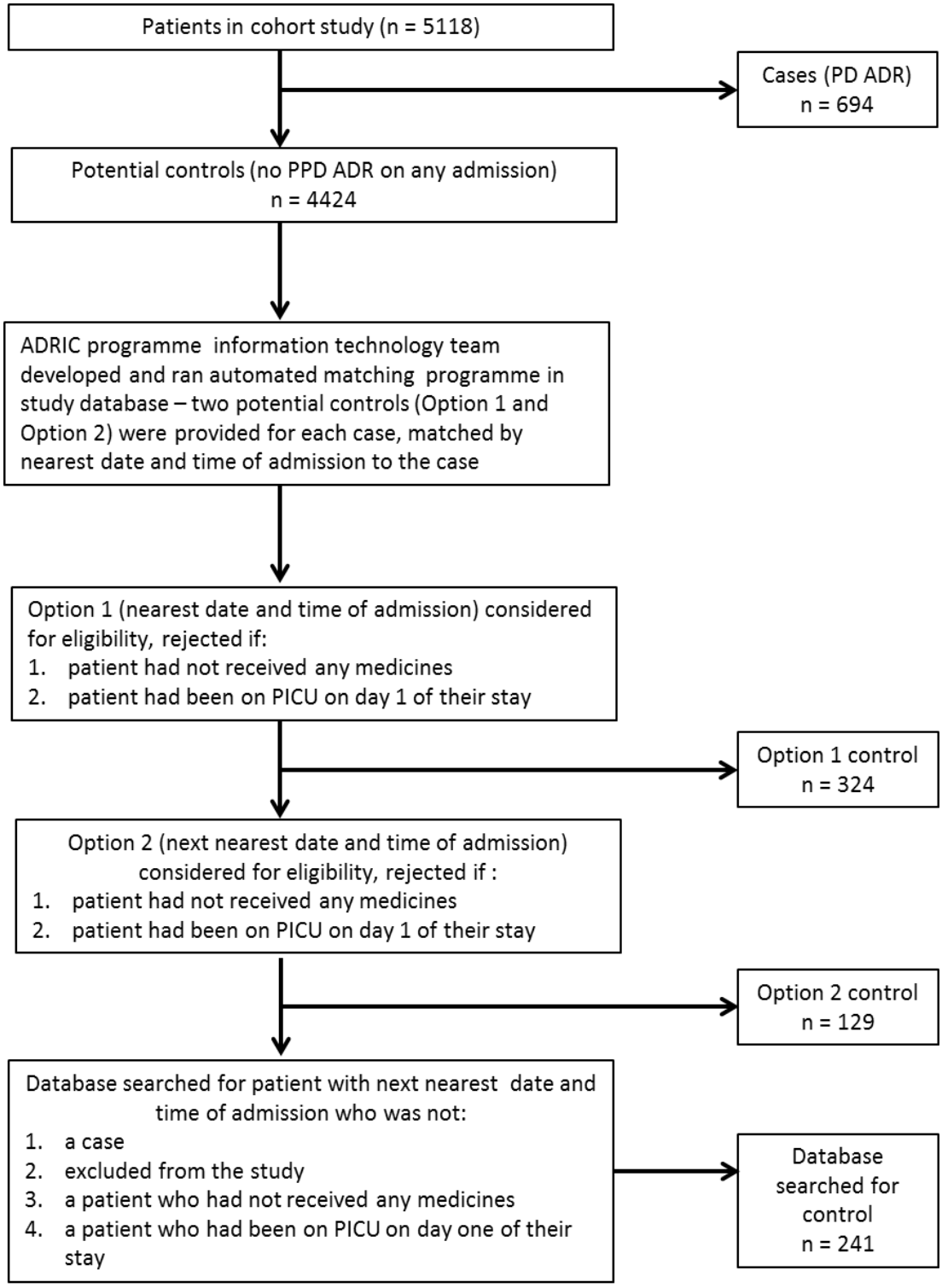
Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Cyclophosphamide Etoposide	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Cyclophosphamide Etoposide	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	-	Irinotecan Temozolomide capsules	-
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	2	Cytarabine	Fludarabine Phosphate	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Neutropenia	3	Unavoidable	Definite	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid
Neutropenia	3	Unavoidable	Probable	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid
Neutropenia	3	Unavoidable	Definite	2	-	-	Mercaptopurine oral liquid Methotrexate oral liquid
Thrombocytopenia	3	Unavoidable	Probable	2	Cytarabine	Etoposide	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Anaemia Neutropenia Thrombocytopenia	3	Unavoidable	Definite	1	-	-	Mercaptopurine oral liquid
Immunosuppression	3	Unavoidable	Possible	1	-	-	Methotrexate oral liquid
Immunosuppression Neutropenia	3	Unavoidable	Probable	1	-	-	Mercaptopurine oral liquid
Immunosuppression	3	Unavoidable	Definite	1	-	Cyclophosphamide	-
Neutropenia	3	Unavoidable	Definite	1	-	Vinblastine	-

Description Of ADR(S)	Severity[xlii]	Avoidability	Causality	Total Number Of Medicines Implicated	Categories of medicines implicated		
					Authorised	Off-label	Unlicensed
Neutropenia Thrombocytopenia	3	Unavoidable	Definite	1	-	Methotrexate injection	-
Vomiting	3	Possibly Avoidable	Probable	1	-	Imatinib tablets	-

Appendix 4 Identification and selection of controls



Appendix 5 Decision trees for off-label medicine use

For each use of a medicine licensed for use in children, follow **Tree 1 + either Trees 2 or Tree 3.** This two stage layout for medicines licensed for use in children is to accommodate all the necessary steps on a single page. For each use of a medicine NOT licensed for use in children, follow **Tree 4.**

Guidance notes for use of the decision trees

For the contents of each box answer the question 'does this aspect of use correspond to the terms of the MA outlined in the SmPC?'

The answer will either be:

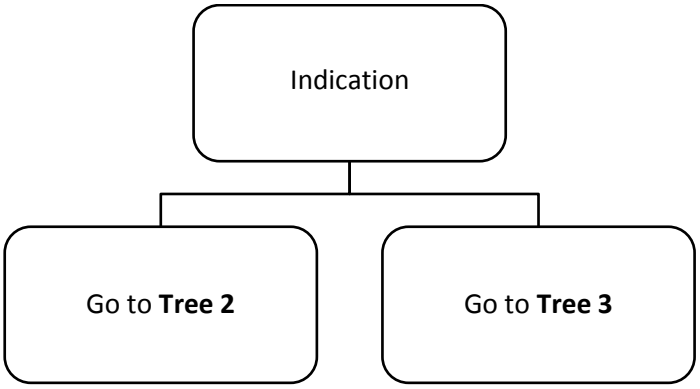
Y = this aspect of use is authorised

N= this aspect of use is not authorised

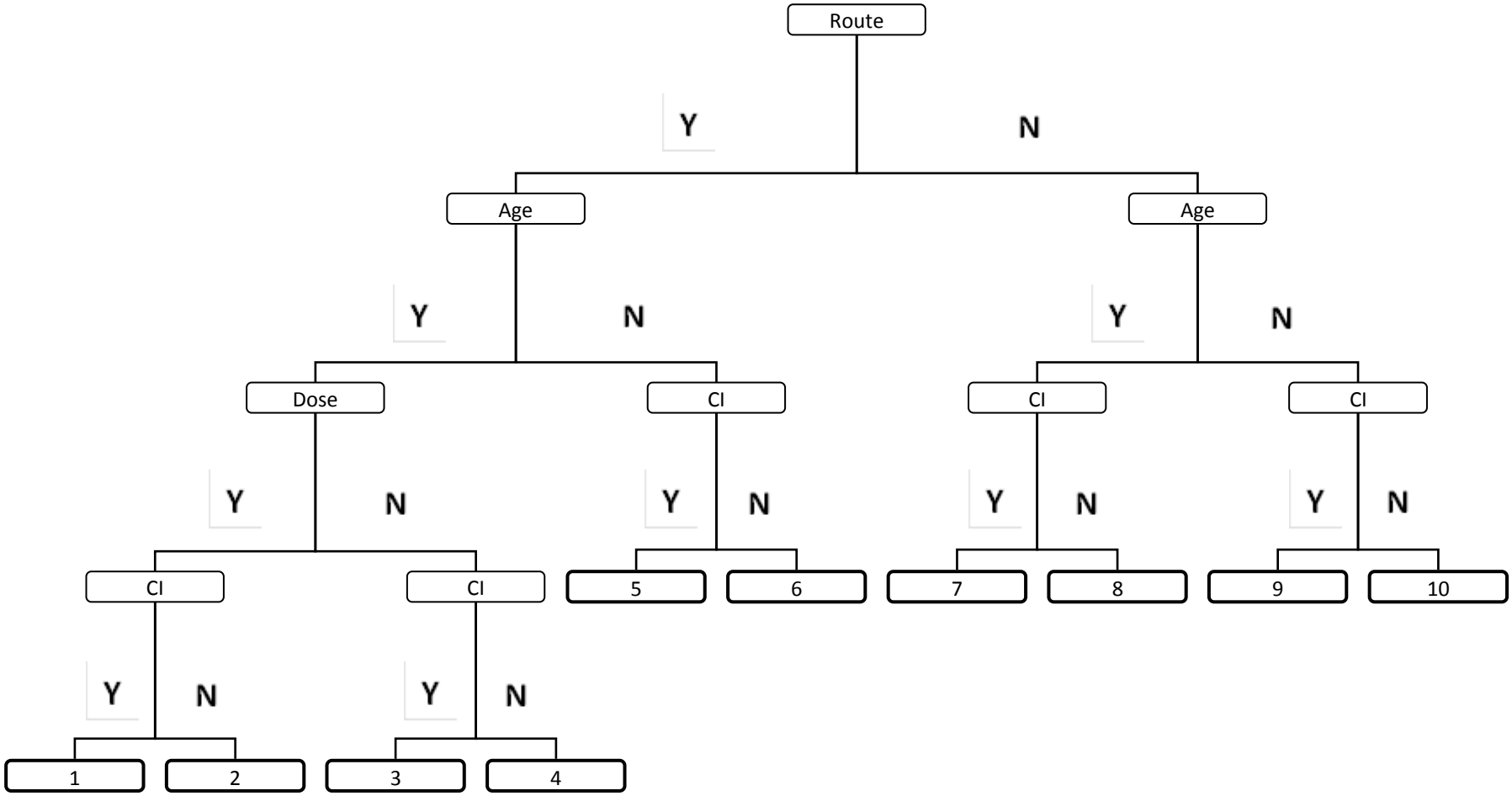
- Authorised use of licensed medicines will fall into category 1 because we can select **Y** for every aspect of use.
- When considering contraindications (CI), select **Y** if there are no contraindications and **N** if a contraindication exists.
- When considering dose, select **N** if dose > than recommended but **Y** if dose < recommended.

When all questions have been answered, a category (1-28) can be assigned.

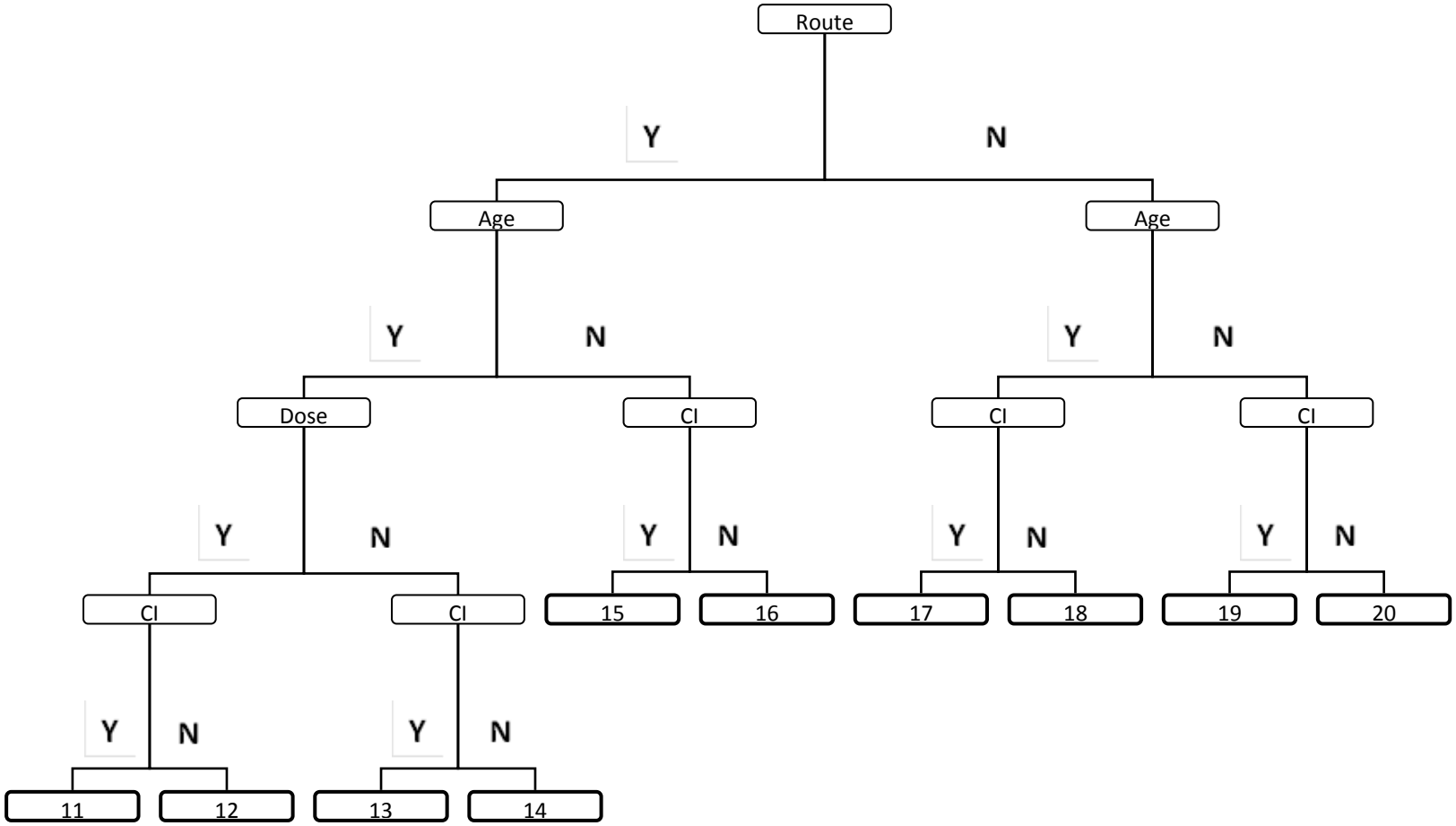
Tree 1– Medicines licensed for use in children



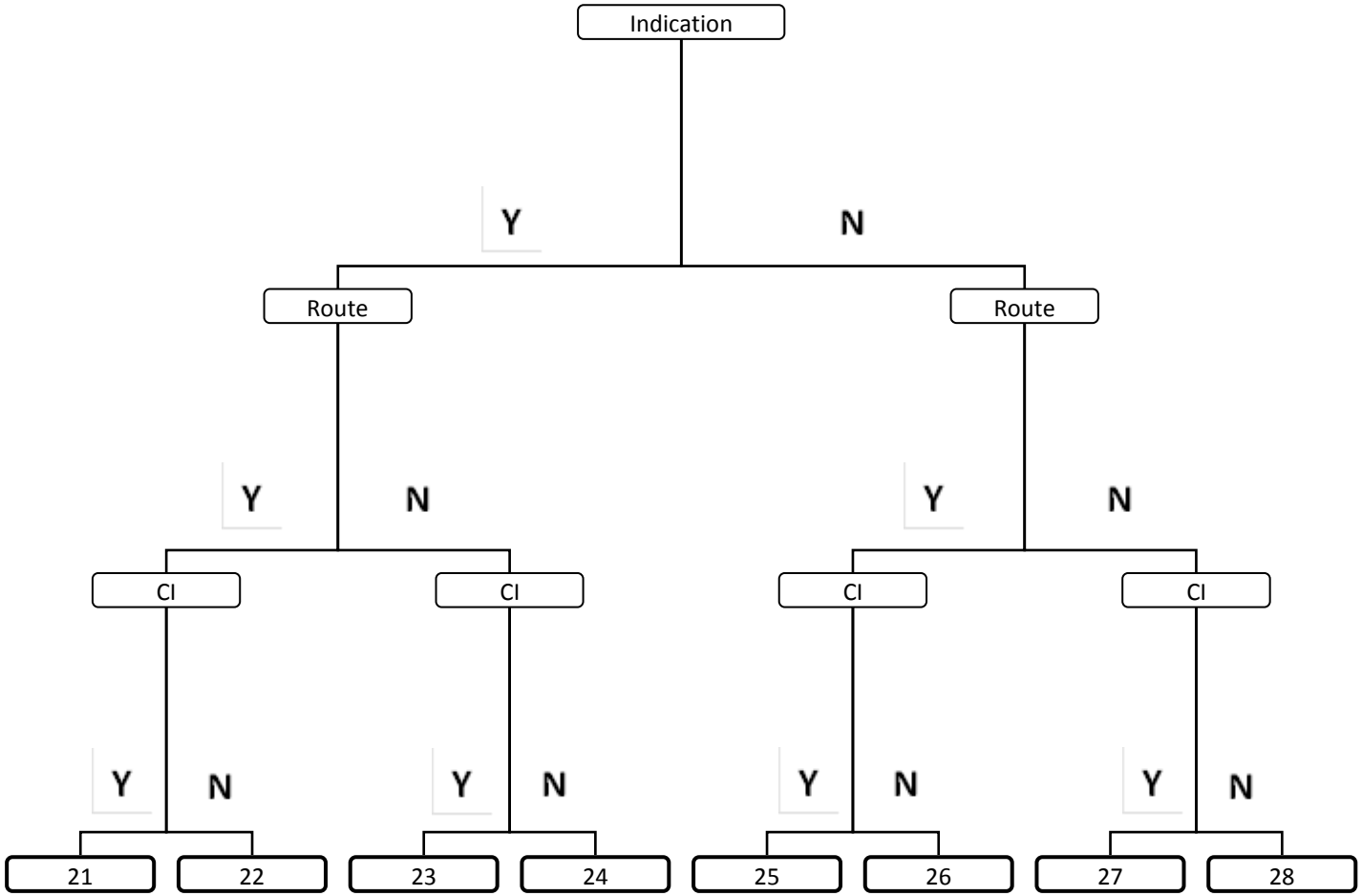
Tree 2 – Medicines licensed for use in children and indication authorised



Tree 3 - Medicines licensed for use in children but indication not authorised



Tree 4 – Medicines not licensed for use in children



Appendix 6 Unlicensed medicines recorded in the study by category

Drug Name	Preparation	Category
Acetazolamide	Acetazolamide 250mg In 5ml	31
Acetazolamide	Acetazolamide 250mg In 5ml Suspension	31
Acetylcysteine	Acetylcysteine 10% Oral Solution	31
Acetylcysteine	Acetylcysteine 20% Oral Solution	31
Acetylcysteine & Sodium Chloride	Acetylcysteine 10% In Sodium Chloride 0.9% For Nebulisation	31
Allopurinol	Allopurinol (Sugar Free) 100mg In 5ml Suspension	32
Amikacin	Amikacin 2mg In 1ml Line Lock	31
Amikacin	Amikacin 5mg In 5ml Line Lock	31
Amiodarone	Amiodarone 10mg In 1ml Suspension	31
Amlodipine	Amlodipine 1mg In 1ml Suspension	31
Amphotericin	Amphotericin 100mg In 1ml Suspension	31
Amphotericin B	Amphotericin B 1mg In 1ml Line Lock	31
Amphotericin B	Amphotericin B For Addition To PD Fluid	31
Arginine Hydrochloride	Arginine 10% Infusion	31
Arginine Monohydrochloride	Arginine Monohydrochloride 400mg In 1ml Oral Solution	31
Azathioprine	Azathioprine 10mg Capsules	32
Azathioprine	Azathioprine 10mg In 1ml Suspension	32
Bio-Kult Capsules	Bio-Kult Capsules	none - food supplement
Caffeine Citrate	Caffeine Citrate 50mg In 5ml Injection	32
Caffeine Citrate	Caffeine Citrate 50mg In 5ml Oral Solution	32
Calcium Carbonate	Calcium Carbonate 500mg Capsules	32

Drug Name	Preparation	Category
Calcium Carbonate	Calcium Carbonate Liquid 100 000 Units / Ml (250mg/5ml)	32
Captopril	Captopril 1mg In 1ml Suspension	32
Captopril	Captopril 5mg In 1ml Oral Solution	32
Ceftazidime	Ceftazidime 125mg In 0.63ml Subconjunctival Injection	31
Ceftazidime	Ceftazidime Intravenous Injection	31
Cefuroxime	Cefuroxime Eye Drops	31
Chloral Hydrate	Chloral Hydrate 50mg Suppositories	32
Chloral Hydrate	Chloral Hydrate 500MG In 5ML	32
Chlorothiazide	Chlorothiazide 250mg In 5ml Suspension	32 or 33
Chlorothiazide	Chlorthiazide Oral Solution	34
Cholesterol	Cholesterol (C-8503) Oral Powder	32
Cholic Acid	Cholic Acid 75mg & 150mg Capsules	32
Ciprofloxacin	Ciprofloxacin 0.2% Eye Drops	31
Ciprofloxacin	Ciprofloxacin 0.2mg In 0.1ml Intravitreal Injection	31
Ciprofloxacin	Ciprofloxacin 2mg In 1ml Line Lock	31
Clindamycin	Clindamycin Liquid, 75 Mg/5 Ml	32
Clobazam	Clobazam 5mg In 5ml Suspension	31
Clonazepam	Clonazepam 2.5mg In 1ml Drops	34
Clonazepam	Clonazepam 2mg In 5ml Sugar Free Oral Solution	32
Clonidine	Clonidine 50micrograms In 1ml Suspension	31
Clonidine + Levobupivicaine	Clonidine + Levobupivicaine Epidural	31
Co-Careldopa	Co-Careldopa(Sinemet) 62.5mg In 10ml Suspension	31
Codeine Phosphate	Codeine Phosphate 10mg Suppositories	32

Drug Name	Preparation	Category
Codeine Phosphate	Codeine Phosphate 2mg, 3mg	32
Colecalciferol	Colecalciferol 3000units In 1ml	32
Colistin	Colistin 100mg Base(3 Mega Units) In 1ml Oral Solution	31
Colistin, Tobramycin, Amphotericin	SDD Paste	31
Colomicin & Tobramycin & Amphotericin	SDD(Col/Tob/Amph 2%) Gel	31
Corticotrophin	Corticotropin Releasing Hormone (HCRF) 100microgram Ampoule	34
Creatine	Creatine Monohydrate Oral Powder	34
Cyclizine	Cyclizine 5mg In 5ml Suspension	31
Dantrolene	Dantrolene 25mg In 5ml Suspension	31
Defibrotide	Defibrotide 200MG (2.5ml Ampoule)	34
Deflazacort	Deflazacort 22.75mg In 1ml Oral Drops	34
Diazoxide	Diazoxide 250mg In 5ml Suspension	31
Diazoxide	Diazoxide 50mg In 5ml Suspension	31
Diclofenac	Diclofenac 10mg Dispersible Tablets	32
Dinoprostone	Dinoprostone Oral Solution	31
Docosahexaenoic Acid / Arachidonic Acid	DHA Powder	34
Asparaginase	E-Coli L-Asparaginase 500units Injection (Medac)	34
Enalapril	Enalapril Liquid	Unknown - not used at Alder Hey
Enoxaparin	Enoxaparin Subcutaneous Injection	31
Fentanyl + Levobupivicaine	Fentanyl + Levobupivicaine Epidural	32
Filgrastim	G-CSF(Filgrastim) Subcutaneous Injection	31
Flecainide	Flecainide 5mg In 1ml Oral Solution	32
Fludrocortisone	Fludrocortisone 10micrograms In 1ml Suspension	31

Drug Name	Preparation	Category
Gabapentin	Gabapentin 250mg In 5ml	31
Gentamicin	Gentamicin 10mg In 0.25ml Subconjunctival Injection	31
Gentamicin	Gentamicin 1mg In 1ml Line Lock	31
Gentamicin	Gentamicin 2mg In 1ml Line Lock	31
Glibenclamide	Glibenclamide 5mg/5ml	31
Glycopyrolate	Glycopyrolate 1mg/5ml Oral Solution	31
Glycopyrronium + Neostigmine	Glycopyrronium + Neostigmine 0.5/2.5 Injection	31
Glycopyrronium	Glycopyrronium Bromide 1mg Tablets	34
Gonadorelin	Gonadorelin 100micrograms Ampoule (Relefact Lh-Rh)	34
Heparin	Heparin 1unit In 1ml Infusion (50ml)	31
Hydralazine	Hydralazine 10mg In 5ml Suspension	31
Hydralazine	Hydralazine 10mg In 5ml Mixture	31
Hydrocortisone	Hydrocortisone Oral Liquid	32
Hydrocortisone	Hydrocortisone 10mg In 5ml Suspension	32
Hydroxychloroquine	Hydroxychloroquine 35mg In 5ml Suspension	31
Hyoscone Hydrobromide	Hyoscine Hydrobromide 100 Micrograms In 1ml Mixture	32
Iloprost	Iloprost 50micrograms In 250ml Sodium Chloride 0.9% Intravenous	31
Iloprost	Iloprost 100micrograms In 1ml Injection	34
Indometacin	Indometacin 25mg In 5ml Suspension	34
Isoniazid	Isoniazid 50mg In 5ml Elixir	32
Isoprenaline	Isoprenaline Sulphate 2.25mg In 2ml Injection	32
Ketamine	Ketamine 100mg In 1ml Oral Solution	31
LAT Gel	Lat (Lidocaine 4% & Adrenaline 0.1% & Tetracaine 0.5%) Gel	32

Drug Name	Preparation	Category
Levomepromazine	Levomepromazine 1mg In 1ml Suspension	31
Levothroxine	Levothyroxine Sodium 25micrograms In 5ml Suspension	31
Lisinopril	Lisinopril Liquid	32
Lomustine	Lomustine 20mg In 5ml Suspension	31
Loperamide	Loperamide 1mg Oral Powder	32
Magnesium Glycerophosphate	Magnesium Glycerophosphate 1mmol In 1ml Mixture	32
Magnesium Glycerophosphate	Magnesium Glycerophosphate 2mmol (500mg) Capsules	32
Melatonin	Melatonin 1mg/1ml Liquid	Unknown - not used at Alder Hey
Melatonin	Melatonin 2mg Capsules	32
Melatonin	Melatonin 3mg (6 Hour Timed Release) Capsule	34
Mercaptopurine	Mercaptopurine 100mg In 5ml Suspension	32
Methotrexate	Methotrexate 10mg Syringe	31
Methotrexate	Methotrexate 12.5mg Syringe	31
Methotrexate	Methotrexate 7.5mg Syringe	31
Methotrexate	Methotrexate 10mg In 5ml Oral Solution	32
Metoprolol	Metoprolol 10mg In 1ml Mixture	31
Midazolam	Midazolam Hydrochloride 2.5mg In 1ml Oral Solution	31
Midazolam	Midazolam 10mg In 1ml Buccal Liquid	32
Morphine Sulphate	Morphine Sulphate 500micrograms In 1ml Oral	32
Nadolol	Nadolol 10mg In 5ml Suspension	31
Nifedipine	Nifedipine 2% Drops (20mg/Ml)	34
Olive Oil	Olive Oil Ear Drops	33
Omeprazole	Omeprazole 10mg In 5ml	31

Drug Name	Preparation	Category
Oxybutinin	Oxybutynin 5mg In 15ml Bladder Instillation	31
Paracetamol	Paracetamol Intravenous Infusion	31
Paracetamol	Paracetamol 30mg Paediatric Suppositories	32
Paraldehyde	Paraldehyde Enema	32
Phenytoin	Phenytoin 90mg in 5ml Suspension	32
Potassium Acetate	Potassium Acetate 4.9g In 10ml Injection	32
Potassium Acid Phosphate	Potassium Acid Phosphate 1mmol In 1ml Oral Solution	32
Potassium Bicarbonate	Potassium Bicarbonate 500mg Capsule	32
Potassium Canrenoate	Potassium Canrenoate 200mg Injection	32
Potassium Chloride	Potassium Chloride 2mmol/Ml	31
Potassium Dihydrogen Phosphate	Potassium 1mmol & Phosphate 1mmol In 1ml Oral Solution	31
Potassium Dihydrogen Phosphate	Potassium Dihydrogen Phosphate 13.6% Injection (50ml)	32
Pyridostigmine	Pyridostigmine 15mg In 5ml Suspension	31
Pyridoxal	Pyridoxal 5 Phosphate 50mg Capsule	34
Pyridoxine	Pyridoxine Hydrochloride 150mg In 5ml Mixture	31
Pyridoxine	Pyridoxine Hydrochloride Powder Code 440865q	34
Pyrimethamine	Pyrimethamine 2mg In 1ml Oral Suspension	31
Ribavirin	Ribavirin Injection	34
Sildenafil	Sildenafil 2.5mg In 1ml Suspension	31
Sildenafil	Sildenafil 5mg In 5ml Suspension	31
Sodium Acid Phosphate	Sodium Acid Phosphate Powder	32
Sodium Benzoate	Sodium Benzoate 500mg In 5ml Oral Solution	32
Sodium Bicarbonate	Sodium Bicarbonate 1mmol In 1ml Oral Solution	32

Drug Name	Preparation	Category
Sodium Bicarbonate	Sodium Bicarbonate 500mg Capsules	32
Sodium Chloride	Sodium Chloride 0.9% Nasal Drops	31
Sodium Chloride	Sodium Chloride 30% Syrup	31
Sodium Chloride	Sodium Chloride 5mmol In 1ml Sterile Oral Solution (100ml)	31
Sodium Chloride	Sodium Chloride 5% Drops	32
Sodium Chloride	Sodium Chloride 500mg Capsules	32
Sodium Chloride	Sodium Chloride 7% Nebules	Classed as a medical device not pharmaceutical
Sodium Phenylbutyrate	Sodium Phenylbutyrate 1g In 5ml Injection	32
Spironolactone	Spironolactone 25mg/5ml Suspension	32
Stiripentol	Stiripentol 250mg Capsules	34
Stiripentol	Stiripentol 250mg Sachet	34
Sucrose	Sucraid	34
Sucralfate	Sucralfate Paste	31
Sucrose	Sucrose 12% Solution	34
Sultiame	Sultiame 200mg Tablets	34
Sultiame	Sultiame 50mg & 200mg Tablets	34
Tacrolimus	Tacrolimus 2.5mg In 5ml Suspension	32
Taurolin	Taurolin 2%	34
Teicoplanin	Teicoplanin 1mg In 0.1ml Intravitreal Injection	31
Thiamine	Thiamine Hydrochloride 100mg In 1ml Oral Solution	31
Tobramycin	Tobramycin Base	31
Tranexamic Acid	Tranexamic Acid 500mg In 5ml Oral Solution	32
Urokinase	Urokinase 40 000units In 40ml Sodium Chloride 0.9% Intra-Pleural	31

Drug Name	Preparation	Category
Urokinase	Urokinase Line Lock	31
Vancomycin	Intraocular Injection Vancomycin 1mg In 0.1ml Sodium Chloride	31
Vancomycin	Intravitreal Injection Vancomycin 1mg In 0.1ml Sodium Chloride	31
Vancomycin	Vancomycin 10mg In 2ml Intraventricular/Intrathecal	31
Vancomycin	Vancomycin 2mg In 1ml Line Lock	31
Vancomycin	Vancomycin 500mg In 30ml Oral Solution	31
Vancomycin	Vancomycin Solution For Nebulisation	31
Vitamin A	Vitamin A (Retinol) Aqueous 150,000u/Ml Oral Solution	34
Vitamin E	Vitamin E 100mg Chewable Tablets	34
Vitamin E	Vitamin E 100mg In 2ml Injection	34
Vitamin K	Vitamin K 1mg Capsules	Unknown – not used at Alder Hey
Warfarin	Warfarin 1mg In 1ml Oral Suspension (Sugar Free)	32
Zonisamide	Zonisamide 10mg In 1ml Oral Suspension	31

Appendix 7 Database Search Strategies

BioSciences Information Service of Biological Abstracts (BIOSIS) Citation Index via webofknowledge.com

1. TS=(nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*) OR TI=(nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*)

2. TS=(non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*) OR TI=(non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*)

3. TS=(aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or

loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac) OR TI=(aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone

or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac)

4. TS=(azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine) OR TI=(azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine)

5. (#1 OR #2 OR #3) AND #4

6. TS=((tonsil* adj3 surgery) or (remov* adj3 tonsil*) or (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*)) OR TI=((tonsil* adj3 surgery) or (remov* adj3 tonsil*) or (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*))

7. TS=(child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under eighteen* or under age* or pediatric* or paediatric*) OR TI=(child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or underage 18* or under eighteen* or under age* or pediatric* or paediatric*)

8. TS=(young adj (person* or people or adult* or individual* or women or woman or men or man)) OR TI=(young adj (person* or people or adult* or individual* or women or woman or men or man))

9. #7 OR #8

10. (#5 AND #6 AND #9) OR (#4 AND #6 AND #9)

Cumulative Index to Nursing and Allied Health Literature (CINAHL®) via ebscohost.com

1. exp ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL

2. nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*.ti,ab.

3. non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*.ti,ab

4. aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam.ti,ab

5. pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or

resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac.ti,ab.

6. DEXAMETHASONE/

7. azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine.ti,ab

8. (OR/1-5) AND (OR/6-7)

9. TONSILLECTOMY/

10. (tonsil* adj3 surgery). ti,ab.

11. (remov* adj3 tonsil*).ti,ab.

12. tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*.ti,ab.

13. OR/9-12

14. exp CHILD/

15. exp INFANT/

16. ADOLESCENT HEALTH SERVICES/OR exp ADOLESCENCE/OR ADOLESCENT, HOSPITALIZED/

17. exp STUDENTS/

18. exp PEDIATRICS/

19. child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or underage 18* or under eighteen* or under age* or pediatric* or paediatric*.ti,ab

20. (young adj person*).ti,ab

21. (young adj people) .ti,ab

22. (young adj adult*).ti,ab

23. (young adj individual*).ti,ab

24. (young adj women) .ti,ab

25. (young adj woman) .ti,ab

26. (young adj men) .ti,ab

27. (young adj man) .ti,ab

28. OR/14-27

29. (8 AND 13 AND 28) OR (OR/6-7 AND 13 AND 28)

Cochrane Library, The http://www.thecochranelibrary.com/view/0/index.html

1. MeSH descriptor Anti-inflammatory Agents, Non-steroidal explode all trees

2. (nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*):ti

3. (nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*):ab

4. (non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*):ti

5. (non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*):ab

6. (aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen):ti

7. (aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or

bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen):ab

8. (fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam):ti

9. (fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam):ab

10. (mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam):ti

11. (mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam):ab

12. (pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or

resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac):ti

13. (pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac):ab

14. MesH descriptor Dexamethasone explode all trees

15. (azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine):ti

16. (azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine):ab

17. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #16

18. MeSH descriptor Tonsillectomy explode all trees

19. (tonsil* adj3 surgery):ti

20. (tonsil* adj3 surgery):ab

21. (remov* adj3 tonsil*):ti

22. (remov* adj3 tonsil*):ab

23. (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*):ti

24. (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*):ab

25. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

26. MeSH descriptor Child explode all trees

27. MeSH descriptor Infant explode all trees

28. MeSH descriptor Adolescent explode all trees

29. MeSH descriptor Students explode all trees

30. MeSH descriptor Pediatrics explode all trees

31. (child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or underage 18* or under eighteen* or under age* or pediatric* or paediatric*):ti

32. (child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or underage 18* or under eighteen* or under age* or pediatric* or paediatric*):ab

33. (young adj person*):ti

34. (young adj person*):ab

35. (young adj people):ti

36. (young adj people*):ab

37. (young adj adult*):ti

38. (young adj adult*):ab

39. (young adj individual*):ti

40. (young adj individual*):ab

41. (young adj women):ti

42. (young adj women*):ab

43. (young adj woman):ti

44. (young adj woman*):ab

45. (young adj men):ti

46. (young adj men*):ab

47. (young adj man):ti

48. (young adj man):ab

49. #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48

50. #17 AND #25 AND #49

Database of Abstracts of Reviews of Effectiveness (DARE)
http://www.crd.york.ac.uk/CMS2Web

1. MeSH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES:

2. (nsaid*) OR (non-steroidal anti-inflammatory agent*) OR (nonsteroidal anti-inflammatory agent*) OR (non-steroidal antiinflammatory agent*) OR (nonsteroidal antiinflammatory agent):IN DARE, NHSEED, HTA

3. (non steroidal anti inflammatory drug*) OR (non steroidal antiinflammatory drug*) OR (nonsteroidal antiinflammatory drug*) OR (nonsteroidal anti inflammatory drug*) OR (non-steroidal anti-rheumatic agent*):IN DARE, NHSEED, HTA

4. (non-steroidal antirheumatic agent*) OR (nonsteroidal anti-rheumatic agent*) OR (nonsteroidal antirheumatic agent*) OR (anti-inflammatory analgesic*) OR (antiinflammatory analgesic*):IN DARE, NHSEED, HTA

5. (aspirin-like agent*) OR (non-steroid anti-inflammatory agent*) OR (nonsteroid anti-inflammatory agent*) OR (non-steroid antiinflammatory agent*) OR (nonsteroid anti-inflammatory):IN DARE, NHSEED, HTA

6. (non steroid anti inflammatory drug*) OR (non steroid anti-inflammatory drug*) OR (nonsteroid antiinflammatory drug*) OR (nonsteroid anti inflammatory drug*) OR (non-steroid anti-rheumatic agent*) :IN DARE, NHSEED, HTA

7. (non-steroid antirheumatic agent*) OR (nonsteroid anti-rheumatic agent*) OR (nonsteroid antirheumatic agent*) :IN DARE, NHSEED, HTA

8. (aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or

nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac): IN DARE, NHSEED, HTA

9. or/1-8

10. MeSH DESCRIPTOR Dexamethasone EXPLODE ALL TREES:

11. (azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine): IN DARE, NHSEED, HTA

12. or/10-11

13. MeSH DESCRIPTOR Tonsillectomy EXPLODE ALL TREES:

14. MeSH DESCRIPTOR Adenoidectomy EXPLODE ALL TREES:

15. ((tonsil* adj3 surgery) OR (remov* adj3 tonsil*) OR (tonsillectom* OR tonsilectom* OR adenotonsil* OR adeno-tonsill*)): IN DARE, NHSEED, HTA

16. or/13-15

17. MeSH DESCRIPTOR Child EXPLODE ALL TREES:

18. MeSH DESCRIPTOR Infant EXPLODE ALL TREES:

19. MeSH DESCRIPTOR Adolescent EXPLODE ALL TREES:

20. MeSH DESCRIPTOR Students EXPLODE ALL TREES:

21. MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES:

22. (child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or

underage 18* or under eighteen* or under age* or pediatric* or paediatric*): IN DARE, NHSEED, HTA

23. (young adj (person* or people or adult* or individual* or women or woman or men or man)): IN DARE, NHSEED, HTA

24. or/17-23

25. (9 and 12) and 16 and 24

26. 12 and 16 and 24

27. 25 or 26

Excerpta Medica database (EMBASE™) via www.library.nhs.uk

1. NONSTEROID ANTIINFLAMMATORY AGENT/

2. (nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*).ti,ab.

3. (non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*).ti,ab.

4. (aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or

dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenac OR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indomethacin) .ti,ab
5. indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or

pranoprofen or prinomide or proglumetacin or proglumetacin maleate or

propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium

or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic

acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or

suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin

or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or

tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen

or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or

tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or

zaltoprofen or zidometacin or zinc salicylate or zoliprofen or

zomepirac).ti,ab

6. or/1-5

7. exp DEXAMETHASONE/ OR exp DEXAMETHASONE 17 VALERATE/ OR exp DEXAMETHASONE ACETATE/ OR exp DEXAMETHASONE CIPECILATE/ OR exp DEXAMETHASONE DERIVATIVE/ OR exp DEXAMETHASONE SODIUM PHOSPHATE/ OR exp DEXAMETHASONE 17,21 DIPROPIONATE/ OR exp DEXAMETHASONE 21 MESILATE/ OR exp DEXAMETHASONE ISONICOTINATE/ 8. (azium or colofoam or decadron or decadrone or decaesadril or

decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort

or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth

or dexamethason or dexamethasone or dexamethazon or dexamethazone or

dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone

or dexone or diodex or fluorocort or fortecortin or gammacorten or

hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or

methylfluorprednisolone or millicorten or opticortinol or oradexon or

oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or

thilodexine).ti,ab

9. or/7-8

10. TONSILLECTOMY/

11. ((tonsil* adj3 surgery) or (remov* adj3 tonsil*) or (tonsillectom* or

tonsilectom* or adenotonsil* or adeno-tonsill*)).ti,ab.

12. or/10-11

13. exp CHILD/

14. exp INFANT/

15. exp ADOLESCENT/

16. exp STUDENT/

17. exp PEDIATRICS/

18. (child* or adolescen* or kid or kids or youth* or youngster* or minor or

minors or teen* or juvenile* or student* or pupil or pupils or boy or boys

or girl or girls or under 18* or underage 18* or under eighteen* or under

age* or pediatric* or paediatric*).ti,ab

19. (young ADJ person* OR young ADJ people OR young ADJ adult* OR young ADJ individual* OR young ADJ women OR young ADJ woman OR young ADJ men OR young ADJ man).ti,ab

20. or/13-19

21. (6 and 9 and 12 and 20) or (9 and 12 and 20)

Medical Literature Analysis and Retrieval System Online (MEDLINE®) via ovid.com

1. anti-inflammatory agents, non-steroidal/

2. (nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*).ti,ab.

3. (non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*).ti,ab.

4. (aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or

dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenac OR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indomethacin)ti,ab

5. (indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or

pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac).ti,ab.

6. or/1-5

7. exp Dexamethasone/

8. (azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine).ti,ab.

9. or/7-8

10. Tonsillectomy/

11. ((tonsil* adj3 surgery) or (remov* adj3 tonsil*) or (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*)).ti,ab.

12. or/10-11

13. exp child/

14. exp Infant/

15. exp adolescent/

16. exp Students/

17. exp Pediatrics/

18. (child* or adolescen* or kid or kids or youth* or youngster* or minor or

minors or teen* or juvenile* or student* or pupil or pupils or boy or boys

or girl or girls or under 18* or underage 18* or under eighteen* or under

age* or pediatric* or paediatric*).ti,ab.

19. (young ADJ person* OR young ADJ people OR young ADJ adult* OR young ADJ individual* OR young ADJ women OR young ADJ woman OR young ADJ men OR young ADJ man).ti,ab

20. or/13-19

21. ((6 and 9) and 12 and 20) or (9 and 12 and 20)

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1. TS=(nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*) OR TI=(nsaid* or non-steroidal anti-inflammatory agent* or nonsteroidal anti-inflammatory agent* or non-steroidal antiinflammatory agent* or nonsteroidal antiinflammatory agent* or non steroidal anti inflammatory drug* or non steroidal antiinflammatory drug* or nonsteroidal antiinflammatory drug* or nonsteroidal anti inflammatory drug* or non-steroidal anti-rheumatic agent* or non-steroidal antirheumatic agent* or nonsteroidal anti-rheumatic agent* or nonsteroidal antirheumatic agent* or anti-inflammatory analgesic* or antiinflammatory analgesic* or aspirin-like agent*)

2. TS=(non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*) OR TI=(non-steroid anti-inflammatory agent* or nonsteroid anti-inflammatory agent* or non-steroid antiinflammatory agent* or nonsteroid antiinflammatory agent* or non steroid anti inflammatory drug* or non steroid antiinflammatory drug* or nonsteroid antiinflammatory drug* or nonsteroid anti inflammatory drug* or non-steroid anti-rheumatic agent* or non-steroid antirheumatic agent* or nonsteroid anti-rheumatic agent* or nonsteroid antirheumatic agent*)

3. TS=(aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or

mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac) OR TI=(aceclofenac or acemetacin or acetylsalicyl* or actaritajulemic acid or alclofenac or alminoprofen or aloxiprin or amfenac or aminosalicylic acid or ampiroxicam or amtolmetin guacil or anacin or anirolac or antiflammin or apadenoson or arthrotec or ascriptin or balsalazide or bardoxolone or bendazac or benorilate or benoxaprofen or bermoprofen or bimosiamose or bromfenac or broperamole or bucloxic acid or bucolome or bufexamac or butibufen or camobucol or carbasalate calcium or carprofen or celecoxib or centchroman or cicloprofen or cimicoxib or cinmetacin or cinnoxicam or clidanac or clofenamic acid or clofezone or clonixin or cloximate or dehydrozingerone or demethoxycurcumin or deracoxib or dexibuprofen or dexketoprofen or diclofenac or didemethoxycurcumin or diflunisal or diftalone or dimethyl sulfoxide or diphenpyramide or ditazole or droxicam ebselen or emorfazone or endolac or enfenamic acid or epirizole or etodolac or etofenamate or etoricoxib or excedrin or felbinac or fenamic acid derivative or fenbufen or fenclofenac or fenclozic acid or fendosal or fenflumizole or fenoprofen or fentiazac or fepradinol or feprazone or firategrast or firocoxib or flobufen or flosulide or flufenamate aluminum or flufenamic acid or flunixin or flunoxaprofen or fluproquazone or flurbiprofen or fosfosal or furaprofen or furobufen or furofenac or glucametacin or gluconate zinc or guacetisal or guaimesal or gw 406381 or ibufenacOR ibuprofen or ibuproxam or icoduline or iguratimod or imidazole salicylate or incb 3284 or incyclinide or indameth or indometacin or indoprofen or ipsalazide or isofezolac or isonixin or isoxepac or isoxicam or kebuzone or ketoprofen or ketorolac or leflunomide or licofelone or lonazolac or lornoxicam or loxoprofen or lumiracoxib or lyprinol or lysine acetylsalicylate or magnesium salicylate or manoalide or mavacoxib or meclofenamate sodium or meclofenamic acid or mefenamic acid or meloxicam or mesalazine or metamizol or metiazinic acid or metoxibutropate or mirococept or miroprofen or mofebutazone or mofezolac or morazone or morniflumate or nabumetone or naproxcinod or naproxen or nepafenac or neurofenac or neurotropin or nictindole or niflumic acid or nimesulide or olsalazine or orpanoxin or oxaceprol or oxametacin or oxaprazine or oxaprozin or oxicam derivative or oxindanac or oxyphenbutazone or palifermin or parecoxib or pelubiprofen or pemedolac or perisoxal or phenazone or phenylbutazone or picolamine salicylate or piketoprofen or pimeprofen or pipebuzone or piproxen or pirazolac or piroxicam or pirprofen or pralnacasan or pranoprofen or prinomide or proglumetacin or proglumetacin maleate or propyphenazone or proquazone or pyrazinobutazone or resatorvid or rimazolium or robenacoxib or rofecoxib or romazarit or rosmarinic acid or salicylic acid or salsalate or scalaradial or semapimod or sudoxicam or sulindac or suprofen or suxibuzone or talniflumate or tenidap or tenoxicam or tepoxalin or teriflunomide or tiaprofenic acid or tiaramide or tilmacoxib or tilnoprofen arbamel or tilomisole or timegadine or tioxamast or tioxaprofen or tolfenamic acid or tolmetin or tribuzone or triethanolamine salicylate or

tropesin or ufenamate or valategrast or valdecoxib or ximoprofen or zaltoprofen or zidometacin or zinc salicylate or zoliprofen or zomepirac)

4. TS=(azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine) OR TI=(azium or colofoam or decadron or decadrone or decaesadril or decamethasone or dectancyl or deltafluorene or deronil or dexa-p or dexacort or dexagel or dexame or dexameson or dexametason or dexametasone or dexameth or dexamethason or dexamethasone or dexamethazon or dexamethazone or dexamonozon or dexan or dexascheroson or dexason or dexasone or dexmethsone or dexone or diodex or fluorocort or fortecortin or gammacorten or hexadecadrol or hexadrol or isopto-dex or isopto-maxidex or maxidex or methylfluorprednisolone or millicorten or opticortinol or oradexon or oradexone or orgadrone or ozurdex or policort or posurdex or prednisolone or thilodexine)

5. (#1 OR #2 OR #3) AND #4

6. TS=((tonsil* adj3 surgery) or (remov* adj3 tonsil*) or (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*)) OR TI=((tonsil* adj3 surgery) or (remov* adj3 tonsil*) or (tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*))

7. TS=(child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under eighteen* or under age* or pediatric* or paediatric*) OR TI=(child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or underage 18* or under eighteen* or under age* or pediatric* or paediatric*)

8. TS=(young adj (person* or people or adult* or individual* or women or woman or men or man)) OR TI=(young adj (person* or people or adult* or individual* or women or woman or men or man))

9. #7 OR #8

10. #5 AND #6 AND #9

11. #4 AND #6 AND #9

12. #10 OR #11

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1. TITLE-ABS-KEY(nsaid*) OR TITLE-ABS-KEY(non-steroidal anti-inflammatory agent*) OR TITLE-ABS-KEY (nonsteroidal anti-inflammatory agent*) OR TITLE-ABS-KEY (non-steroidal antiinflammatory agent*) OR TITLE-ABS-KEY(nonsteroidal antiinflammatory agent*) OR TITLE-ABS-KEY(non steroidal anti inflammatory drug*) OR TITLE-ABS-KEY(non steroidal antiinflammatory drug*) OR TITLE-ABS-KEY(nonsteroidal antiinflammatory drug*) OR TITLE-ABS-KEY(nonsteroidal anti inflammatory drug*) OR TITLE-ABS-KEY(non-steroidal anti-rheumatic agent*) OR TITLE-ABS-KEY(non-steroidal antirheumatic agent*) OR TITLE-ABS-KEY(nonsteroidal anti-rheumatic agent*) OR TITLE-ABS-KEY(nonsteroidal antirheumatic agent*) OR TITLE-ABS-KEY(anti-inflammatory analgesic*) OR TITLE-ABS-KEY(antiinflammatory analgesic*) OR TITLE-ABS-KEY(aspirin-like agent*)

2. TITLE-ABS-KEY (non-steroid anti-inflammatory agent*) OR TITLE-ABS-KEY(nonsteroid anti-inflammatory agent*) OR TITLE-ABS-KEY(non-steroid antiinflammatory agent*) OR TITLE-ABS-KEY(nonsteroid antiinflammatory agent*) OR TITLE-ABS-KEY(non steroid anti inflammatory drug*) OR TITLE-ABS-KEY(non steroid antiinflammatory drug*) OR TITLE-ABS-KEY(nonsteroid antiinflammatory drug*) OR TITLE-ABS-KEY(nonsteroid anti inflammatory drug*) OR TITLE-ABS-KEY(non-steroid anti-rheumatic agent*) OR TITLE-ABS-KEY(non-steroid antirheumatic agent*) OR TITLE-ABS-KEY(nonsteroid anti-rheumatic agent*) OR TITLE-ABS-KEY(nonsteroid antirheumatic agent*)

3. TITLE-ABS-KEY(taceclofenac) OR TITLE-ABS-KEY(acemetacin) OR TITLE-ABS-KEY(acetylsalicyl*) OR TITLE-ABS-KEY(actaritajulemic acid) OR TITLE-ABS-KEY(alclofenac) OR TITLE-ABS-KEY(alminoprofen) OR TITLE-ABS-KEY(aloxiprin) OR TITLE-ABS-KEY(amfenac) OR TITLE-ABS-KEY(aminosalicylic acid) OR TITLE-ABS-KEY(ampiroxicam) OR TITLE-ABS-KEY(amtolmetin guacil) OR TITLE-ABS-KEY(anacin) OR TITLE-ABS-KEY(anirolac) OR TITLE-ABS-KEY(antiflammin) OR TITLE-ABS-KEY(apadenoson) OR TITLE-ABS-KEY(arthrotec) OR TITLE-ABS-KEY(ascription) OR TITLE-ABS-KEY(balsalazide) OR TITLE-ABS-KEY(bardoxolone) OR TITLE-ABS-KEY(bendazac) OR TITLE-ABS-KEY(benorilate) OR TITLE-ABS-KEY(benoxaprofen) OR TITLE-ABS-KEY(bermoprofen) OR TITLE-ABS-KEY (bimosiamose) OR TITLE-ABS-KEY(bromfenac) OR TITLE-ABS-KEY(broperamole) OR TITLE-ABS-KEY(bucloxic acid) OR TITLE-ABS-KEY(bucolome) OR TITLE-ABS-KEY(bufexamac) OR TITLE-ABS-KEY(butibufen) OR TITLE-ABS-KEY(camobucol) OR TITLE-ABS-KEY(carbasalate calcium) OR TITLE-ABS-KEY(carprofen) OR TITLE-ABS-KEY (celecoxib) OR TITLE-ABS-KEY(centchroman) OR TITLE-ABS-KEY(cicloprofen) OR TITLE-ABS-KEY(cimicoxib) OR TITLE-ABS-KEY(cinmetacin) OR TITLE-ABS-KEY(cinnoxicam) OR TITLE-ABS-KEY(clidanac) OR TITLE-ABS-KEY(clofenamic acid) OR TITLE-ABS-KEY(clofezone) OR TITLE-ABS-KEY(clonixin) OR TITLE-ABS-KEY(cloximate) OR TITLE-ABS-KEY (dehydrozingerone) OR TITLE-ABS-KEY(demethoxycurcumin) OR TITLE-ABS-KEY(deracoxib) OR TITLE-ABS-KEY (dexibuprofen) OR TITLE-ABS-KEY(dexketoprofen) OR TITLE-ABS-KEY(diclofenac) OR TITLE-ABS-KEY(didemethoxycurcumin) OR TITLE-ABS-KEY(diflunisal) OR TITLE-ABS-KEY(diftalone) OR TITLE-ABS-KEY(dimethyl sulfoxide) OR TITLE-ABS-KEY(diphenpyramide) OR TITLE-ABS-KEY(ditazole) OR TITLE-ABS-KEY (droxicam ebselen) OR TITLE-ABS-KEY(emorfazone) OR TITLE-ABS-KEY(endolac) OR TITLE-ABS-KEY(enfenamic acid) OR TITLE-ABS-KEY(epirizole) OR TITLE-ABS-KEY(etodolac) OR TITLE-ABS-KEY(etofenamate) OR TITLE-ABS-KEY (etoricoxib) OR TITLE-ABS-KEY(excedrin) OR TITLE-ABS-KEY(felbinac) OR TITLE-ABS-KEY(fenamic acid derivative) OR TITLE-ABS-KEY(fenbufen) OR TITLE-ABS-KEY(fenclofenac) OR TITLE-ABS-KEY(fenclozic acid) OR TITLE-ABS-KEY (fendosal) OR TITLE-ABS-KEY(fenflumizole) OR TITLE-ABS-KEY(fenoprofen) OR TITLE-ABS-KEY(fentiazac) OR TITLE-ABS-KEY(fepradinol) OR TITLE-ABS-KEY(feprazone) OR TITLE-ABS-KEY(firategrast) OR TITLE-ABS-KEY(firocoxib) OR TITLE-ABS-KEY(flobufen) OR TITLE-ABS-KEY(flosulide) OR TITLE-ABS-KEY(flufenamate aluminium) OR TITLE-ABS-KEY(flufenamic

acid) OR TITLE-ABS-KEY(flunixin) OR TITLE-ABS-KEY(flunoxaprofen) OR TITLE-ABS-KEY(fluproquazone) OR TITLE-ABS-KEY(flurbiprofen) OR TITLE-ABS-KEY(fosfosal) OR TITLE-ABS-KEY(furaprofen) OR TITLE-ABS-KEY(furobufen) OR TITLE-ABS-KEY(furofenac) OR TITLE-ABS-KEY(glucametacin) OR TITLE-ABS-KEY(gluconate zinc) OR TITLE-ABS-KEY(guacetisal) OR TITLE-ABS-KEY(guaimesal) OR TITLE-ABS-KEY(gw 406381) OR TITLE-ABS-KEY(ibufenacOR ibuprofen) OR TITLE-ABS-KEY(ibuproxam) OR TITLE-ABS-KEY(icoduline) OR TITLE-ABS-KEY(iguratimod) OR TITLE-ABS-KEY(imidazole salicylate) OR TITLE-ABS-KEY(incb 3284) OR TITLE-ABS-KEY(incyclinide) OR TITLE-ABS-KEY(indameth) OR TITLE-ABS-KEY(indometacin) OR TITLE-ABS-KEY(indoprofen) OR TITLE-ABS-KEY(ipsalazide) OR TITLE-ABS-KEY(isofezolac) OR TITLE-ABS-KEY(isonixin) OR TITLE-ABS-KEY(isoxepac) OR TITLE-ABS-KEY(isoxicam) OR TITLE-ABS-KEY(kebuzone) OR TITLE-ABS-KEY(ketoprofen) OR TITLE-ABS-KEY(ketorolac) OR TITLE-ABS-KEY(leflunomide) OR TITLE-ABS-KEY(licofelone) OR TITLE-ABS-KEY(lonazolac) OR TITLE-ABS-KEY(lornoxicam) OR TITLE-ABS-KEY(loxoprofen) OR TITLE-ABS-KEY(lumiracoxib) OR TITLE-ABS-KEY(lyprinol) OR TITLE-ABS-KEY(lysine acetylsalicylate) OR TITLE-ABS-KEY(magnesium salicylate) OR TITLE-ABS-KEY(manoalide) OR TITLE-ABS-KEY(mavacoxib) OR TITLE-ABS-KEY(meclofenamate sodium) OR TITLE-ABS-KEY(meclofenamic acid) OR TITLE-ABS-KEY(mefenamic acid) OR TITLE-ABS-KEY(meloxicam) OR TITLE-ABS-KEY(mesalazine) OR TITLE-ABS-KEY(metamizol) OR TITLE-ABS-KEY(metiazinic acid) OR TITLE-ABS-KEY(metoxibutropate) OR TITLE-ABS-KEY(mirococept) OR TITLE-ABS-KEY(miroprofen) OR TITLE-ABS-KEY(mofebutazone) OR TITLE-ABS-KEY(mofezolac) OR TITLE-ABS-KEY(morazone) OR TITLE-ABS-KEY(morniflumate) OR TITLE-ABS-KEY(nabumetone) OR TITLE-ABS-KEY(naproxcinod) OR TITLE-ABS-KEY(naproxen) OR TITLE-ABS-KEY(nepafenac) OR TITLE-ABS-KEY(neurofenac) OR TITLE-ABS-KEY(neurotropin) OR TITLE-ABS-KEY(nictindole) OR TITLE-ABS-KEY(niflumic acid) OR TITLE-ABS-KEY(nimesulide) OR TITLE-ABS-KEY(olsalazine) OR TITLE-ABS-KEY(orpanoxin) OR TITLE-ABS-KEY(oxaceprol) OR TITLE-ABS-KEY(oxametacin) OR TITLE-ABS-KEY(oxaprazine) OR TITLE-ABS-KEY(oxaprozin) OR TITLE-ABS-KEY(oxicam derivative) OR TITLE-ABS-KEY(oxindanac) OR TITLE-ABS-KEY(oxyphenbutazone) OR TITLE-ABS-KEY(palifermin) OR TITLE-ABS-KEY(parecoxib) OR TITLE-ABS-KEY(pelubiprofen) OR TITLE-ABS-KEY(pemedolac) OR TITLE-ABS-KEY(perisoxal) OR TITLE-ABS-KEY(phenazone) OR TITLE-ABS-KEY(phenylbutazone) OR TITLE-ABS-KEY(picolamine salicylate) OR TITLE-ABS-KEY(piketoprofen) OR TITLE-ABS-KEY(pimeprofen) OR TITLE-ABS-KEY(pipebuzone) OR TITLE-ABS-KEY(piproxen) OR TITLE-ABS-KEY(pirazolac) OR TITLE-ABS-KEY(piroxicam) OR TITLE-ABS-KEY(pirprofen) OR TITLE-ABS-KEY(pralnacasan) OR TITLE-ABS-KEY(pranoprofen) OR TITLE-ABS-KEY(prinomide) OR TITLE-ABS-KEY(proglumetacin) OR TITLE-ABS-KEY(proglumetacin maleate) OR TITLE-ABS-KEY(propyphenazone) OR TITLE-ABS-KEY(proquazone) OR TITLE-ABS-KEY(pyrazinobutazone) OR TITLE-ABS-KEY(resatorvid) OR TITLE-ABS-KEY(rimazolium) OR TITLE-ABS-KEY(robenacoxib) OR TITLE-ABS-KEY(rofecoxib) OR TITLE-ABS-KEY(romazarit) OR TITLE-ABS-KEY(rosmarinic acid) OR TITLE-ABS-KEY(salicylic acid) OR TITLE-ABS-KEY(salsalate) OR TITLE-ABS-KEY(scalaradial) OR TITLE-ABS-KEY(semapimod) OR TITLE-ABS-KEY(sudoxicam) OR TITLE-ABS-KEY(sulindac) OR TITLE-ABS-KEY(suprofen) OR TITLE-ABS-KEY(suxibuzone) OR TITLE-ABS-KEY(talniflumate) OR TITLE-ABS-KEY(tenidap) OR TITLE-ABS-KEY(tenoxicam) OR TITLE-ABS-KEY(tepoxalin) OR TITLE-ABS-KEY(teriflunomide) OR TITLE-ABS-KEY(tiaprofenic acid) OR TITLE-ABS-KEY(tiaramide) OR TITLE-ABS-KEY(tilmacoxib) OR TITLE-ABS-KEY(tilnoprofen arbamel) OR TITLE-ABS-KEY(tilomisole) OR TITLE-ABS-KEY(timegadine) OR TITLE-ABS-KEY(tioxamast) OR TITLE-ABS-KEY(tioxaprofen) OR TITLE-ABS-KEY(tolfenamic acid) OR TITLE-ABS-KEY(tolmetin) OR TITLE-ABS-KEY(tribuzone) OR TITLE-ABS-KEY(triethanolamine salicylate) OR TITLE-ABS-KEY(tropesin) OR TITLE-ABS-KEY(ufenamate) OR TITLE-ABS-KEY(valategrast) OR TITLE-ABS-KEY(valdecoxib) OR TITLE-ABS-KEY(ximoprofen) OR TITLE-ABS-KEY(zaltoprofen) OR TITLE-ABS-KEY(zidometacin) OR TITLE-ABS-KEY(zinc salicylate) OR TITLE-ABS-KEY(zoliprofen) OR TITLE-

ABS-KEY(zomepirac)

4. TITLE-ABS-KEY(azium) OR TITLE-ABS-KEY(colofoam) OR TITLE-ABS-KEY(decadron) OR TITLE-ABS-KEY(decadrone) OR TITLE-ABS-KEY(decaesadril) OR TITLE-ABS-KEY(decamethasone) OR TITLE-ABS-KEY(dectancyl) OR TITLE-ABS-KEY(deltafluorene) OR TITLE-ABS-KEY(deronil) OR TITLE-ABS-KEY(dexa-p) OR TITLE-ABS-KEY(dexacort) OR TITLE-ABS-KEY(dexagel) OR TITLE-ABS-KEY(dexame) OR TITLE-ABS-KEY(dexameson) OR TITLE-ABS-KEY(dexametason) OR TITLE-ABS-KEY(dexametasone) OR TITLE-ABS-KEY(dexameth) OR TITLE-ABS-KEY(dexamethason) OR TITLE-ABS-KEY(dexamethasone) OR TITLE-ABS-KEY(dexamethazon) OR TITLE-ABS-KEY(dexamethazone) OR TITLE-ABS-KEY(dexamonozon) OR TITLE-ABS-KEY(dexan) OR TITLE-ABS-KEY(dexascheroson) OR TITLE-ABS-KEY(dexason) OR TITLE-ABS-KEY(dexasone) OR TITLE-ABS-KEY(dexmethsone) OR TITLE-ABS-KEY(dexone) OR TITLE-ABS-KEY(diodex) OR TITLE-ABS-KEY(fluorocort) OR TITLE-ABS-KEY(fortecortin) OR TITLE-ABS-KEY(gammacorten) OR TITLE-ABS-KEY(hexadecadrol) OR TITLE-ABS-KEY(hexadrol) OR TITLE-ABS-KEY(isopto-dex) OR TITLE-ABS-KEY(isopto-maxidex) OR TITLE-ABS-KEY(maxidex) OR TITLE-ABS-KEY(methylfluorprednisolone) OR TITLE-ABS-KEY(millicorten) OR TITLE-ABS-KEY(opticortinol) OR TITLE-ABS-KEY(oradexon) OR TITLE-ABS-KEY(oradexone) OR TITLE-ABS-KEY(orgadrone) OR TITLE-ABS-KEY(ozurdex) OR TITLE-ABS-KEY(policort) OR TITLE-ABS-KEY(posurdex) OR TITLE-ABS-KEY(prednisolone) OR TITLE-ABS-KEY(thilodexine)

5. (#1 OR #2 OR #3) AND #4

6. TITLE-ABS-KEY(tonsil* W/3 surgery) OR TITLE-ABS-KEY(remov* W/3 tonsil*) OR TITLE-ABS-KEY(tonsillectom*) OR TITLE-ABS-KEY(tonsilectom*) OR TITLE-ABS-KEY(adenotonsil*) OR TITLE-ABS-KEY(adeno-tonsill*)

7. TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY(adolescen*) OR TITLE-ABS-KEY(kid) OR TITLE-ABS-KEY(kids) OR TITLE-ABS-KEY(youth*) OR TITLE-ABS-KEY(youngster*) OR TITLE-ABS-KEY(minor) OR TITLE-ABS-KEY(minors) OR TITLE-ABS-KEY(teen*) OR TITLE-ABS-KEY(juvenile*) OR TITLE-ABS-KEY(student*) OR TITLE-ABS-KEY(pupil) OR TITLE-ABS-KEY(pupils) OR TITLE-ABS-KEY(boy) OR TITLE-ABS-KEY(boys) OR TITLE-ABS-KEY(girl) OR TITLE-ABS-KEY(girls) OR TITLE-ABS-KEY(under 18*) OR TITLE-ABS-KEY(underage 18*) OR TITLE-ABS-KEY(under eighteen*) OR TITLE-ABS-KEY(under age*) OR TITLE-ABS-KEY(pediatric*) OR TITLE-ABS-KEY(paediatric*)

8. TITLE-ABS-KEY (young W/person*) OR TITLE-ABS-KEY(young W/people) OR TITLE-ABS-KEY(young W/adult*) OR TITLE-ABS-KEY(young W/individual*) OR TITLE-ABS-KEY(young W/women) OR TITLE-ABS-KEY(young W/woman) OR TITLE-ABS-KEY(young W/men) OR TITLE-ABS-KEY(young W/man))

9. #7 OR #8

10. #4 AND #6 AND #9

11. #5 AND #6 AND #9

12. #10 OR #11

Appendix 8 Restricted Interface Search Strategies

Agency for Health & Research Quality http://www.ahrq.gov/

With at least one of the words (tonsillectomy adenotonsillectomy adenoidectomy tonsil* tonsillectom* tonsilectom* adenotonsil* adeno-tonsill*)

Results can occur anywhere in the page

British Nursing Index (BNI) via www.library.nhs.uk

1. adenotonsillectomy.ti,ab
2. adenoidectomy.ti,ab
3. tonsil$.ti,ab
4. tonsillectomy$.ti,ab
5. tonsilectom$.ti,ab
6. adenotonsil$.ti,ab
7. adeno-tonsill$.ti,ab
8. (tonsil$ adj3 surgery).ti,ab
9. (remov$ adj3 tonsil$).ti,ab
10. OR/1-9

British Library Direct http://direct.bl.uk/bld/Home.do

1. (tonsillectomy or adenotonsillectomy or adenoidectomy or tonsil$ or tonsillectomy$ or tonsilectom$ or adenotonsil$ or adeno-tonsill$).ti

   OR

2. (tonsil$ adj3 surgery) or (remov$ adj3 tonsil$)).ti

Current Controlled trials http://www.controlled-trials.com/

Search each term and screen results of each search

1. tonsillectomy
2. adenotonsillectomy
3. adenoidectomy
4. tonsil*
5. tonsillectom*
6. tonsilectom*
7. adenotonsil*
8. adeno-tonsill

Faculty of 1000 http://f1000.com/

Search each term and screen results of each search

1. tonsillectomy
2. adenotonsillectomy
3. adenoidectomy
4. tonsil*
5. adenotonsil*

Iowa Drug Information Service (IDIS) via http://www.uiowa.edu/idis

1. "DEXAMETHASONE 68040003"
2. Disease(s): "TONSILLECTOMY/ADENOIDECTOMY 28.2"
3. 1 AND 2

Medscape http://www.medscape.com/

Search each term and screen results of each search

Reference & Education

1. tonsillectomy
2. adenotonsillectomy
3. adenoidectomy
4. tonsil
5. adenotonsillar

Scirus http://www.scirus.com/

1. Any of the words (tonsillectomy or adenotonsillectomy or adenoidectomy).article title

OR

2. Any of the words (tonsil* or tonsillectom* or tonsilectom* or adenotonsil* or adeno-tonsill*).article title

Search Journal Sources only

Deselect: MEDLINE / PubMed, Pubmed Central, Wiley-Blackwell, Science Direct

Toxicology Information Online (TOXLINE®) – US National Library of Medicine via proquest.com

Combine the following terms with OR

Include PubMed = No

1. tonsillectomy
2. adenoidectomy
3. tonsillectom*
4. tonsilectom*
5. adenotonsil*
6. adeno-tonsill*

TRIP database http://www.tripdatabase.com/

Any of these words (tonsillectomy adenotonsillectomy adenoidectomy tonsil* tonsillectom* tonsilectom* adenotonsil* adeno tonsill*).title only

UK Clinical Research Network Portfolio Database http://public.ukcrn.org.uk/search/

Search database by looking at the studies listed under the following categories:	
Topic: Generic Relevance & Cross-cutting themes	
Specialty groups:	Anaes Peri-Op Med & Pain
	Other
	Surgery
Topic: Meds for Children	
Specialty groups:	Anaes., IC & Pain Control
	General Paediatric
	Not Assigned
	Pharmacy and Pharmacology

US Food & Drug Administration http://www.fda.gov/

With at least one of the words (tonsillectomy adenotonsillectomy adenoidectomy tonsil* tonsillectom* tonsilectom* adenotonsil* adeno-tonsill*)
Advisory Committees, Drugs, Guidance, MedWatch, Warning Letters
Results can occur anywhere in the page

Appendix 9 Study Eligibility Screening Form

Study ID:	**Assessor:**	**Date:**
Question 1: Did some or all of the participants receive dexamethasone or dexamethasone + NSAID? (excluding dexamethasone by peri-tonsillar infiltration)	If no: EXCLUDE If yes: go to **Question 2** If unsure: go to **Question 2**	
Question 2: Are some or all of the participants Children <18 years undergoing tonsillectomy with or without adenoidectomy?	If no: EXCLUDE If yes: go to **Question 3** If unsure: go to **Question 3**	
Question 3: Does the paper report a randomised controlled trial or a non-randomised study which included >20 patients?	If no: EXCLUDE If yes: INCLUDE If unsure: INCLUDE	

Appendix 10 Data collection form for randomised studies

Paper ID:	**Reviewer:**	**Date:**
Study Characteristics		
Number of participants		
Number of participants in each intervention group		
Year completed		
Setting		
Inclusion criteria		
Definition of post-operative haemorrhage		
Length of follow up		
Participants		
Age		
Gender		
Underlying disease		
Indication for surgery		
Interventions		
Number of intervention groups		
Pre-operative medicines (inclusive of dose, frequency and duration)		
Intra-operative medicines (inclusive of dose)	Anaesthesia Analgesia Anti-emetics Anti-biotics Other (specify)	
Post-operative medicines (inclusive of dose, frequency and duration)	Analgesia Anti-emetics Antibiotics	

	Other (specify)
Surgical technique	
Outcomes	
Post-operative haemorrhage rate	
Additional Data Relating to Haemorrhage	
Additional data on haemorrhages	Timing (primary/secondary) Severity Need for intervention

Appendix 11 Data collection form for non-randomised studies

Paper ID:	**Reviewer:**	**Date:**
Study Characteristics		
Number of participants		
If there were two intervention groups, number of participants in each intervention group		
Year completed		
Setting		
Inclusion criteria		
Definition of post-operative haemorrhage		
Length of follow up		
Participants		
Age		
Gender		
Underlying disease		
Indication for surgery		
Interventions		
Surgical technique		
Pre-operative medicines (inclusive of dose, frequency and duration)		
Intra-operative medicines (inclusive of dose)		Anaesthesia Analgesia Anti-emetics Anti-biotics Other (specify)
Post-operative medicines (inclusive of dose, frequency and duration)		Analgesia Anti-emetics

	Antibiotics Other (specify)
Outcomes	
Post-operative haemorrhage	
Additional Data Relating to Haemorrhage	
Additional data on haemorrhages	Timing (primary/secondary) Severity Risk factors identified

Appendix 12 Elements adapted from McHarm Scale

1. Was haemorrhage pre-defined using standardised or precise definitions?
2. Was the mode of haemorrhage rate data collection specified as active?
3. Was the mode of haemorrhage rate data collection specified as passive?
4. Did the study specify the timing and frequency of the haemorrhage rate data collection?
5. Did the authors use standard scales (s) or checklist(s) for haemorrhage rate data collection?
6. Is there a possibility of selective outcome reporting?

Appendix 13 Letter from Liverpool Paediatric Research Ethics Committee

NHS
National Research Ethics Service

Liverpool Paediatric Research Ethics Committees
Bishop Goss Complex
Victoria Building
Rose Place
Liverpool
L3 3AN

Tel : 0151 330 2071
Fax : 0151 330 2075

27 November 2007

Professor Rosalind L Smyth,
Brough Professor of Paediatric Medicine,
Head of Division of Child Health Services,
School of Reproductive and Developmental Medicine,
Institute of Child Health,
Alder Hey Children's Hospital,
Eaton Road,
Liverpool, L12 2AP

Dear Professor Smyth

Further to your correspondance dated 03 October 2007 received into our office 2 November 2007 (postal strike delayed the receipt) regarding a programme to develop evaluation tools for the detection of adverse drug reactions (ADR's) in hospitalised children.

I can confirm that the Chair agrees with your summary, detailed below

Study 1 ADRs among children admitted acutely to hospital
*Audit – does **not** require a REC opinion*

Study 2 ADRs among children who are in-patients for more than 12 hours
*Audit – does **not** require a REC opinion*

Study 3 Systematic Review of ADRs in children
*Review of extant data and therefore does **not** require a REC opinion*

Study 4 Family members' views on reporting of ADRs in children
*Involves contact with patients and staff accessed via the NHS and so **requires** a REC opinion*

Study 5 Screening tools for ADRs among hospitalised children
*Audit – does **not** require a REC opinion*

Study 6 To develop evidence –based guidelines for the assessment of suspected ADRs and also for the preventtion of ADRs in children
*Audit – does **not** require a REC opinion*

Study 7 Evaluation of evidence-based guidelines
*Audit – does **not** require a REC opinion*

Yours sincerely

Adam Lewis
Committee Administrator

Email: adam.lewis@liverpoolpct.nhs.uk

Copy to: Ms Dot Lambert
R&D Manager
Alder Hey Children's Hospital

Appendix 14 Licence agreements

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