ACADEMIC DIVISION OF CHILD HEALTH
SCHOOL OF GRADUATE ENTRY MEDICINE
AND HEALTH
UNIVERSITY OF NOTTINGHAM

DRUG TOXICITY IN CHILDREN: PAEDIATRIC RANDOMISED CONTROLLED DRUG TRIALS AND GLOBAL CHILD HEALTH

By Khairun Nain Bin Nor Aripin, MBChB, MSc

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DEDICATION

To my future students, this is part of how I dedicate my career to teach you to use medicines, so that you can help and heal your patients in the best way.

To my family, this is part of how I dedicate my life for your happiness.

To children in poor areas, although you may suffer from many more injustices, you can add my voice to the many speaking on your behalf.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ADE	Adverse Drug Event
ADHD	Attention Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
ATC	Anatomical Therapeutic Chemical Classification
BMJ	British Medical Journal
BPA	British Paediatric Association (now RCPCH)
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CCG	Children's Cancer Group (United States)
CCSG	Children's Cancer Study Group (United Kingdom)
CI	Confidence Interval
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CRD	(Cochrane) Centre for Reviews and Dissemination
DALY	Disability Adjusted Life Years
DAMOCLES (group)	Data Monitoring Committees: Lessons, Ethics, Statistics
DARE	Database of Abstracts of Reviews of Effects
DSMB	Data Safety Monitoring Board
EMEA	European Medicines Agency
EMBASE	Excerpta Medica Database
ESDP	European Society for Developmental, Perinatal and Paediatric Pharmacology
EU	European Union
FDA	Food and Drug Administration (United States)
G-CSF	Granulocyte Colony Stimulating Factor
GDP	Gross Domestic Product
GP	General Practice or Practitioner
HDI	Human Development Index
HIC	High Income Country
HIV	Human Immunodeficiency Virus
HSSS	Highly Sensitive Search Strategy (Cochrane)
ICD	International Classification of Diseases (World Health Organisation)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQR	Inter Quartile Range
JAMA	Journal of the American Medical Association
LMIC	Low and Middle Income Countries
MEDLINE	US National Library of Medicine's bibliographic database
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
MSDI	Multinational Studies recruiting in countries in Different Income levels

NEC	Necrotizing Enterocolitis
NEJM	New England Journal of Medicine
NLM	National Library of Medicine (United States)
PD	Pharmacodynamic
PhD	Doctor of Philosophy
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PPP	Purchasing Power Parity
PUMA	Paediatric Use Marketing Authorisation
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SIOP	International Society of Paediatric Oncology
SMC	Safety Monitoring Committee
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
UN	United Nations
UNICEF	United Nations Children Fund
WHO	World Health Organization

ABSTRACT

Concern with potential toxicity due to the widespread use of unlicensed and off label drugs in children has led to regulatory changes aimed to strengthen the evidence base for paediatric drugs. This thesis examines paediatric randomised controlled trials (RCTs), the highest level of evidence, and assesses them in relation to global child health.

A systematic review was performed using validated methods to search three major databases for paediatric RCTs published in 2007. More than 600 RCTs were identified involving more than 100,000 children. The RCTs appear to study the appropriate clinical areas however few studies involved neonates. The RCTs also seem to be of good methodological quality with a mean Jadad score of 3.22.

The reporting of RCTs that involve both adults and children needs to be improved to add to the evidence base of paediatric medicines. More attention is also needed on the reporting of safety information from the RCTs to provide useful toxicity data. Although severe and moderate ADRs were seen in 25% of the RCTs, few RCTs (12%) established safety monitoring committees (SMCs). SMCs are vital to ensure patients in paediatric RCTs are protected from toxicity.

The burden of childhood disease is heaviest in low and middle income countries (LMIC). A minority of the RCTs were performed in LMIC, although they are increasingly globalised. RCTs conducted in LMIC appear to have lower methodological quality, and reported less well on ethical approval and adverse events.

In conclusion high quality, ethical paediatric RCTs should add to the evidence base for paediatric medicines. However they should correspond with the health needs of children on a global basis.

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CHAPTER ONE: INTRODUCTION

In this thesis I aim to describe drug toxicity experienced by paediatric patients, specifically within randomised controlled trials (RCTs). RCTs compare two or more treatments in a group of patients differentiated only by chance; thereby allowing any arising adverse events to be assessed while having to exclude the minimum amount of other (confounding) factors apart from the treatment. The toxicity data has been gained from a sample of paediatric RCTs acquired from a broad systematic review of RCTs involving children published in 2007.

The primary goal of this thesis is to contribute to the body of knowledge so that toxicity can be reduced in paediatric clinical trials as well as children in general who use medicines. To do this, I explore the epidemiological, methodological and reporting characteristics of paediatric RCTs in my sample to identify areas where improvements can be made. I also aim to relate paediatric RCTs to the burden of disease experienced by children worldwide, considering that the burden of childhood disease lies overwhelmingly in poor or developing countries.

In this chapter, I provide the context of my thesis by reviewing the broader scientific literature regarding medicines in children.

1. BACKGROUND

The background for this thesis is that medicines given to children are inadequately studied in their own paediatric population groups (Bonati et al. 1999, Choonara 2000, Smyth 1999). Clinicians, policy-makers and parents have long allowed children to be given medicines based on research conducted in adults and in certain cases, on no research at all (Smyth 2001). This situation is now overwhelmingly regarded as untenable. Arguments against this extrapolation or generalisation have been made on many occasions previously. Essentially children cannot be regarded as small adults; they are afflicted with many conditions and disease processes that are different to those in adults, particularly in the neonatal or infantile period. Drugs may behave differently within children (different pharmacokinetics) compared to adults and also cause different effects (different pharmacodynamics) in children (Klassen et al. 2008). Paediatric patients require specific formulations of drugs and may experience specific adverse effects not suffered by adults.

Thus paediatric patients are in a disadvantaged situation. On one hand, insufficient information on the efficacy of drugs can lead to suboptimal treatment. On the other hand, without safety data gained from clinical trials, children may be exposed to serious unintended harms arising from drug toxicity (Choonara et al. 1996).

1.1 ‘Therapeutic Orphans’

This is not a recent concern. In 1968, Shirkey described children as ‘therapeutic orphans’ after observing that many drugs carry disclaimers such as

"Not to be used in children”

“ ... is not recommended for use in infants and young children since few studies have been conducted in this age group”

“ ... clinical studies have been insufficient to establish any recommendations for use in *infants* and *children* ... should not be given to children".

Children at the time were deprived of the use of many medications and yet many doctors continued to prescribe the restricted medications to children in spite of the disclaimers. Shirkey argued that testing of these drugs in the situation of use or “by ordeal” rather than the controlled situation of a clinical trial is unlawful and would expose children to the risk of toxicity. He noted that drug companies were reluctant to bear the costs of clinical trials for the smaller and less profitable paediatric market. The regulatory climate discouraged clinicians to pursue clinical drug trials in the paediatric population, for example written consent of the participant was required by law but in the absence of clear guidelines for studies in children. He called for a much greater amount of activity in testing drugs in infants and children, with greater involvement from three main groups; the drug industry, paediatricians and the government especially the US FDA (Shirkey, 1999).

In response, the FDA stated their regulatory position clearly that drugs for use in children must be tested in children (Wilson, 1999). Unfortunately little changed in the next two decades. Wilson also noted that 78% drugs in the 1975 US Physicians' Desk Reference lacked information for use in children, and that this was unchanged almost 20 years later according to another report in 1991 (Gilman and Gal, 1991) that found that 81% of the drugs in the Physicians' Desk Reference lacked paediatric information.

The same situation was also seen in Europe. Turner et al. (1998) found that a quarter of prescriptions to children in a paediatric hospital were either unlicensed or off-label. In more than a third of all admissions, children received unlicensed or off-label medicines. Conroy et al.'s (1999) report of the particularly heavy use of unlicensed or off-label drugs in neonates received great attention and provoked serious discussions in the United Kingdom. A further study by Conroy et al. (2000a) showed that the problem was widespread across Europe.

Subsequently in the late 1990s, there were significant changes to the US drug regulatory framework to address the continuing problem of inadequate drug testing in children.

2. DEVELOPMENT OF DRUG REGULATION

It is ironic that significant regulatory changes meant to improve the situation for children took such a long time to be put in place, considering that prominent events of drug toxicity affecting children were the catalysts for major developments in drug regulation in the 20th century.

In 1938, the US Congress passed the Federal Food, Drug and Cosmetic Act requiring new drugs to be proven safe before marketing, thereby initiating a new system of drug regulation. This act was put in place following a major therapeutic disaster caused by an untested drug. Once sulfanilamide became available in the 1930s, a liquid preparation was needed to administer the drug to small children. As the drug dissolved poorly in water, the Massengill pharmaceutical company developed an elixir of sulfanilamide using diethylene glycol as the solvent. 107 deaths were directly associated with diethylene glycol poisoning after ingesting the Elixir. At the time, the safety of drugs was not required to be established prior to clinical use (Steinbrook, 2000).

The thalidomide tragedy involving thousands of children born with congenital deformities particularly phocomelia in the 1960s led to another major revision of drug regulation. The Kefauver-Harris drug amendments passed by the US Congress in 1962 required, for the first time, that drug companies prove the efficacy of a drug prior to marketing. Therefore, drug manufacturers would now need to show evidence of both safety (1938 Act) and efficacy (1962 amendments) of drugs before receiving marketing approval. Thus, the authority of the US FDA in regulating drugs and clinical trials was now firmly established (Steinbrook, 2000).

The United Kingdom parliament enacted the Medicines Act in 1968 in response to the thalidomide catastrophe. The Medicines Control Agency (now known as the Medicines and Healthcare products Regulatory Agency, MHRA) was conferred the authority to regulate drugs in much the same way as the FDA; drug companies are required to show evidence of efficacy, safety and quality of drugs before they can be marketed (Choonara and Dunne, 1998).

The situation with medicines for children as highlighted by Shirkey (1968, 1999) persisted after the major developments of the 1960s. The FDA passed several minor policies (Federal Register 1978, 1983) largely meant to develop clearer guidelines on protecting children participating in research and to review information on labels of drugs used in children. The US Pharmacopoiea established a Paediatric Advisory panel in 1975 with Shirkey as the first chairperson (Wilson, 1999). Nonetheless, no real incentive existed to encourage clinical trials of drugs in the paediatric population. Furthermore, the many (perceived) barriers to undertake these clinical trials remained.

3. CHALLENGES TO CONDUCTING CLINICAL TRIALS IN CHILDREN

There is a fundamental dilemma in conducting clinical drug trials in children. Clinicians and parents are hesitant to expose children to the potential risks, or at the very least the inconvenience, of being a subject in a clinical trial. Yet by giving them medicines that are not supported by sufficient knowledge, children are exposed to risks of therapeutic failure and unintended harms. Unlike the situation in adults where clinical drug trials underwent significant progress post-1960s, trials in children were hampered by major challenges contained within two broad categories – ethical and methodological – which often overlap with each other (Kauffman, 2000, Caldwell et al., 2004, Smyth, 2001).

3.1 Ethical Challenges

The Nuremberg Code of 1947 (Shuster, 1997) and the Declaration of Helsinki of 1964, latest amended form 2008 (World Medical Association, 2009) established the principles of protecting research participants in clinical trials. Consent must be obtained from participants while the researchers must ensure that there is no undue risk, putting the wellbeing of the participant above all other interests. Although guidelines for ethical issues surrounding paediatric clinical trials have existed for some time, for instance from the American Academy of Paediatrics, AAP (1977, revised 1995, Committee on Drugs, 1995) and from the British Paediatric Association, BPA later known as Royal College of Paediatrics and Child Health, RCPCH (RCPCH, 2000) the involvement of children in clinical trials present many ethical challenges.

The overarching ethical requirement of clinical trials is that participants give their informed and freely volunteered consent to take part, documented in writing. Children are considered to have a limited capacity to understand the implications and risks of clinical trials, or to make independent decisions for their inclusion or withdrawal from trials, although this is variable across the paediatric age groups (Kauffman, 2000).

Thus the process of obtaining consent which is not straightforward even in purely adult trials brings another layer of complexity to paediatric clinical trials. The Declaration of Helsinki has provisions allowing for proxy consent from the legal representative for children, in most cases the parents. Despite this, Shirkey (1999) observed difficulties obtaining this consent unless a particularly good relationship existed between doctor and parents. Both parents (Caldwell et al., 2002) and doctors (Caldwell et al., 2003, Sammons et al., 2007) would often place the concerns regarding the individual child for instance, risk of adverse effect, likelihood to be given an ineffective treatment or placebo and inconvenience, above the benefit to the general paediatric population (perhaps rightly so). Therefore consent may not be easily forthcoming.

Parents require information that is clearly presented and enough time to consider and understand the information (Tait et al., 2003). This is often difficult to achieve, for example when the child is acutely ill especially in neonates (Levene et al., 1996, Mason and Allmark, 2000, McKechnie and Gill, 2006) or when the severity of illness is particularly distressing for instance in paediatric cancer (Kupst et al., 2003, Eden, 1994). Previous studies have shown that even when consent has been obtained, many parents report that they felt obliged to participate (van Stuijvenberg et al., 1999) rather than giving it voluntarily.

In addition to the practical challenges of obtaining consent from parents, there is the conceptual challenge of obtaining informed consent for paediatric trials. Because the consent is obtained from a surrogate, it may be less morally robust; in keeping with the ultimate bioethical principle of autonomy. Kodish (2003) believes that informed consent "may not be possible in the strict philosophical sense, [paediatric] investigators, parents and older children have an important obligation to approximate truly informed consent to the greatest extent possible". He proposes using the term 'parental permission', in combination with child assent in any situation where it is possible.

There is increasing recognition and requirement that assent from the paediatric patient should be obtained from clinical trials (AAP, Committee on Drugs, 1995, RCPCH, 2000). Assent is defined as 'active agreement' by the AAP and 'acquiescence' by the RCPCH of the paediatric participant who is below the legal age of being able to consent. This presents further challenges to investigators as it is not a simple task to apply the concept universally to the heterogeneous mix of paediatric patients. In many instances assent is not needed, for example, when neonates, sedated or unconscious children are studied or in certain studies of therapies used in emergency situations.

Further questions remain - for example, at what age does a child become capable of understanding the procedures, risks and benefits of research, how much does the child understand, what counts as dissent (John et al., 2008) and who can override dissent, how and when. Ondrusek et al.'s (1998) work suggests that most children under the age of 9 cannot be expected to provide meaningful assent.

For children who are expected to be able to meaningfully assent, additional issues need to be addressed including how to present information to them adequately and how to document the assent; whether a signature is required or not (Ungar et al., 2006). Nevertheless despite the many challenges presented to investigators by the consent and assent processes, both are essential to protect the autonomy of the paediatric patient in a clinical trial.

Another ethical challenge is seen in the assessment of risks and benefits of the clinical trial to the paediatric patient. The benefits of clinical trials are now well-established both to the wider group of children as well as to the participants themselves. Children in general stand to benefit from safer and more efficacious therapies, contributed by scientific testing in their age groups (Choonara, 2006).

The direct benefits to the participants themselves may be considerable. According to Smyth (1999), "if the hypothesis on which therapeutic research is based is well founded, at least half the patients in a randomised controlled trial may benefit while those in the control arm will be no worse off than if the research has not been done". Furthermore, a number of studies suggest that participants in clinical trials have better outcomes compared to non-participants (Vist et al., 2005). Schmidt et al. (1999) found that neonates participating in a RCT of antithrombin therapy assigned to placebo needed significantly shorter ventilation periods compared to non-participants, seemed to suffer fewer and less severe intraventricular haemorrhages and had a lower mortality rate. All the non-participating neonates were eligible to participate but were not randomised and all neonates received the same care otherwise.

To evaluate the risks for paediatric patients participating in a clinical trial, broadly similar guidelines are provided by the AAP (Committee on Drugs, 1995) and RCPCH (2000) in which risk assessment is based on the concept of 'minimal risk' (Kauffman, 2000). Minimal risk is defined as "a level of risk similar to the risk encountered in the child's usual daily activity" (AAP, 1995) or "a probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine [tests]". The guidelines further state that any studies exposing paediatric participants to more than minimal risk require close ethical scrutiny before it can be performed.

If the definition of 'minimal risk' were strictly followed, it would be very difficult to justify conducting a clinical trial involving children. Thus, the wordings require a wide scope of interpretation in deciding on what constitutes 'minimal risk'. The guidelines may be a reflection of the prevailing attitudes prior to the major developments occurring following the turn of the new millennium, and probably are in need of updating. For example, a study by Shah et al. (2004) found that institutional review board chairs in the US varied in their application of risk and benefit categories in paediatric research. The decision is probably more challenging in paediatric trials compared to adults since adult participants can play an active role in risk-benefit assessments, while in paediatric trials, a surrogate decision is made, as seen in the consent process as well.

In conclusion, conducting clinical trials in the paediatric population pose multiple ethical challenges that are not found in adult trials. The significant amounts of time, effort and thought required to address these challenges have likely contributed to the dearth of clinical trials underpinning evidence based medicines use in paediatrics.

3.2 Methodological Challenges

Conducting a paediatric clinical trial requires many study design characteristics that are different from adults. Transferring a study protocol from an adult trial and simply adjusting the age range would often lead to an undoable study or a study with inappropriate requirements such as pregnancy testing in preschoolers (Kauffman, 2000). Thus in addition to the unique ethical requirements of paediatric clinical trials, investigators are presented with methodological challenges.

One of the biggest methodological hurdles in conducting a paediatric clinical trial is recruitment. Paediatric patient populations are much smaller, more heterogeneous and are undergoing different stages of physiological development (Steinbrook, 2000, Smyth, 1999). Many childhood diseases are rare compared to the adult form, for example juvenile arthritis or diabetes, or are heterogeneous in their presentation such as cerebral palsy and Down syndrome. For relatively prevalent diseases such as asthma, developing selection criteria and measuring differences in treatment effect can be challenging due to the inherent heterogeneity and development processes of children. The resulting small sample populations would mean that the trial would have inadequate statistical power to detect small or moderate differences in treatment outcomes (Smyth, 2001).

Other practical issues exist, for instance straightforward sampling procedures in adult trials present challenges to investigators in paediatric trials. Venepuncture in children requires specific justification, strategies and expertise. The small blood circulating volume of neonates and infants necessitates the use of sensitive assay methods to analyse minute sample volumes such as the dried blood spot technique (Patel et al., 2010).

Less invasive sampling procedures such as urine and breath assays, population pharmacokinetic approaches and microanalytical methods can be used but require further effort to develop and adapt them to paediatric patients (Conroy et al., 2000b).

Paediatric drug trials also require specific age-appropriate formulations for example liquid preparations or granules, especially for younger children. Frequently, these formulations are not readily available (Mulla et al., 2007), thus requiring additional costs and time to develop them. For clinical trials using extemporaneous drug formulations, it would be difficult to generalise the results to clinical practice as the study validity depends on being able to replicate the formulation aside from the design, execution and analysis of the trial (Schreiner and Greeley, 2002). Developing appropriate paediatric formulations requires sufficient knowledge of pharmacokinetic parameters that needs to be obtained from pharmacokinetic studies, thereby presenting an additional encumbrance prior to comparative trials to evaluate efficacy and safety.

The various unique challenges presented by paediatric clinical trials would need highly trained and experienced researchers to address the issues. Unfortunately, there are few experienced investigators in paediatric clinical pharmacology worldwide. This shortage of expertise has been previously highlighted both in the United States (Wilson, 1999) and also in Europe. It was noted in 2000 that there were only 2 paediatric clinical pharmacologists in the United Kingdom (Conroy et al., 2000b). In 2004, there were 3 paediatric clinical pharmacologists and 3 trainees when a formal training programme was established by the Royal College of Paediatrics and Child Health (Choonara et al., 2004).

In 2005, a survey of the European Society of Developmental, Perinatal and Paediatric Pharmacology (ESDP) revealed only 18 paediatric clinical pharmacologists and 23 trainees throughout Europe (Bonati et al., 2006). Efforts are on-going to increase the capacity in the field of paediatric clinical pharmacology (Gazarian, 2009).

3.3 The Example of Paediatric Oncology

With such myriad barriers to performing paediatric clinical trials, the reluctance to study medicines in the paediatric population was perhaps reasonable. However the experience in paediatric oncology with clinical trials provided evidence to the contrary. According to Mitchell (2007), RCTs have "been the mainstay of paediatric oncological practice for decades". Large multicentre cooperative groups such as the UK Children's Cancer Study (UKCCSG), US children's Cancer Group (CCG) and the International Society of Paediatric Oncology (SIOP) were formed and the majority of paediatric oncology patients were recruited into clinical trials. The resulting treatment regimens contributed to a remarkable change in the prognosis for paediatric cancer.

From a situation where virtually all children with malignancy died, currently more than 75% will survive long term (Mitchell, 2007). Hargrave et al. (2001) has shown that treatment-related deaths in children with leukaemia progressively decreased from 9% to 2% within the large clinical trials between 1980 and 1997, indicating the value of scientific information gained from clinical trials conducted in children. Furthermore, the successful development of therapy for Wilm's tumour (Pritchard-Jones and Pritchard, 2004) exemplified the benefit of conducting RCTs, even for very rare diseases in children.

Thus the success of paediatric oncology in utilising clinical trials demonstrates two major points; firstly barriers to involving paediatric patients in clinical trials are not insurmountable and secondly, the knowledge gained from the studies can be invaluable in improving treatment outcomes in children as well as reducing the risk of unwanted effects of the drugs.

3.4 The Economic Reason

An important distinction to make is that paediatric oncological trials are mostly driven by the cooperative groups and are non-commercial while drug development is largely the domain of the pharmaceutical industry. Children represent a smaller commercial market for drugs and therefore provide less financial incentive for drug companies to pursue research in the paediatric population compared to adults (Conroy et al., 2000b, Budetti, 2003). Considering that on average to develop a drug to reach the market would cost roughly USD 800 million (DiMasi et al., 2000), it is no surprise that the pharmaceutical industry would be reluctant to invest in paediatric studies for a new drug when the financial return is questionable. This holds true to an even greater degree in drugs that are out of patent or approaching the end of their patent. There are considerable costs and probably no financial incentive in studying older medicines in children.

To summarise, there are numerous barriers to clinical trials being conducted in the paediatric patient population despite the oft-highlighted need for adequate scientific evaluation of medicines being used in them. These challenges can be addressed and the knowledge gained from conducting such studies can be invaluable in improving treatment outcomes, as has been demonstrated in paediatric oncology. Unfortunately without significant financial incentive, the pharmaceutical industry will remain reluctant to pursue paediatric clinical research of medicines.

4. UNLICENSED AND OFF-LABEL MEDICINES

As earlier mentioned, drug licensing authorities will not grant a license unless there is sufficient evidence for the efficacy, safety and quality of a drug. Therefore the end result of the many obstacles to performing paediatric clinical trials as commented above is that many drugs are not licensed for use in children. The use of these 'unlicensed' drugs is commonplace in paediatric practice. Furthermore, licensed drugs are frequently prescribed outside the established labelling information that accompanies the license, for example they are used in a different dosage, age, indication, route or formulation that is stated on the label. This is called 'off-label' use.

There has been considerable interest in the prevalence of unlicensed and off-label prescription in paediatric departments in the past decade. According to Pandolfini and Bonati (2005) there were at least 30 studies investigating unlicensed and off-label drug prescribing in paediatric patients. More studies were published in the following years (Di Paolo et al., 2006, Dell'area et al., 2007, Kumar et al., 2008). The results show that the use of unlicensed or off-label drugs was widespread in paediatrics. Overall, 11% to 80% of all drugs prescribed in paediatrics were either unlicensed or off label.

Primary care appear to have the lowest rates of unlicensed or off-label prescribing (Pandolfini and Bonati, 2005) ranging between 11-37%. In the United Kingdom, McIntyre et al. (2000) observed that for children under 12, around 11% received an off-label prescription but very few (0.3%) received an unlicensed drug. A study of GP prescriptions throughout Scotland found that paediatric patients received off-label drugs at a rate of 26% (Ekins-Daukes et al., 2004).

Various rates are seen in primary care in other countries, for example France (33%, Chalumeau et al., 2000), Holland (29%, T Jong et al., 2002) and Germany (13% Bucheler et al., 2002).

Higher rates of unlicensed or off-label prescribing were seen in paediatric inpatients. Turner et al. (1998) found that 25% of all prescriptions in a UK children's hospital were unlicensed or off-label. A large study involving paediatric wards in five European countries found even higher rates; 46% of all the prescriptions were either unlicensed or off-label (Conroy et al., 2000a). Of 11 studies of off-label or unlicensed medicines in paediatric wards, 16% to 62% of prescriptions were off-label or unlicensed (Pandolfini and Bonati, 2005).

The highest rates of unlicensed or off-label prescriptions are seen in neonates. Between 80 and 97% of neonates in 7 studies were prescribed unlicensed or off-label drugs and off-label or unlicensed prescriptions constituted between 55% and 80% of all prescriptions (Pandolfini and Bonati, 2005). When different paediatric units in a single hospital were compared directly, neonatal wards showed the highest rates of unlicensed or off-label prescriptions (Conroy et al., 1999, t'Jong et al., 2001). Slightly lower rates were seen in more recent studies; Dell'area et al. (2007) reported that 35% of prescriptions in an Italian neonatal unit and Kumar et al. (2008) reported that 45% of parenteral prescriptions in an American neonatal intensive care unit were unlicensed or off-label.

The different definitions and classification methods used by these studies made the results difficult to compare and generalise among different paediatric centres or countries. There is a growing concensus on a common definition of unlicensed or off-label medicines especially in Europe (Neubert et al., 2008). Nonetheless, methodological issues do not detract from the fact that the use of unlicensed or off-label drugs is widespread in paediatric patients up to the present time.

5. ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) include any noxious, unintended or undesired effect of a drug which occurs at doses used for prophylaxis, diagnosis or therapy. This definition excludes therapeutic failures, poisonings, drug abuse and adverse events due to administration or medication errors as well as non-compliance (WHO, 2007). Lazarou et al. (1998) estimated that ADRs were the cause of around 5% of hospital admissions and that approximately 11% of hospital inpatients experience them. This very large systematic review of 39 studies from the United States suggest that ADRs account for in excess of 100,000 deaths per year, making it between the fourth and sixth most common cause of death in the United States. In the United Kingdom, a large prospective study found that 6.3% of admissions were related to an ADR and that the admissions accounted for 4% of hospital bed capacity although only adults above 16 years old were included in this study (Pirmohamed et al, 2004).

It is important to differentiate ADRs from another commonly used term, adverse drug events (ADEs) which is a more inclusive definition. ADEs involve any injury resulting from administration of a drug. Thus ADRs are detected in a situation where the drug has been used in proper doses, administered correctly and for approved indications. However the situation is less well delineated in paediatric patients since the commonplace use of unlicensed or off label medicines means that doses, administration as well as indications often lie outside of approved guidelines. This leads to a greater imperative to study ADRs in children.

Impicciatore et al. (2001) performed a meta analysis of 17 ADR studies in the paediatric population published from 1973 to 2000. The authors estimated that 9.5% of hospitalised children experienced ADRs; ADR incidence rates ranged from 4.4% to 16.8% in the studies. Admissions due to ADRs appeared to be lower compared to adults, accounting for 2% of all hospital admissions. In outpatients, the incidence rate of ADRs was 1.5%. There were studies from 7 different countries included in the analysis.

Clavenna and Bonati (2009) conducted an updated analysis involving studies published after the review by Impicciatore et al. They used the same meta analytic procedures and found 8 studies from 6 different countries. The results showed similar ADR rates in children with the incidence of ADRs in hospitalised children estimated to be 10.9%. ADRs accounted for 1.8% of admissions to hospital while paediatric outpatients experienced ADRs at a rate of 1%. The data suggest that hospitalised children suffer similar ADR rates with hospitalised adults although ADRs accounted for a lower percentage of admissions for the paediatric populations.

Recent studies in the United States that looked at ADEs provided further information on prevalence rates. A nationwide active surveillance program estimated that almost 160,000 children and adolescents were treated in emergency departments across the US for ADEs annually. Roughly half (49%) consisted of young children 1 to 4 years old. Unintentional overdoses led to about 45% of the presentations while the remainder were primarily ADRs; 35% caused by allergic reactions, 13% by adverse effects and 6% by vaccine reactions (Cohen et al., 2008).

Another study analysed 11 years of data from paediatric presentations to all health care facilities in the United States. The authors found that almost 600,000 visits annually were attributed to ADEs, the majority (78%) to outpatient clinics. There were sizable numbers of ADRs including allergic reactions in younger children and adverse effects in adolescents (Bourgeois et al., 2009).

In paediatric patients, the correlation of unlicensed or off-label drug use with the rate of adverse events has been investigated (Choonara and Conroy, 2002). Although many studies have described the prevalence of unlicensed or off-label prescriptions in paediatric patients, there have been relatively few studies that have explored the relationship of such prescriptions to the rates of adverse events. Turner et al. (1999) performed a prospective study evaluating the relative risk of an adverse drug reaction (ADR) occurring associated with the use of an unlicensed or off-label medicine. They found that the use of unlicensed or off-label drugs was associated with an increased risk of an adverse drug reaction occurring (RR 1.74, 95% CI 0.89-3.41), although this was confounded by the fact that the presence of polypharmacy was the greatest contributory factor to the development of an ADR.

Another prospective study by Neubert et al. (2004) in a German paediatric unit found that unlicensed or off-label drugs did not cause significantly more ADRs compared to licensed prescriptions. However, patients who received unlicensed or off-label drugs had a significantly higher incidence of ADRs compared to those who had received only licensed drugs (28% vs 8%, $p<0.05$).

Although the evidence that unlicensed or off-label drugs can cause a higher risk of toxicity is limited, their widespread use in paediatric practice is widely regarded as untenable. The risk of ADRs can be disguised by under-reporting (Waller, 2007). Prescribing a medicine without sufficient clinical evidence of their efficacy and safety is using it in an uncontrolled, unsystematic and ultimately unscientific manner (Budetti, 2003).

In summary, adverse drug reactions are a significant public health issue in children. They appear to suffer similar rates of ADRs with adults, particularly among hospitalised patients. The large numbers of children affected emphasise the importance of further research into drug toxicity occurring in children, in view of the previously highlighted deficiency in scientific evaluation underlying many of the medicines used in the paediatric population.

5.1 Prominent occurrences of drug toxicity in children

Prominent episodes of drug toxicity suffered by children underline the need for paediatric medicines to be based on adequate evaluation of their efficacy, safety and quality. As discussed earlier, two major episodes of drug toxicity mainly affecting children played a vital role in the development of drug regulation, namely the sulphanilamide-diethylene glycol and the thalidomide tragedies.

Tragically, diethylene glycol has been repeatedly used as a solvent especially for paediatric formulations of paracetamol, even up to the present time. This has caused many fatalities in children; 47 children in Nigeria in 1992, 51 children in Bangladesh in 1995, 85 children in Haiti in 1998 (Choonara and Rieder, 2002) and as recently as 2008 where 84 children died (Bonati, 2009).

Around the period of the thalidomide saga, another prominent occurrence of drug toxicity came to light. Several neonates died after being administered chloramphenicol. The grey baby syndrome was identified after the causative relationship was discovered (Weiss et al., 1960). The immature metabolic pathways in the neonate led to a accumulation of chloramphenicol in plasma causing severe toxicity which ultimately caused the death of several neonates. According to Choonara and Rieder (2002), appropriate clinical studies to design age-appropriate dosing could have averted the tragedy.

The mechanism of valproate hepatotoxicity in young children is also thought to be related to abnormal metabolism The majority of fatalities were children under 3 years of age (Brown, 1988, Choonara et al., 1996). These episodes demonstrate the danger of extrapolating dosing regimes of paediatric medicines from adult data.

Another prominent case of drug toxicity involving children is the development of Reye's syndrome with aspirin use. Reye's syndrome is an acute encephalopathy occurring in children and adolescents that has been linked to aspirin use during a febrile illness. The association with aspirin is sufficiently strong that aspirin is no longer used in the paediatric population (Glasgow, 2006). The dramatic decline in the incidence of the syndrome following public health warnings in the 1980s support the case for a causal link (Belay et al., 1999).

The propofol infusion syndrome as reviewed by Kam and Cardone (2007) caused at least 20 paediatric deaths. Several case reports of paediatric deaths appeared with the use of propofol infusions, before an unpublished randomised controlled trial of the use of propofol infusions was conducted in 2001 involving patients in a paediatric intensive care unit in the US (Felmet et al., 2003). The trial was terminated when a dose-effect relationship was seen in relation to mortality rate in the children. As a result, the US FDA issued a warning against the use of propofol for long term sedation in children. This episode of drug toxicity provided an important lesson on the potentially severe risks, while at the same time demonstrating the life-saving information that can be provided by clinical trials in children.

In conclusion, prominent cases of drug toxicity involving children have been the catalyst for major developments in regulatory activities. Many lessons can be learnt from these episodes; particularly the importance of sound scientific evaluation of medicines used in children as well as the need to be vigilant on any adverse effects that are experienced by children when using the medicines.

6. NEW LEGISLATION TO ENSURE BETTER MEDICINES FOR CHILDREN

The mounting awareness that drug therapies for children require studies with the same level of scientific rigor in their own population led to major regulatory efforts in the 1990s. The first changes were seen in 1994, when the FDA issued the first paediatric labelling rule. This regulation requested manufacturers of marketed drugs to alter the labels of the product to include paediatric information where available. The rule allowed efficacy information to be extrapolated from adults to a paediatric population provided the condition and therapeutic response is similar; with paediatric dosage (pharmacokinetic) information included. When paediatric information was not available (as is commonly the case), manufacturers are allowed to include a disclaimer stating paediatric safety and efficacy has not been established (FDA, 1994). Although intended to encourage clinical studies in the paediatric population, the availability of a disclaimer meant that pharmaceutical companies did not see any incentive to pursue clinical studies in children.

In response, the FDA introduced a set of regulatory measures including both a voluntary incentive and a mandatory requirement, to motivate drug company sponsors to pursue paediatric clinical research. This was termed the 'carrot and stick' (Steinbrook, 2000). The voluntary incentive provision was contained within the FDA Modernization Act enacted in 1997. For the first time an exclusivity incentive was introduced, where drug companies that complied with a written request by the FDA to conduct clinical studies in the paediatric population would be awarded a 6-month extension to the marketing exclusivity of their product.

The 'stick' was FDA's paediatric rule enacted in 1998 (FDA, 1998). This legislation gave the FDA a mandate to require paediatric clinical studies for any new or marketed drug where a significant use or benefit to children is expected.

As expected, the rule encountered heavy opposition from the pharmaceutical industry since it conferred the FDA with considerable regulatory power to actively require paediatric clinical studies from sponsors. Several pharmaceutical lobby groups managed to successfully apply for the rule to be struck down in a federal court in 2002. Nevertheless, considerable efforts led by the FDA managed to persuade the US Congress to uphold the rule in 2003 and it was codified as the Pediatric Research Equity Act. Similarly, the FDA Modernization Act was renewed in 2002 as the Best Pharmaceuticals for Children Act (Cooper, 2002, Federal Register, 2002, 2003).

These legislative changes drastically altered the landscape for medicines in children. The FDA has now gained the authority to firstly incentivise pharmaceutical companies to pursue clinical studies of medicines in children but also to require mandatory research involving paediatric populations when necessary.

Across the Atlantic, regulatory developments did not take long to follow American developments. Following tri-party discussions between the United States, Japan and the EU states, the International Conference on Harmonisation (ICH) developed a guideline to harmonise pharmaceutical regulation between the three sectors in 1998. This ICH guideline was then adopted by the European Medicines Agency (EMEA) in 2002 and became a European guideline titled 'Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population'.

However there is a suggestion that the voluntary nature of the guidance meant that it was largely ineffective in stimulating paediatric studies by drug companies (t Jong et al. 2002). Finally the Regulation on Medicinal Products for Paediatric Use was passed in the European Parliament in 2007 (Choonara and Bonati, 2007). This regulation conferred the EMEA with authority similar to the FDA in regard to paediatric studies.

Pharmaceutical companies are now required to submit a Paediatric Investigation Plan (PIP) or an application for a waiver, for any drug seeking marketing approval. For drugs already marketed, a PIP is also required for any alterations in indication, formulation or route of administration. Furthermore, there is also a voluntary provision within the regulation for a paediatric use marketing authorisation (PUMA) that would award a 10-year data and marketing protection for off-patent drug therapies that are developed specifically for paediatric populations .

Another component within the regulation is the formation of an expert Paediatric Committee. The task of this committee is to advise the EMEA on the development of medicines for use in children, in accordance with the legislation. Also contained within the regulation is the stipulation that all paediatric clinical trials must be registered on a database that is accessible to the public (EudraCT). Further, all details of the results of paediatric clinical trials, including those terminated prematurely, must be accessible to the public (Choonara, 2007).

Thus, the many legislative changes on both sides of the Atlantic have provided a very stimulating environment for paediatric clinical studies to be conducted, in the effort to provide rigorous scientific evidence on the safety, efficacy and quality of paediatric medicines thereby ensuring more rational use of medicines in children (Hoppu, 2008).

7. THE GLOBAL SITUATION: HEALTH RESEARCH DISCREPANCY

On a global scale, clinical research is concentrated in high income countries. This situation is expected, since clinical research requires considerable resources, expertise, commitment from multiple levels including academia, health authorities and especially an invested healthcare industry. On the other hand, in this era of rapid globalisation coupled with a higher awareness of bioethical awareness, there is growing recognition that this discrepancy in clinical research needs to be addressed. Essentially the idea is that clinical research should benefit the whole of mankind.

The Commission on Health Research for Development (1990) published a landmark report that found a large discrepancy in global health research. Overall, only 5% of the total funding spent on health research were directed towards addressing the health issues in developing countries, whose population accounted for 93% of the global burden of preventable diseases. Several years later the Global Health Forum, a non-profit organisation in partnership with the World Health Organization (WHO) developed the term 10-90 gap to describe this imbalance between the lack of resources for health research in poor countries and the size of health problems suffered by their populations.

Although health research encompasses a very wide range of topics and activities, research on medicines is clearly an important area within health research. Firstly there is concern on the 'morally uncomfortable drug gap' (Cohen-Kohler, 2007) which indicates that millions of the global population are denied the basic human right of essential medicines due to the economic paradigm where medicines are regarded as a product to be used only by those who can pay for them. Secondly, there is evidence that drug development is geared almost exclusively for financial profit alone.

For example, Trouiller (2004) reported that only 13 out of 1393 of new drugs approved between 1975 and 1999 were for tropical diseases that affect vast populations in LMIC.

Further evidence is seen in published clinical trials. Horton (2003) highlighted the significant underrepresentation of diseases affecting the developing world in leading medical journals and called for a greater exposure of research to address global health needs. Rochon et al. (2004) found that the majority of RCTs published in 6 leading medical journals was not relevant to global health needs and that more than half of the 40 leading causes of the global disease burden was not represented by any RCT. Isaakidis et al. (2002) found that few RCTs are conducted in sub-saharan Africa in contrast to the enormous burden of disease suffered by the human population living in the area. In an overview of systematic reviews contained within two major databases namely the Cochrane Database and the Database of Abstracts of Reviews of Effects (DARE), Swingler et al. (2003) suggested that systematic reviews were more responsive to disease burden in high income countries rather than to the global burden of disease.

There have been a dearth of research looking at whether paediatric clinical research is related to the global burden of disease suffered by children. What is clear is that the global burden of childhood disease lies overwhelmingly in poor or developing countries. According to UNICEF (2009) 99% of under-5 mortality occur in low and middle income countries, nearly half occurring in sub-saharan Africa.

There is growing opinion that drug toxicity in children living in LMIC are being overlooked. There is also a conspicuous absence of research looking at this topic in the medical literature. Recognising the situation, WHO produced a publication titled 'Promoting Safety of Medicines in Children' in 2007 to draw attention to the issue of safety of medicines in all children but also with emphasis on children in developing countries (Watts 2007, Choonara 2008). This report estimates that less than 10% of ADRs are reported globally and that many developing countries lack safety monitoring and reporting mechanisms.

Just a few months later WHO launched a major worldwide campaign; 'Make Medicines Child Size' to address the need for access to safe and child-specific medicines globally. This campaign, endorsed by multiple agencies including UNICEF, aims to encourage research to develop medicines specifically for children as well as promoting improved measures to ensure that children can access essential medicines, particularly in poor countries. Major targets by the campaign include tackling priority research gaps where medicines do not exist or safety and efficacy is unknown, tackling development gaps where medicines are known but require adapting for children and finally addressing the access gaps to allow medicines to reach children that need them. The campaign has a 5 year time frame and publishes regular progress reports.

Thus, efforts are now underway to address the health research disparity between rich and poor countries. WHO is spearheading a large movement to address the need for paediatric medicines with emphasis on children in poor countries who form the majority of unwell children globally.

8. SUMMARY

The situation in paediatric medicines has developed through several stages. It was ironic that although drug toxicity suffered largely by children led to the development of drug regulation, the paediatric population were mostly neglected in clinical drug research. Although the problem was recognised, the situation persisted for an extended period. The numerous perceived challenges meant that few clinical drug trials were conducted in the paediatric population. Ethical and methodological challenges were often cited, but perhaps the main obstacle was the lack of financial incentive to pursue clinical research where the market for the paediatric drugs was much smaller compared to adults. Nonetheless, the experience in paediatric oncology demonstrated the challenges were surmountable and that clinical drug trials provided invaluable returns in respect to treatment outcome.

The resulting scenario was that paediatric patients were frequently given medicines that lacked marketing approval (unlicensed) or differently from the way described by the label (off label). Subsequent studies showed that unlicensed and off label use was widespread. There is data to support that unlicensed and off label medicines predispose to a higher risk of adverse drug reactions in children. The growing concern with using unlicensed and off label medicines in children led to a growing demand for a change in the situation.

High profile changes in drug regulation on both sides of the Atlantic signalled a potential improvement to the situation. There now exists a stimulatory environment for paediatric clinical trials of medicines with the pharmaceutical industry incentivised by a 6 month exclusivity provision. The FDA and EMEA has been awarded the mandate to require paediatric testing before marketing approval can be conferred.

Finally in this era of globalisation, there is growing awareness of the clinical research discrepancy between clinical research which is concentrated in rich countries and the burden of disease which overwhelmingly lies in poor countries. The same situation applies to medicines in children. Cognizant of this, WHO is now spearheading efforts to address the need for safe and accessible child-specific medicines, with the worldwide campaign ‘make medicines child size’.

9. OUTLINE OF THESIS

Chapter 2: Methodology

In this chapter, I outline the methodological steps that I took to perform a systematic review of paediatric randomised controlled drug trials that were published in 2007. I present the development of the search strategies for the three major electronic databases of publications, the inclusion and exclusion criteria for studies, data extraction, management and analysis.

Chapter 3: Demographical and Epidemiological Characteristics

Here I start to describe my findings in relation to the demographical and epidemiological characteristics of the trials.

Chapter 4: Methodological and Reporting Characteristics

In this chapter I present my findings in terms of the methodological and reporting quality of the trials. I report on the descriptions of safeguards put in place to protect trial participants including ethical measures.

Chapter 5: Safety characteristics and Adverse Drug Reactions (ADRs)

In this chapter I describe the adverse events reported by the trials as well as assessments on whether the participants experienced adverse drug reactions.

Chapter 6: Relation to Global Disease Burden

Here I discuss my re-analysis of a previously assembled database of paediatric randomised controlled drug trials published from 1996 to 2002 to investigate the relevance to global disease burden. I then present findings from my current systematic review in relation to the global disease burden in childhood disease.

Chapter 7: Conclusion

In this final chapter I discuss the findings of my systematic review in the context of the current situation of medicines in children.

CHAPTER 2: METHODS

For this thesis I have undertaken a systematic review of randomised controlled trials (RCTs) involving the paediatric population from scientific reports published in 2007. The methods are largely based on those developed and validated by the Cochrane Collaboration. However several unique alterations were made and novel techniques were used in this review to correspond with the original objectives of this research. In this chapter these methods are described in a detailed and stepwise manner.

2.1 INTRODUCTION

For this research, randomised controlled drug trials (RCTs) are selected as the main focus of study for several reasons. RCTs are the most robust experimental design available in clinical research and are regarded as the highest level or the 'gold standard' of evidence for healthcare interventions (Sackett et al., 1996). The allocation of treatment purely by chance allows unbiased comparisons to be made on the efficacy (Campbell et al., 1998) and also safety of the treatment in question (Akobeng, 2005a, Ashby, 2008).

Healthcare professionals, researchers and regulatory bodies pay considerable attention to findings from RCTs (Caldwell et al., 2004). Regulatory agencies such as the FDA and EMEA now require RCTs to be performed before marketing approval is conferred (EMEA, 2001, Choonara, 2007, Rodriguez et al., 2008, Hoppu, 2008).

On the other hand, it is acknowledged that there are several limitations and disadvantages of RCTs (Jadad and Enkin, 2007). According to Rawlins (2008), these include:

- Inappropriateness due to practical (especially rare diseases), bioethical or legal reasons
- Irrelevance of the null hypothesis underpinning RCTs in many instances
- The many difficulties with the theories of probability; particularly those presented by potentially misleading statistical phenomenons such as regression to the mean and multiplicity, as well as the infrequent use of potentially valuable Bayesian approaches
- Concern with the generalisability of the results, both on efficacy and harms

- Substantial costs involved in conducting RCTs

RCTs are primarily concerned with demonstrating efficacy while safety data are usually obtained from observational studies in the post marketing and licensing period (Papanikolaou et al., 2006). This is because individual RCTs are usually underpowered to detect adverse effects which are infrequent events (Vandenbroucke, 2004). Nevertheless large-scale RCTs or systematic reviews of RCTs can convey useful safety data (Papanikolaou and Ioannidis, 2004). This relies on safety results from RCTs; which unfortunately are poorly reported (Ioannidis and Lau, 2001, Ioannidis et al., 2004, Ioannidis, 2009, Pitrou et al., 2009,).

In paediatrics, Sammons et al. (2008) found that more than a quarter of clinical trials published between 1996 and 2002 did not report that they monitored safety (Sammons et al., 2008). There is further evidence that the reporting of safety and toxicity information in RCTs involving children is inadequate (Ioannidis and Lau, 2001, Cohen et al., 2007, Anon., 2007, Klassen et al., 2008).

In conclusion, this thesis is set in the context where RCTs are given high importance in evidence-based medicine but also where the limitations and disadvantages of RCTs are recognised (Rawlins, 2008). Thus, the aim is to explore the characteristics of RCTs published in 2007; focussing on important aspects such as demography, epidemiology, methodology, toxicity and others; to add to previous reviews (Campbell et al., 1998, Sammons et al., 2005). The ultimate goal is to highlight the essential role of RCTs in providing evidence to make medicines safe and effective for children (Vandenbroucke, 2004).

2.1.1. WHAT IS A SYSTEMATIC REVIEW?

A systematic review attempts to answer a specific research question by using explicit methods to systematically search and critically appraise the scientific literature available (Akobeng, 2005b). There is a detailed description on how the review was conducted so that it is reproducible by an interested reader and this primarily is how it is different from narrative reviews (Jadad, 2007).

A systematic review includes clearly stated objectives, predefined eligibility criteria for studies, a replicable methodology mainly of a systematic search for relevant studies, critical analysis and synthesis of characteristics and findings of the included studies (Higgins and Green, 2009).

As stated in the previous chapter, the aim of this thesis is to elucidate drug toxicity in paediatric randomised controlled trials. Here is the first distinction from a Cochrane systematic review whereby a Cochrane review is usually concerned with answering a single research question; this systematic review attempts to answer several questions with a generally broader scope. The main research questions are listed in the following list.

2.1.2 MAIN RESEARCH QUESTIONS

1. What are the characteristics of paediatric randomised controlled drug trials published in 2007?
    a. What are the characteristics of the paediatric participants taking part?
    b. What are the types of drugs and diseases studied?
2. What are the methods used in the trials?
    a. What comparisons are used and are they appropriate?
    b. Have the trials been reported adequately?
3. What toxicities are experienced within the trials?
    a. Are there adequate safeguards to protect trial participants from possible toxicity?
    b. Are safety characteristics adequately reported?
4. Where are the trials performed and how do they relate to the global burden of disease?

From this list, the difference from a Cochrane review becomes more apparent. Cochrane reviews often attempt to synthesize multiple outcomes from the different studies into a single estimate of the effects of a particular intervention. This is known as a meta-analysis (Moher et al., 1999, Jadad, 2007). The main interest of this systematic review is examining the characteristics of paediatric randomised drug trials covering the whole breadth of specialities and the multitude of different disease classes. This project can be better described as a descriptive or explorative systematic review, in contrast to an analytical systematic review concerned with examining the effects of a certain intervention.

Answering the main research questions require the analysis of many variables related to the RCTs. These will be further commented on later in the methods section as well as in the results.

In summary this is a descriptive systematic review of RCTs involving children published in 2007. It aims to study toxicity occurring within the trials but also analyzes many of the following aspects of the RCTs; participants, drugs, diseases, methods and locations.

2.2 ELIGIBILITY CRITERIA

Eligibility criteria are another distinguishing feature of a systematic review compared to a narrative review (Higgins and Green, 2009, Akobeng, 2005b). To determine the type of studies that best address the main research questions listed earlier, the inclusion and exclusion criteria for this review are specified as follows.

2.2.1 TYPE OF STUDY: RANDOMISED CONTROLLED TRIALS (RCTs)

For this review, a distinction is made between randomised controlled trials and controlled clinical trials. Only randomised controlled trials are included in this review. All types of RCTs are eligible including parallel trials, factorial design trials as well as cross-over trials (Jadad, 2007). The random allocation procedure is a key eligibility criterion (Akobeng, 2005a). Studies where randomisation is not mentioned or described are excluded.

2.2.2 TYPE OF PEOPLE: THE PAEDIATRIC POPULATION

In this review, the people or population of interest is the paediatric population. Defining this as an eligibility criterion provides unique challenges. 'Child' or 'paediatric' can carry very different meanings in many different perspectives. For this project I have elected to use guidelines produced by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (Food and Drug Administration, 2000, EMEA, 2001). The ICH is a joint collaboration of both regulators and industry experts from the European Union, Japan and the USA concerned with the study of human medicines. ICH guidance is endorsed by both the FDA and the EMEA.

ICH guidelines have been adopted for the classification of age groups in the paediatric population. The categories are as follows:

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

This categorization system leads to another difficulty that is also acknowledged by the ICH guidelines (EMEA, 2001). The paediatric population does not fall neatly in these age groupings and may actually move across the categories over the course of a study. Furthermore many paediatric RCTs recruit patients across several different categories and many trials even recruit from both the adult and paediatric age groups (Sammons et al., 2005). This may present issues in the process of classifying the studies according to age groups, due to the overlapping categories. Another challenge is deciding the cut-off age of participants. For instance how should trials involving patients between 16 and 30 years old, or 17 and 45 years old be categorised? As seen in the suggested age categories the ICH guidelines are unclear on this matter, describing adolescents as being up to 16 or 18 years of age depending on region.

Therefore the ICH age categories are further refined to be used as eligibility criteria for RCT in this systematic review. They are described as follows:

- All RCTs involving (but not limited to) patients from preterm neonates up to 16 years old
    - This would mean that mixed studies involving both paediatric and adult populations would also be included, for example RCTs with a sample population of 15-45 year old patients
- Each intervention arm of the RCT would need to have a patient of 16 years or below
- All age categories for each RCT would be reflected in the database when classifying age groups
    - For example, a trial with patients between 12 months to 12 years of age would be classed as involving all three categories i.e. infants, children and adolescents

One exclusion criterion is the opposite of the above criteria i.e. RCTs without any participants below the age of 17 would be excluded from the systematic review.

2.2.3 TYPE OF INTERVENTION: DRUG TRIALS

As with the word ‘child’, there is a multitude of ways to define the meaning of the word ‘drug’. This review is primarily concerned with pharmaceutical products used mostly in therapeutic situations but also including diagnostic, anaesthetic and prophylactic indications. The word ‘drug’ is used in this context and trials where the primary intervention studied can be classed to one of the above categories would be eligible for the review.

Conversely several categories of interventional trials that would be excluded have been predefined. They are as follows:

- Physiological treatments such as continuous positive airway pressure (CPAP) and physiotherapy
- Dietary and food supplement or enrichment products including micronutrients, macronutrients, probiotics and prebiotics
- Dental products
- Herbal, homeopathic, traditional or any medicinal products where the active pharmaceutical ingredient is undefined

To allow for the broadest range of drug RCTs to be included in the review I have not specified any limitations for route of administration, compared to the previous review by Sammons et al. (2007) where only trials of intravenous and oral drugs were included.

2.2.4 PUBLICATION YEAR: 2007

This project was conceptualised in 2007 with data collection beginning in 2008. The year 2007 was chosen as it coincided with the enactment of new European drug legislation as described in chapter 1 (Permanand et al., 2007). Articles are added to electronic databases on almost a daily basis but often with a lengthy lag time from actual publication (Higgins and Green, 2009). Therefore by setting an endpoint to the search at the later end of 2008 would allow sufficient time for reports of RCTs published in 2007 to be indexed and thus available to the electronic search.

2.3 SEARCH STRATEGIES

As mentioned previously, a comprehensive and reproducible search to identify studies relevant to the research questions is a key distinguishing feature of a systematic review. As demonstrated by the eligibility criteria, the wide scope of this systematic review sets it apart from most Cochrane reviews. Therefore the primary goal is to develop an efficient method of identifying the majority of eligible RCTs and then to obtain the relevant information from them.

In this section, the main sources of studies relevant to the review are detailed. Also described are the iterative process of designing and conducting the search strategies, the management of references, the process of data extraction and finally the development of the database for this review.

2.3.1 SOURCES OF STUDIES

The most efficient way to identify reports of studies relevant to this review would be by searching electronic bibliographic databases (Higgins and Green, 2009). There are numerous online databases that compile and index scientific literature. In the medical sciences, the two most widely used databases are MEDLINE (Medical Literature Analysis and Retrieval System Online, US NLM, 2008) and EMBASE (Excerpta Medica Database, Elsevier, 2010).

1. MEDLINE and EMBASE

MEDLINE is maintained by the United States National Library for Science and currently holds some 16 million references to journal articles in the field. For this project, MEDLINE was accessed through the OVID gateway provided by the eLibrary portal of the University of Nottingham.

Although MEDLINE contains a vast amount of literature, research has shown that systematic reviews utilising MEDLINE as the only bibliographic database is no longer acceptable as there could be large numbers of relevant studies that would be potentially missed (Dickersin et al., 1994, Woods et al., 1998, Suarez-Almazor et al., 2000, Sampson et al., 2003). Nieminen and Isohanni (1999) noted that MEDLINE has a more North American emphasis and may provide insufficient coverage of European clinical research. Sampson et al. (2003) suggested that there is a risk of introducing bias into the meta-analyses from reviews that search MEDLINE solely.

EMBASE is another bibliographic database that is widely used for accessing medical literature. It is run by Elsevier and contains 20 million references to scientific articles. EMBASE appears to have more European exposure (Nieminen and Isohanni, 1999). Although there is a significant degree of overlap between the two databases; there are more than a thousand of journals uniquely indexed in each database (Higgins and Green, 2009). It is now standard practice for systematic reviews conducted presently to search both MEDLINE and EMBASE.

Relevant to this review there is evidence that EMBASE provides a larger coverage of pharmacology-related articles (Robinson, 2005). Nonetheless, I expect to encompass a wide range of the relevant medical literature by including both of these major databases in this systematic review. EMBASE was accessed via the same OVID gateway as MEDLINE.

2. COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS

Along with EMBASE and MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) is included as the three most important sources of trial reports used for systematic reviews (Higgins and Green, 2009). CENTRAL is different in nature from MEDLINE or EMBASE. It began as an effort by the US National Library of Sciences working with the Cochrane Collaboration to identify all randomised or controlled healthcare studies in their MEDLINE database (Dickersin et al., 2002). The identified reports are then tagged electronically to allow systematic reviewers to efficiently search for the studies, thereby becoming a virtual register of clinical trials indexed in MEDLINE.

CENTRAL underwent further development when two deficiencies became apparent; that is was infrequently updated and that it would be limited to trials indexed in MEDLINE only meaning that many trials would be potentially missed by reviewers (Dickersin et al., 2002, Higgins and Green, 2009). As a result the Cochrane Collaboration greatly expanded the resources searched to contribute to trials listings in CENTRAL. Currently all relevant randomised or controlled trials identified in searches by all Cochrane Review Groups or centres in the course of their systematic reviews would be listed in CENTRAL.

These trials are identified by two primary methods; electronic searches of bibliographic databases and handsearching of reports in conference proceedings, journals or other material.

Following work on searching EMBASE (Lefebvre, 1996) and the inclusion of many regional databases and specialised registers in searches by Cochrane reviewers, the databases searched are no longer limited to MEDLINE. The handsearches access a vast amount of material, including isolated abstracts and conference proceedings, grey and even unpublished work. As of January 2008 CENTRAL lists in excess of 500,000 reports, the majority of which were sourced from MEDLINE (310,000 reports) and EMBASE (50,000 reports) (Higgins and Green, 2009). For this review CENTRAL was accessed via the Wiley Interscience library portal accessible online at the following website:

http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html

3. OTHER SOURCES and FINALISING

Cochrane reviewers attempt to minimize bias by including the greatest breadth of evidence possible. This involves searching many sources of relevant studies (as seen in the process of contributing to CENTRAL). It was decided to exclude the following sources due to low yields or resource limitations.

- Handsearching of journals, conference proceedings, books, unpublished and grey literature was dropped at the outset of the search due to limited resources.
- Regional databases were excluded after trial runs revealed difficulties in developing efficient search strategies, low yields and resource limitations as non-English results required translation facilities which were not available to me.
- Specialised registers were excluded for the same reasons.

4. WHY NOT JUST SEARCH CENTRAL?

All three of the major databases, MEDLINE, EMBASE and CENTRAL, were searched for this systematic review in line with the recommended procedure for all Cochrane reviews (Higgins, 2009). However the question might arise that since efficiency is crucial in this project, why not just search CENTRAL as it actually contains of the result of searches on MEDLINE, EMBASE and various other sources as seen in the following illustration?

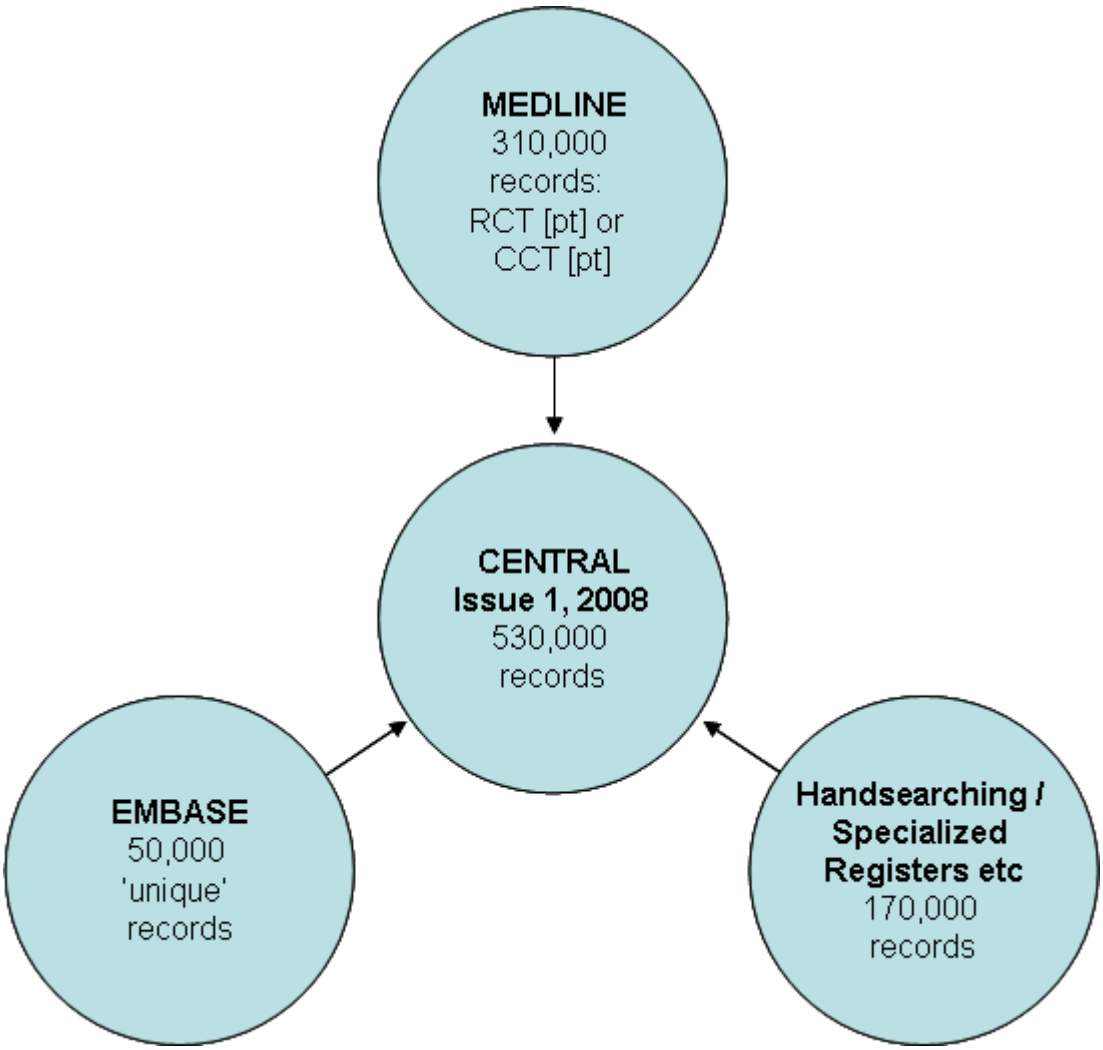


Illustration from Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009] (Higgins and Green, 2009)

Firstly the effort of identifying and tagging relevant reports indexed in MEDLINE by the US-based workers actually ceased in 2004 (personal communication via email from Bobbi Scherer, Associate Director of US Cochrane Centre). Therefore the listings in CENTRAL for studies published in 2005 up to the present are limited to contributions by the individual Cochrane Review Groups.

Secondly the contributing Cochrane Review Groups are organised around disparate specialities or medical fields. It is reasonable to expect that coverage does not extend to all fields where paediatric trials are conducted.

Thirdly, there is a significant delay from the time any report appears in MEDLINE or EMBASE before it is potentially indexed in CENTRAL. For MEDLINE records this may be several months and between 1-2 years for EMBASE records; as CENTRAL is only updated quarterly (Higgins and Green, 2009).

For example a search of CENTRAL limited to the year 2007, conducted in July 2008, would potentially miss:

- studies in MEDLINE in areas where there are no active Cochrane Group reviews as there is no retagging effort for 2007
- reports of studies indexed in MEDLINE in late 2007 onwards
- reports of studies added to EMBASE beginning from late 2006 onwards

Finally the low proportion of paediatric systematic reviews have been noted previously (Martinez-Castaldi et al., 2008) . Thus many published paediatric clinical trials would probably be absent from CENTRAL as there have been limited effort in searching for and appraising them.

2.3.2 SEARCH STRATEGIES

Considering the specific type of trial reports examined by this review (drug RCTs involving the paediatric population published in 2007), MEDLINE and EMBASE were searched using highly developed search strategies. CENTRAL was searched using a tested paediatric filter.

1. MEDLINE

In 1994, Carol Lefebvre designed a highly sensitive search strategy to identify RCTs in MEDLINE (Dickersin et al., 1994). This strategy became known as the Cochrane Highly Sensitive Search Strategy (HSSS) and was used widely by systematic reviewers including my supervisors (Sammons et al, 2005).

A decade later there was a major effort (involving Carol Lefebvre, Julie Glanville and other colleagues) to develop a search strategy using objective and research-based approaches, similar to that used in designing and evaluating a diagnostic test (Glanville et al., 2006). The workers selected a gold standard of known reports of RCTs as well as a comparison group on non-RCT reports indexed in MEDLINE. This selection was then used to identify keywords that can be used as search terms. The ability of the keywords to discriminate between RCTs and non-RCTs were ascertained using logistic regression and were tested on other MEDLINE records. The result was six different search strategies that can be used depending on whether the emphasis of the search was sensitivity or specificity. These strategies were later tested on another gold standard set namely the McMaster Clinical Hedges Database with similar results (Wilczynski et al., 2007).

The most sensitive strategy developed by Glanville et al. (2006) uses 7 keywords to retrieve 99.5% of RCTs from their own gold standard group of studies and 98.5% of RCTs from the McMaster gold standard. This strategy was named the CRD/Cochrane HSSS (2005 revision). This strategy has been used to search for RCTs in MEDLINE. Only human studies were included.

To narrow the search down to drug trials, two medical subject heading (MeSH) phrases previously utilised by Sammons et al. (2005) were used – 'dt.fs' and 'exp Drug Therapy/'. The term 'dt.fs' means 'drug therapy in floating subheading' and will retrieve all drug therapy related articles indexed under that subheading, whereas the term 'exp Drug Therapy/' explodes the subject heading of drug therapy to retrieve relevant articles. These two MeSH phrases were combined with the Boolean operator 'OR' thus allowing for a broad and sensitive search of drug related studies in the search strategy yet at the same time narrowing down the scope of the search.

In the same year of the work by Glanville et al. (2006), the Hedges team at McMaster University performed a similar study of age-specific search terms to retrieve clincial trial reports relevant to the different age groups (Kastner et al., 2006). In this study the gold standard were results of a manual handsearch of 161 core medical journals. Again the results were several combinations of keywords that can be selected depending on whether a sensitive or specific search was needed in the review. For this systematic review, the most sensitive combination of keywords for paediatric medicine and neonatal medicine were adopted from their study (combined with the Boolean operator 'OR').

Finally the search was limited to studies published in 2007. The full search strategy is as follows.

	Searches	Comments
1	clinical trial.pt.	CRD/Cochrane HSSS (2005 revision) (Glanville et al., 2006)
2	randomized.ab.	Note the original strategy included 7 terms including 'dt.fs', this term is inserted below
3	placebo.ab.	
4	randomly.ab.	
5	trial.ab.	
6	groups.ab	
7	1 or 2 or 3 or 4 or 5 or 6	Combining all 6 terms
8	Animals/	
9	Humans/	
10	8 and 9	Studies where both humans and animals were studied
11	8 not 10	Isolating studies where only animals were studied
12	7 not 11	Excluding trials where no humans were studied
13	dt.fs.	Focussing on drug studies (Sammons et al., 2005)
14	exp Drug Therapy/	
15	13 or 14	

	Searches	Comments
16	12 and 15	Combining human RCTs with drug studies
17	child:.mp.	Validated age specific search strategy by Hedges Team (Kastner et al., 2006)
18	adolescent.mp.	
19	infan:.mp.	
20	gestation:.tw.	
21	17 or 18 or 19 or 20	Combining all 4 terms
22	16 and 21	Combining human drug RCTs with paediatric age groups
23	limit 22 to yr="2007"	Reports published in 2007 only

2. EMBASE

Initially less effort has gone into developing search strategies for EMBASE. Carol Lefebvre did some early work (Lefebvre, 1996), however MEDLINE was searched more often than EMBASE in systematic reviews. This was reflected in records held by CENTRAL where EMBASE contributed less than 10% of the studies held while MEDLINE-sourced reports constituted almost 60% of all the studies (Higgins and Green, 2009). As previously mentioned, evidence then accumulated on the importance of searching both MEDLINE and EMBASE as well as other sources when conducting systematic reviews. This led to more work on search strategies for EMBASE notably by the Hedges team at McMaster University.

Sharon Wong and colleagues identified relevant search terms and tested them on results from handsearches of 55 medical journals indexed in EMBASE (Wong et al., 2006). They then developed several search strategies for RCTs indexed in EMBASE from the combination of search terms identified. A three keyword combination that was found to be the best optimisation of sensitivity (94.5% of handsearched trials) and specificity (92.6% of non-relevant studies from handsearches) was selected for this review.

There does not seem to be any age-specific search strategies developed for EMBASE in the literature. Therefore the age group classifiers provided by the Ovid Gateway were used for this study. I did not use any terms to narrow the search to drug trials only. Trials of non-drug interventions were identified and excluded when the individual abstracts were reviewed (see section 2.5). Again Boolean operators were used to combine search terms as appropriate and the search results were limited to studies published in 2007. The full search strategy can be seen as follows.

	Searches	Comments
1	Random:.tw.	Optimised strategy by Wong et al (2006).
2	placebo:.mp.	
3	double-blind:.tw.	
4	1 or 3 or 2	Combining all three terms
5	limit 4 to yr="2007"	Studies published in 2007 only
6	limit 5 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	Age group categories provided by Ovid Gateway for EMBASE

3. CENTRAL

The BestBETs (Best Evidence Topics) team is a Manchester-based group that has embraced evidence based medicine by providing brief, well-structured reviews of the best available evidence of a specific clinical topic. In 2002 (updated in 2003) they developed and tested a sensitive paediatric filter to identify any paediatric related studies in MEDLINE (Mackway-Jones K, 2002). This maximally sensitive filter has 49 search terms. These search terms were adapted to be used for CENTRAL, resulting in a list of 18 search terms. Where appropriate, the wildcard character denoted by an asterisk '*' were used to allow for plural versions and differences in spelling as well as terminology.

Screen capture of the search webpage for Cochrane CENTRAL via Wiley Interscience portal.

The list of paediatric-related search terms that have been used is as follows.

	Keywords
1	preterm*
2	prematur*
3	perinat*
4	neonat*
5	newborn*
6	bab*
7	infan*
8	toddler*
9	child*
10	pediatr*
11	paediatr*
12	boy*
13	girl*
14	kid*
15	juvenil*
16	teen*
17	adoles*
18	Pubescen*

4. SUMMARY

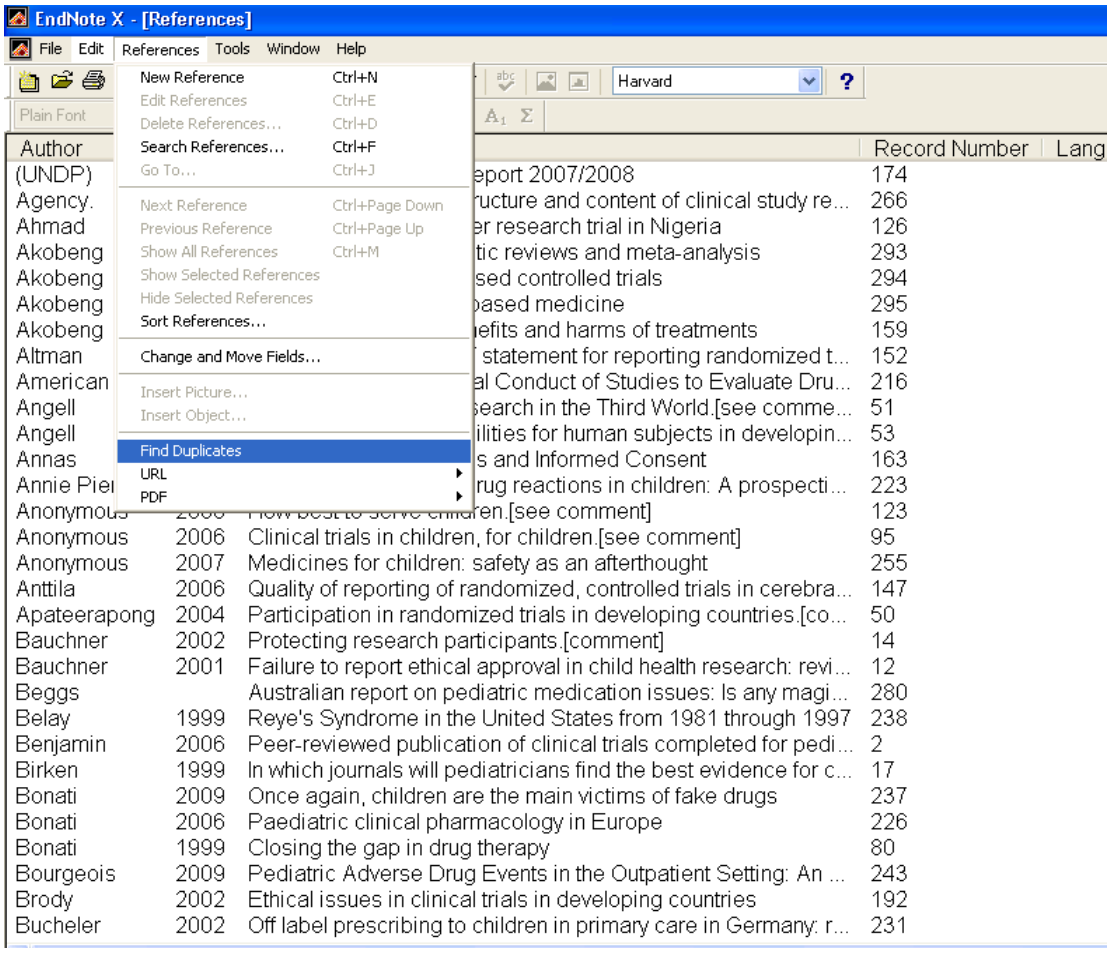
In summary MEDLINE and EMBASE were searched for RCTs using validated search strategies. The results of the searches were then narrowed down according to the pre-specified eligibility criteria. Boolean operators (‘AND’, ‘OR’ and ‘NOT’) were used to combine validated keywords representing the different aspects of the eligibility criteria. For CENTRAL a set of validated age-specific keywords were utilised to search for relevant studies. There was no language restriction applied for any of the three search strategies. These unique search strategies are designed for the highest sensitivity in identifying relevant studies for this systematic review.

2.4 MANAGING REFERENCES

Storing and processing the thousands of references resulting from the search strategies detailed previously required bibliographic software. The main characteristics required were user-friendliness, availability of technical support and the ability to detect duplicate references, particularly with the subtle differences in indexing used by the different databases. With these in mind, the Endnote software was used (Version X, Philadelphia, USA, copyright owned by Thomson Reuters).

After executing the search strategies for MEDLINE and EMBASE, each and every resulting reference on the Ovid gateway was exported into individual libraries on Endnote. The search page provided by Wiley InterScience for CENTRAL has only five input slots for search terms. Therefore the 18 age-specific keywords developed earlier were entered in four separate stages. The four files of search results were then exported into an Endnote library. All available fields for all the references were exported into Endnote.

The three libraries were then combined into a single Endnote library and the ‘find duplicates’ command in Endnote was executed (as depicted in the screen capture). All duplicates were highlighted below the originating reference. Each duplicate pair was carefully inspected to ensure there were no unique references that might be erroneously deleted. After inspection was completed, all detected duplicates were deleted.



Screen capture of Endnote software showing ‘Find Duplicates’ tool.

Note: Database shown not used for this systematic review

2.5 SELECTING AND OBTAINING STUDIES

The title and abstract for each remaining reference was read and any of the inclusion or exclusion criteria identified, to determine whether the report should be included in the review. Whenever there was insufficient information in the title or abstract, all the other fields on Endnote were searched for any additional information. I consulted my supervisors for any reports whenever I was unsure of the suitability and obtained the full paper if needed. A low threshold of hesitancy was implemented in the assessment; any paper where eligibility was unclear was further assessed.

Although the Cochrane Handbook recommends that two independent reviewers assess the eligibility of the study, this was not possible for this PhD. Nonetheless the precautions taken should minimise the introduction of bias or human error. Furthermore this systematic review has a wide scope with a prominent descriptive focus rather than a solely analytical purpose; therefore minimisation of bias during assessment of eligibility is felt not to be crucial to the study.

The unit of interest for this review are the individual RCTs. However this may not be the same as the *reports* of the studies as there may be multiple reports of a single study being published (Higgins and Green, 2009). Therefore all reports assessed as being eligible for this review were double-checked by examining adjacent references, especially the author, title and abstract fields in Endnote. The most complete or recently updated report of a study where multiple reports are present was selected. Where different result sections have been reported in separate papers, data was collected from all the papers.

No authors of the selected papers were contacted for clarification. This was not possible considering the very large numbers of references obtained, in addition to time and resource constraints.

The full article was obtained for all studies deemed eligible for this review. The bulk of these were obtained from fulltext online publications. If not published online, print copies were obtained directly from the University of Nottingham library or from the Interlibrary Loan service. Each article was then labelled with the corresponding record number of the reference within the Endnote library.

2.6 DATA EXTRACTION AND MANAGEMENT

In the context of this review, data is defined as information about or derived from a study (Higgins and Green, 2009). I have determined what data to be included based on the main research questions (section 2.1.1), corresponding to the major themes studied in this systematic review. A 1-page data extraction form was designed to allow comprehensive yet efficient extraction of data from the articles. Piloting of the form with a small sample of RCT reports was successful in terms of practicality when dealing with the large amounts of reports and data. The data extraction form and brief explanation of the data types can be seen on the next page. The types of data collected will be elaborated further in the specific chapters.

The Cochrane handbook strongly recommends that data from each article is extracted by more than one independent reviewer to minimise errors and the introduction of potential biases. As mentioned previously, this was not a realistic proposition in the context of this review as a PhD studentship. Nevertheless a further measure was put in place where both supervisors will review and extract crucial safety data from a significant proportion of the articles. This is described further in chapter 5.

A statistical database was created using the Statistical Package for the Social Sciences software (SPSS version 16.0, SPSS Inc., Chicago, IL, USA) to store and analyse data from the data extraction forms. The variables on the database were coded to correspond closely to the data collection forms. The full SPSS database and all Endnote libraries created and used in this review are included in the CD accompanying this thesis.

No					
Journal					
Country					
HDI	1	2	3		
Income	1	2	3	4	
Index	*ENDNOTE*				
PaedID	YES	NO			
Random (J1)	YES	NO			
GenName					
ATC	*KEY 3*				
ICD10	*KEY 4*				
Consent	YES	NO			
Assent	YES	NO			
TypeofTrial	Safe	Eff.	PK		
TypeofComparison	*KEY 5*				
RouteofAdmin	*KEY 6*				
DoseMent	YES	NO			
DoseUnit	*KEY 7*				
RxType	*KEY 8*				
Formulation	YES	NO			
PrimeOutcome	YES	NO			
SampleSize	YES	NO			
STOP	YES	NO			
Blinding (J2)	0	1	2		
Arms	1	2	3	4	5
Crossover	YES	NO			
Diagram	YES	NO			
Ethics	YES	NO			
CentresNo	1	2	Multi		
Interntnal	YES	NO			
CentreType	Hosp-IN	Hosp-OUT	Comm.		
Mixed	YES	NO			
ChildNo					
Withdr/drop(J3)	YES	NO			
Child No Category	*KEY 10*				
ChildAge	*Preterm*	*Term-27d*	*28d-23mo*	*2-11yrs*	*12-16*
SafeMethod	YES	NO			
SMC/DMSB	YES	NO			
AEs	YES	NO			
AEgrade	*KEY 12*				
ADR	YES	NO			
ADRgrade	Sev	Mod	Mild		
Death	YES	NO			
DeathClass	YES	NO			
Funding	YES	NO			
FundSource	*KEY 13*				
OverseasFund	YES	NO			
Registered	*KEY 14*				
Random Adq (J4)	YES	NO			
Blinding Adq (J5)	YES	NO			

Data collection form designed for this review

Each data type is further described in the results chapters

2.7 CONCLUSION

In conclusion a detailed description of the methods used to perform this systematic review has been provided. Although drawing heavily from the recommendations by the Cochrane Handbook, unique search strategies have been designed to search for paediatric RCTs based on validated techniques developed by several distinguished research groups. However resource limitations meant that certain recommendations from the Cochrane Handbook were not implemented, particularly the requirement of multiple independent reviewers. Nonetheless essential measures were put into place to minimise the introduction of errors or biases. Endnote was used to manage the large number of reports resulting from the search. A SPSS statistical database was created to store and analyse the great amount of data extracted from the eligible studies.

Further details on specific methods will be provided in the subsequent chapters including on the categorisation and coding of variables recorded from the studies and types of statistical analyses.

CHAPTER 3: DEMOGRAPHICAL & EPIDEMIOLOGICAL CHARACTERISTICS

In this chapter, the results from the search strategies in chapter 2 are described. The paediatric randomised controlled trials (RCTs) identified in this systematic review are studied to determine their demographical and epidemiological characteristics; the characteristics of the participating paediatric population, the diseases involved and the drugs being trialled. This is set in the context where relatively little is known on the overall situation of RCTs involving children. Thus the current work hopes to elucidate the current situation of paediatric drug RCTs, add to previous studies, and more importantly to identify areas requiring further attention from paediatric researchers, health professionals and drug regulators.

1. INTRODUCTION

The past two decades has seen a considerable interest in medicines used in children. Previously, paediatric drugs were inadequately evaluated in their population leading to the situation where prescription of unlicensed and off label drugs was widespread. Growing concern with the risks associated with such use, coinciding with rising awareness that medical practice should be evidence based resulted in major changes in drug regulation in North America followed by European enactments later on. Subsequently the World Health Organisation (WHO) initiated global programmes to promote safety of medicines used in children titled Promoting Safety of Medicines for Children (Watts, 2007) and to improve access and availability of child-specific medicines for children all over the world - Make Medicines Child Size (Choonara and Bauchner, 2008).

The main goal of these efforts is to ensure drugs prescribed to children are supported with high quality evidence obtained from paediatric RCTs (except when RCTs are unfeasible). Although RCTs have been well studied, there has been relatively little work done to elucidate the overall situation of RCTs involving children.

Campbell et al., (1998) published one of the earlier efforts to study paediatric RCTs. They handsearched 15 years of the Archives of Disease in Childhood journal (excluding the Fetal and Neonatal edition) between 1982 and 1996 and identified 249 RCTs published within that period. Most of the RCTs (69%) were conducted in the UK. They found that most of the RCTs were small; roughly half recruiting fewer than 40 children in total thereby fewer than 20 patients were studied in each treatment group. More than 80% of the RCTs were single centre trials.

In 2003, the FDA reported on 53 studies involving children of 33 drugs that were granted patent extensions under the new provisions of the Modernization Act of 1997 (Roberts et al., 2003). More than 50,000 patients participated in these studies although the vast majority totalling 41,356 children aged between 6 months and 2 years took part in 2 large studies of ibuprofen over-the-counter products. The information gained from these studies led to labelling changes for the drugs including important dosing and safety revisions. The 53 studies included all types of studies, not just RCTs.

Chan and Altman (2005) undertook a broad review of all randomised trials published in PubMed (which encompasses MEDLINE) in the month of December 2000. They identified 519 RCTs, of which only 37 (7%) were categorised as paediatric. They did not describe any characteristics specific on the paediatric RCTs but lamented on the small sample sizes in the RCTs overall. The median number of participants overall was 80, with 32 patients studied per treatment group. They calculated that with 32 patients per treatment group, a trial has only a 39% power to detect a difference of between 10% and 30% in events at the p=0.05 significance level. Note that the sample sizes in this review were markedly larger than in the paediatric RCTs studied by Campbell et al. (1998).

The first broad review of paediatric clinical trials was performed here in our department by Sammons and Choonara (2005). They examined paediatric clinical trials of oral and intravenous drugs published from 1996 to 2002 that were indexed in MEDLINE. The review included pharmacokinetic trials as well as RCTs but excluded human immunodeficiency virus (HIV) and oncology trials because these areas have been well covered by previous reviews (Hargrave et al., 2001, Nolan et al., 2002).

736 trials were identified; 619 (84%) involved paediatric patients solely while the remainder (117, 16%) included both adult and paediatric patients. There were more multicentre studies (173, 24%) compared to the review by Campbell et al. (1998). The sample sizes also appeared larger, with single centre studies recruiting a median of 50 patients while multicentre studies recruiting a median of 227 patients. The great majority of the trials originated from North America and Europe, consisting 73% of the total number of trials. The most common specialty areas studied were general paediatrics, infectious diseases and neurology.

In the background of the regulatory changes aimed at stimulating paediatric clinical trials recently, several research groups analysed the widely held opinion that paediatric research lagged behind adult research.

Cohen et al. (2007) examined both adult and paediatric RCTs published between 1985 and 2004 in five high-impact medical journals (New England Journal of Medicine [NEJM], Journal of the American Medical Association [JAMA], Lancet, British Medical Journal [BMJ] and Canadian Medical Association Journal [CMAJ]). From 5420 RCTs, they found that there were almost five times as many adult RCTs compared to solely paediatric RCTs. They also found that the number of adult RCTs published increased significantly on an annual basis while the number of paediatric RCTs remained stagnant. From their subset of RCTs published in 2000, they discovered that paediatric RCTs had a smaller sample size compared to adult RCTs (median 272 vs 318 patients), although the difference was not statistically significant.

Martinez-Castaldi et al. (2008) reviewed all articles published in NEJM, JAMA, Annals of Internal Medicine, Pediatrics, Archives of Internal Medicine and Archives of Adolescent and Pediatric Medicine over a three month period in 2005. They found that there were significantly more adult RCTs compared with paediatric RCTs (24% vs 9%). However no specific characteristics of the paediatric RCTs were described.

Pandolfini et al. (2008) conducted a review of European published and ongoing paediatric drug therapy trials between 2004 and 2007. The major disease categories studied by the 379 published trials were Infectious Diseases, Neoplasms and Nervous System Diseases according to the ICD-9 classification system that they used. Again, certain specific characteristics of the published trials such as sample sizes or age groups were not reported.

Thus although a few trends are becoming apparent such as the small sample sizes, the dearth of paediatric RCTs compared to adult studies and that most frequently studied areas were in general paediatrics, infectious and nervous system diseases; epidemiological information on paediatric RCTs overall remains unclear. What is known on the children participating, the diseases studied or the drugs trialled were sourced from sporadic studies. These reviews were either limited to a single paediatric journal (Campbell et al., 1998), a subset of high impact publications (Cohen et al., 2007, Martinez-Castaldi et al., 2008) or a single geographical region (Pandolfini et al., 2008). Furthermore these studies varied widely in their design and analyses, ranging from studying paediatric RCTs specifically (Campbell et al., 1998) to reviewing all RCTs (Chan and Altman, 2005) and examining all articles (Martinez-Castaldi et al., 2008).

In this context I plan to broadly describe paediatric drug RCTs published in 2007, building on the work of Sammons and Choonara (2005); detailing the specific characteristics of the trials, paediatric participants, disease areas and drug types in the RCTs.

2. METHODS

Each paediatric RCT identified using the search detailed in chapter 2 was carefully read to obtain data on the following subjects:

2.1 Location and setting of the RCTs

The country where the RCT was conducted was recorded. In some reports this was obvious or explicitly stated. When unclear, supplementary information, index citations and author affiliations were examined to determine country where the RCT was performed. When the RCT recruited participants from more than one country (ie. cross border or international studies) all participating countries were recorded.

This information was then used to classify the RCT location according to Human Development Index (HDI) of 2007 (UN Development Programme, 2007) and the World Bank Income Level (World Bank, 2007). The HDI is a composite measure including life expectancy, literacy rate, education enrolment and per-capita GDP. It is used to rank countries into developed (high HDI), developing (medium HDI) and underdeveloped (low HDI) categories. The World Bank ranks countries into high, middle and low income categories according to their gross domestic product (GDP) at purchasing power parity (PPP) per capita. Multinational RCTs that recruited across HDI or Income Level categories were noted.

Taking into account the wide variation of the healthcare systems between countries, a simple classification system was used for the setting of the RCT. RCTs were determined to have been performed either in general practice/outpatients, in hospital wards or in the community setting (schools, villages, towns). The number of centres involved was simply classified as either a single centre study or a multicentre study.

2.2 Characteristics of the participants

Firstly it was determined whether the RCT recruited from both the paediatric and adult populations (adult defined as any participants aged 17 and above – see chapter 2). The total number of paediatric patients participating in the RCT was then recorded. Mixed trials where the number of children was not described were identified. The sample sizes were then divided into ranges.

The age range of the participants in each RCT was obtained from the results section. However many of the mixed age group RCTs only described mean ages for the treatment arms. In these cases, the age range was determined from the methods section. It was then determined whether each of the ICH age group categories were present in the RCTs.

2.3 Characteristics of the drugs and diseases

The main drug therapy being trialled in each RCT was determined and recorded. Where the main intervention was a combination of several drugs or a certain drug regimen, this was recorded as well. The treatment under question was then classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2008). The complete ATC classification was obtained for the drug treatment for each RCT and the drugs were coded according to the highest level of the ATC system. The route of administration for the drug under trial was recorded, as well as whether the dose was mentioned and the unit of the dose ie. whether the dose was tailored to body weight, surface area or any other variable.

The disease relating to each RCT report was coded according to the 2007 revision of the WHO International Statistical Classification of Diseases and Related Health Problems (ICD-10, WHO, 2007).

2.4 Funding

The full reports of the RCT were examined to discover any declarations or acknowledgements of funding. The major source of funding for the trial operations were recorded and classified. Complimentary or free-of-charge supply of drug products, instrumentation and software were not considered as study funding.

Any difficulties arising when categorising a trial was presented to my supervisors at supervisory meetings and a consensus decision obtained. The statistical methods used in this descriptive analysis included calculating medians, interquartile ranges (IQRs), means and ranges.

3. RESULTS

The search was finalised and databases were locked in November 2008. The search strategies yielded 15,577 abstracts; 2747 from MEDLINE, 3149 from EMBASE and 9681 from Central respectively. Duplicate citations were then removed using Endnote and 8945 abstracts remained. Each of the abstracts were read to identify eligible paediatric RCTs. Subsequently 582 eligible RCTs were identified, with an additional 22 RCTs that were reported in non-English articles identified from their abstracts provided in English.

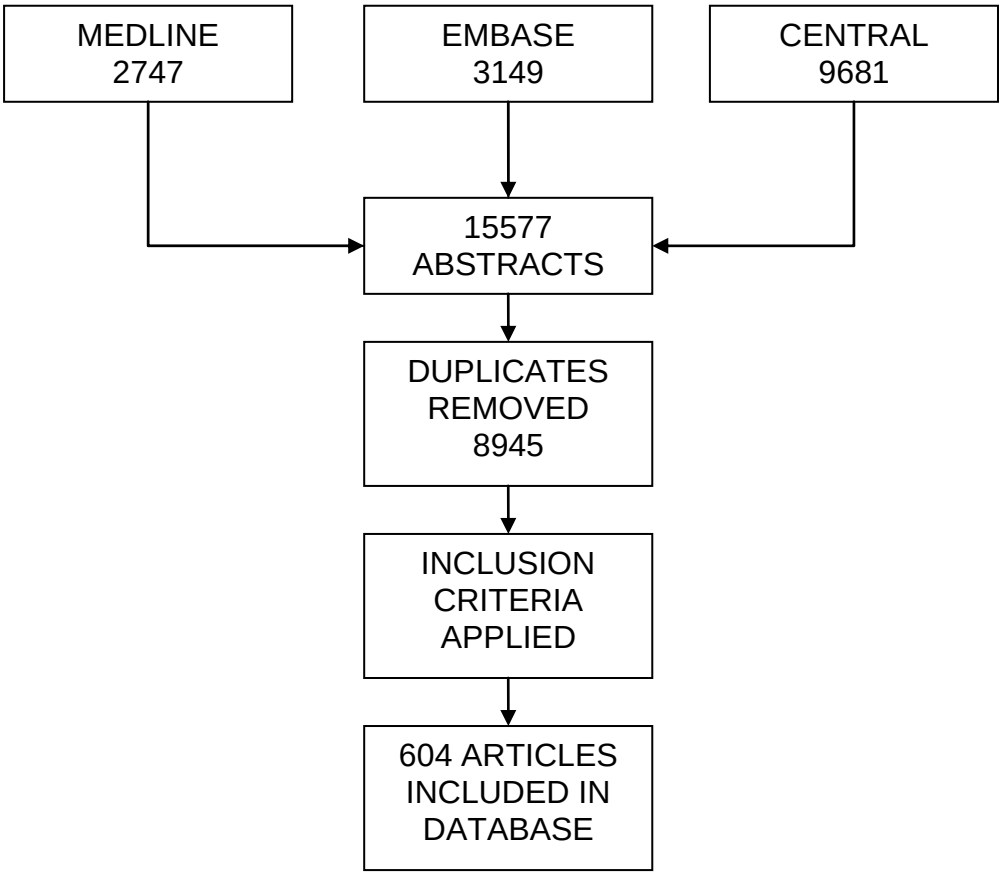


Diagram 1: Citation flow from search strategies

3.1 LOCATIONS AND SETTINGS

1. Trial Locations

There were 96 (16%) RCTs that recruited patients in more than one country. The remaining 508 (84%) recruited within one country. The majority of the cross border studies involved member countries of the European Union including the United Kingdom, as well as the USA and Canada.

For the single country RCTs, almost a quarter (115/508, 23%) were performed in the USA. India had the second highest number of RCTs with 32 (6%) followed by Turkey and Iran (27, 5% and 25, 5% respectively). Please see the appendix for the country locations of the RCTs.

When categorised according to HDI status, 392 (65%) RCTs were conducted in high HDI countries, 153 (25%) RCTs were performed in medium HDI countries while 28 (5%) were from low HDI countries. The remainder of 31 (5%) RCTs were multinational studies that recruited from countries across more than one HDI group.

Human Development Index (HDI) category	No of trials (n)	Percent (%)
High	392	65
Medium	153	25
Low	28	5
Multinational studies recruiting across HDI categories	31	5
Total	604	100

Table 1: Setting of paediatric RCTs published in 2007 categorised according to HDI (U.N. Development Programme, 2007)

Similarly, when classified according to World Bank Income groups the majority of the RCTs were conducted in high and upper middle income countries, consisting almost 70% of the database. There were 95 (16%) studies from lower middle income countries and 51 (8%) studies from low income countries. Forty-two (7%) RCTs were multinational trials that recruited across World Bank income groups, similar to those mentioned previously for the HDI categories.

World Bank Income group	No of trials (n)	Percent (%)
High Income	352	58
Upper Middle Income	64	11
Lower Middle Income	95	16
Low Income	51	8
Multinational studies recruiting across income categories	42	7
Total	604	100

Table 2: Setting of paediatric RCTs published in 2007 categorised to World Bank Income Group (World Bank, 2007)

2. Setting of trials

There were 268 (44%) studies that were performed in more than one centre. The remaining 336 (56%) were single centre RCTs. Approximately one-third (219, 36%) of the trials involved hospital in-patients (including patients admitted for day cases). The rest were conducted in the community; 307 RCTs (51%) were done in community health facilities such as general practices and outpatient departments while 69 RCTs (11%) were based in non-healthcare facilities including schools, villages and towns. In nine of the reports, the type of study setting was unable to be determined.

3.2 PATIENTS

1. Sample Sizes

In all, 428 (71%) of the RCTs recruited from the paediatric population only. The remaining 176 (29%) studies recruited both adult and paediatric patients. A large proportion from the mixed population group RCTs (143/604, 24% of total studies) did not report the number of participants by age group. Therefore the number of children participating in these trials could not be ascertained.

A total of 101,048 neonates, infants, children and adolescents took part in drug RCTs from the reports that indicated their sample population sizes. The median sample size of the RCTs was 89 (IQR= 41-120 patients).

Trial sizes (no of participants)	No of trials (n)	Percent (%)
2-9	16	3
10-49	130	22
50-99	105	17
100-499	164	27
500-999	31	5
1000 and above	15	2
Indeterminate	143	24
Total	604	100

Table 3: Sample sizes of paediatric randomised controlled drug trials published in 2007

The number of paediatric patients in each study ranged from 2 to 8352 patients. There were two studies in which only 2 paediatric patients were recruited; both were mixed age group RCTs. The first was a trial comparing high dose intravenous steroid regimens for acute optic neuritis that recruited a 7 and a 10 year old in each group (Menon et al., 2007). The second compared Buspirone versus placebo to treat spinocerebellar ataxia where a 14 and a 15 year old were included (Assadi et al., 2007).

There were 15 RCTs that recruited more than 1000 children each. The largest trial in the database recruited a total of 8352 children. This trial compared two influenza vaccine types in infants and children between 6 and 59 months of age (Belshe et al., 2007).

2. ICH age groups of trial participants

As with participant numbers, in many reports of mixed population RCTs the ages of paediatric participants were not provided in adequate detail. Most of the trials recruited patients in the ICH 'children' age category of 2-11 years old (397/604 RCTs, 66%) and the 'adolescent' category of 12-16/18 years old (366/604 RCTs, 61%). Over a quarter of the trials in the database recruited infants of 28 days to 23 months of age (157/604, 26%) while there were far fewer studies involving neonates; both preterms (26/604, 4%) and full term babies (23/604, 4%).

Taken together, only 41 trials in the database were neonatal studies of both preterm and full term babies. The neonatal trials involved between 8 and 2017 neonates with a median of 60 participants (IQR=29-181, mean=241). Please see appendix for a full list of the 41 neonatal RCTs.

ICH age group category	No. of trials (n)*	Percent (%)[+]
Preterm neonates	25	4
Full term neonates	22	4
Infants and toddlers	157	26
Children	397	66
Adolescent	366	61

Table 4: ICH paediatric age groups of participants in paediatric drug RCTs published in 2007

* Note that there is overlap between age group categories (as described in chapter 2), for instance studies involving patients between 12 months and 12 years old will span all 3 categories of infants, children and adolescents.

[+] out of 604 RCTs in the database

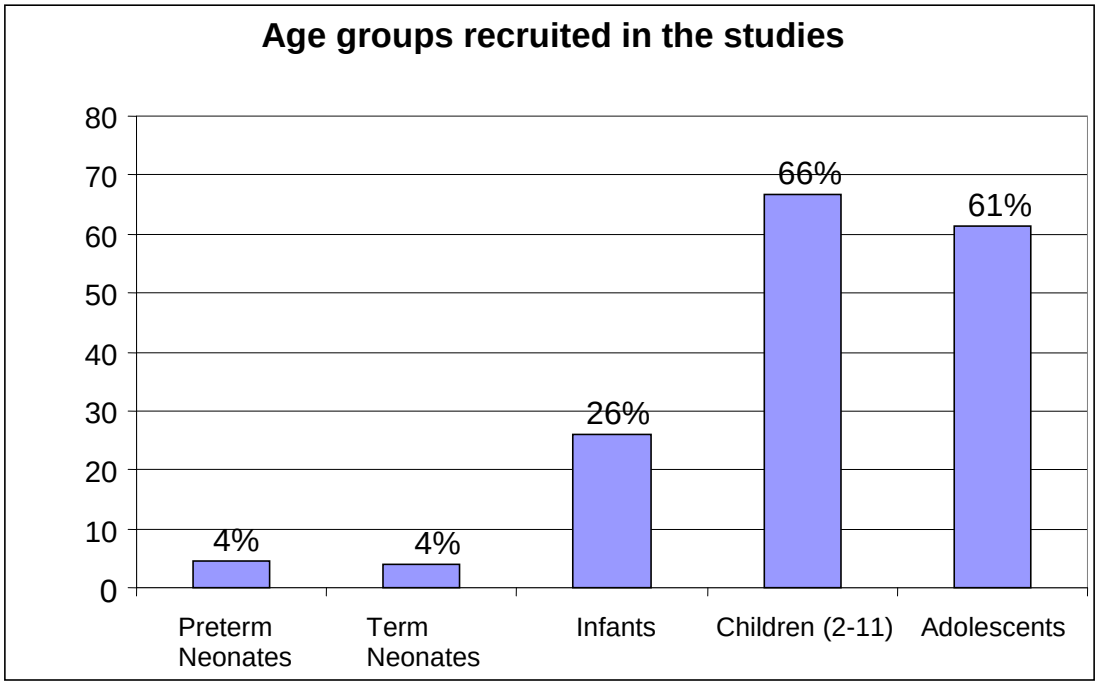


Figure 1: Percentage of trials recruiting each ICH age group category

3.3 DRUGS and DISEASES

1. Drugs

The most common drugs studied in the RCTs belonged to the nervous system (group N) category of the WHO ATC classification system; totalling 155 (26%) of all the RCTs. This was followed by group J or the anti-infectives for systemic use group (101, 17%) and group R - respiratory system drugs (74, 12%). These three areas comprised over half of the RCTs in the database.

ATC CLASS	Group	No. of trials	%
Nervous system	N	155	25.7
Anti-infectives for systemic use	J	101	16.7
Respiratory system	R	74	12.3
Antiparasitic products,insecticides and repellents	P	45	7.5
Systemic hormonal preparations,excl. sex hormones and insulins	H	42	7.0
Alimentary tract and metabolism	A	41	6.8
Antineoplastic and immunomodulating agents	L	41	6.8
Dermatologicals	D	40	6.6
Musculo-skeletal system	M	20	3.3
Blood and blood forming organs	B	15	2.5
Cardiovascular system	C	13	2.2
Sensory organs	S	10	1.7
Genito urinary system and sex hormones	G	4	0.7
Various*	V	3	0.5
Total		604	100.0

Table 5: WHO ATC drug classes studied by paediatric RCTs published in 2007

* These were the following RCTs: amifostine in paediatric osteosarcoma (Gallegos-Castorena et al., 2007), xylitol in acute otitis media (Hautalahti et al., 2007) and dexrazoxane in acute myeloid leukaemia/myelodysplastic syndrome (Tebbi et al., 2007).

Looking at ATC subgroups, the most frequently studied nervous system drugs were anaesthetic agents followed by analgesics and stimulant drugs used in attention deficit hyperactivity disorder (ADHD).

NERVOUS SYSTEM (Group N)	No. of trials (n)	Percent (%)
Anaesthetics	56	36
Analgesics	33	21
Psychoanaleptics (stimulants for ADHD)	29	19
Anti-epileptics	19	12
Psycholeptics	15	10
Other	3	2
Total	155	100

Table 6: Nervous system drug RCTs

The great majority of group J consisted of vaccine and antibacterial drug RCTs.

ANTI-INFECTIVES FOR SYSTEMIC USE (Group J)	No. of trials (n)	Percent (%)
Vaccines	51	50
Antibacterials	32	32
Antimycotics	8	8
Antivirals	4	4
Antimycobacterials	3	3
Immune sera/immunoglobulins	3	3
Total	101	100

Table 7: Anti-infectives for systemic use RCTs

Anti-asthmatic drugs were most frequently studied in the respiratory drug category.

RESPIRATORY DRUGS (Group R)	No. of trials (n)	Percent (%)
Drugs for obstructive airway diseases	54	73
Antihistamines	10	13
Nasal	8	11
Cough and cold	2	3
Total	74	100

Table 8: Respiratory drug RCTs

The major routes of administration for the main drug being trialled were oral (231/604 studies, 39%), intravenous (121/604, 20%), intramuscular (50/604, 8%), local pulmonary and topical dermal (7% each).

Route of administration	No. of trials (n)	Percent (%)
Oral	231	38.2
Intravenous	121	20.0
Intramuscular	50	8.3
Local Pulmonary	45	7.5
Topical Dermal	42	7.0
Subcutaneous	25	4.1
Intranasal/Sublingual/Buccal/Otic	21	3.5
Local tissue infiltration/injection	17	2.8
Caudal/epidural	15	2.5
Ophthalmic	10	1.7
Systemic Pulmonary	9	1.5
Rectal	8	1.3
Intramuscular (injection for local effect only)	6	1.0
undescribed	4	0.7
Total	604	100.0

Table 9: Routes of administering the main study drugs in paediatric RCTs published in 2007

2. Diseases

The predominant disease area studied by the RCTs was infectious and parasitic diseases (135 trials, 22%). This was followed by the symptoms, signs and abnormal findings category (114 trials, 19%) reflecting the many trials in anaesthesia and of analgesic drugs. Respiratory diseases were the third most common disease area in the database (78 trials, 13%).

WHO ICD-10 Categories of disease	No. of trials (n)	Percent (%)
Certain infectious and parasitic diseases	135	22.4
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	114	18.9
Diseases of the respiratory system	78	12.9
Diseases of the skin and subcutaneous tissue	40	6.6
Endocrine, nutritional and metabolic diseases	38	6.3
Diseases of the nervous system	32	5.3
Mental and behavioural disorders	31	5.1
Neoplasms	26	4.3
Injury, poisoning and certain other consequences of external causes	19	3.2
Certain conditions originating in the perinatal period	18	3.0
Diseases of the digestive system	14	2.3
Diseases of the blood and blood-forming organs and certain disorders	11	1.8
Diseases of the genitourinary system	9	1.5
Diseases of the eye and adnexa	8	1.3
Diseases of the ear and mastoid process	7	1.2
Congenital malformations, deformations and chromosomal abnormalities	7	1.2
Diseases of the circulatory system	6	1.0
Diseases of the musculoskeletal system and connective tissue	5	0.8
Factors influencing health status and contact with health services	5	0.8
Pregnancy, childbirth and the puerperium*	1	0.2
Total	604	100.0

Table 10: ICD-10 disease categories of paediatric RCTs published in 2007

*RCT of depo contraception recruiting 14 to 26 year olds (Rickert et al., 2007)

3.4 FUNDING SOURCES

A large proportion of the RCTs did not describe their source of funding, these 226/582 trials constituted 39% of the database (funding data was unable to be extracted from the 22 non-English text RCTs). Of the remaining 356 RCTs (61%), the pharmaceutical industry was declared as the major trial sponsor in 177 trials. There were 79 self-funded RCTs.

Main trial sponsor	No. of RCTs (n)	Percent (%)
Industry	177	50
Academic or self-funded	79	22
Governmental/health authority funding	62	17
Foundation or charitable funding	38	11
Total	356	100
Funding not mentioned	226	-
Unable to ascertain funding source*	22	-

Table 11: Main trial sponsors of paediatric RCTs published in 2007

*RCTs reported in non-English text but with English abstracts provided

4. DISCUSSION

It is reassuring that large numbers of randomised controlled drug trials involving the paediatric population are taking place globally. This review identified 604 paediatric RCTs published in 2007 alone, a relatively large number compared to prior reviews. For instance Chan and Altman (2005) identified 37 paediatric RCTs from Pubmed published in December 2000, Cohen et al. (2007) identified a mean of 35 paediatric RCTs and 43 mixed age RCTs per year over a 20 year period (albeit only from 5 general medical journals), Sammons and Choonara (2005) identified between 93 and 127 clinical trials per year while Pandolfini and Bonati (2008) found 1149 reports over a 4 year period. This increased availability and exposure of paediatric RCTs should increase the evidence base for safe and effective use of paediatric medicines around the world.

Conducting paediatric RCTs require access to substantial resources (Steinbrook, 2002, Caldwell et al., 2004) and suitable expertise (Wilson, 1999, Gazarian, 2009). It is unsurprising that the majority of paediatric RCTs published in 2007 were conducted in rich or highly-developed countries. This is in agreement with the general trend in randomised and controlled trials over the past 60 years (Gluud and Nikolova, 2007) where trial publications predominantly originated from the USA, UK, Germany, Italy, Holland, Canada and France. Nonetheless, the relative obscurity of clinical research from poor and developing countries in medical journals has been lamented before (Horton, 2003) and Tutarel (2005) suggested that the editorial board composition of paediatric journals is contributory to this discrepancy.

Drug-related research is largely driven by commercial interest (Li et al., 2007) in which rich nations are the most relevant. However with the growing awareness that there is a much greater number of ill and dying children in poor and developing countries (Black et al., 2003, Bryce et al., 2005) opinion is growing that pharmaceutical research and development should address the greater need of people in poor nations (Cohen-Kohler, 2007). In recent developments, the WHO is playing a leading role with large campaigns to improve the situation with medicines in children on a global level (Watts, 2007, Choonara, 2008).

This review has established that there are increasing numbers of paediatric RCTs taking place in countries such as India, Turkey, Iran and Brazil. This adds to the mounting evidence of the globalisation of clinical trials (Thiers et al., 2008) although this may be again due to commercial reasons (Glickman et al., 2009) rather than public health concerns. Chapter 6 of this thesis will discuss in further depth on the global situation of paediatric RCTs in relation to the disease burden in children.

Encouragingly I have found a substantial number of multicentre and even multinational paediatric RCTs. That 44% and 16% of all the RCTs were multicentre and international respectively, represents a noteworthy advancement over the 1996-2002 period where 24% were multicentre trials and only 1% of trials were international (Sammons and Choonara, 2005). There appears a growing recognition of the importance and benefit of collaborative studies with national research networks coming to the forefront ((Nunn, 2009, Seibert-Grafe et al., 2009, Weber et al., 2009). There is now a major effort towards developing a global network of paediatric researchers (Koren et al., 2009).

Such cooperation is greatly welcomed and it is hoped that greater involvement of developing countries in addition to the established research centres in North America and Europe will enhance paediatric pharmacological research.

Campbell et al. (1998) first commented on the small sample sizes of paediatric RCTs. RCTs with small sample sizes is not limited to paediatric studies and is observed in RCTs generally (Chan and Altman, 2005). The concern with small sample sizes is that the trials would then be inadequately powered to detect differences between interventions, leading to unreliable evidence from meta-analyses of studies (Rerkasem and Rothwell, 2010). The median number of participants in this review was 89, which although an improvement over numbers reported by Campbell et al., (1998), was only slightly higher than reported by Chan and Altman (2005) and markedly lower than reported by Cohen et al. (2007).

This finding reinforces the importance of collaboration between paediatric researchers to obtain higher recruitment numbers and therefore greater statistical power, as well as better generalisation of RCTs results to the general paediatric population. This does not mean that small RCTs are unimportant; in fact valuable information can be obtained as long as *a priori* power calculations have been performed during the design period preceding the study. This is discussed further in the following chapter.

A major finding of this review is that many RCTs that involve both children and adults inadequately describe the characteristics of the paediatric participants. The heterogeneous paediatric population with differing pharmacokinetic and pharmacodynamic profiles compared to adults lends substantial credibility to the catchphrase ‘children are not small adults’ (Gidding, 2007, Klassen et al., 2008).

The omission of essential details such as the numbers and specific age groups of paediatric participants in such trials impacts negatively on the validity and generalisability of the evidence on the paediatric population. This finding strongly supports the conclusions of a large systematic review examining Cochrane reviews of drug intervention studies by Cramer et al., (2005); in which inadequate reporting of trials contributes to a paucity of child-relevant, child-specific evidence.

Funding declarations is another area where inadequate reporting has been discovered by this review. From the RCTs that declared their funding, roughly half were sponsored by pharmaceutical companies. This emphasises the crucial role of industry in paediatric drug research and development. Building upon the cooperation of paediatric researchers, global dialogue between academia, the pharmaceutical industry and regulatory authorities will be essential to improve healthcare for children (Rose, 2009).

There were relatively few RCTs involving neonates in the database. In contrast, drugs used in neonates are more likely to be unlicensed or off-label among the paediatric age groups. Conroy et al. (1999) were first to describe that 90% of neonates were given either off-label or unlicensed drugs. These high rates were later supported by many other studies (Pandolfini and Bonati, 2005). Moreover, neonates appear to suffer high rates of adverse drug reactions (Kaushal et al., 2001, Moore et al., 2002, Sammons et al., 2008, see also chapter 5). Hence, more research is needed to evaluate the appropriate amount and clinical areas regarding clinical trials involving neonates.

Previous concerns have been raised that studies conducted in children have been in drugs that confer high financial returns rather than in drugs that benefit children the most (Jong et al., 2001). It was noted that from the paediatric studies submitted to the FDA between 1998 and 2004, the highest numbers were in psychotropic drugs (31), anti-hypertensives (22) and studies of conjunctivis/rhinitis drugs (18). Only 11 studies of HIV drugs, 9 of drugs for respiratory infection and 6 studies on anti-malarials were submitted (Benjamin et al., 2006).

The many trials of anti-infective, antiparasitic and respiratory drugs were encouraging as they broadly correspond with the major target areas highlighted by the WHO 'make medicines child size' campaign. There was a preponderance of vaccine and asthma trials, which was again heartening considering the importance of these treatments for children worldwide (Shann and Steinhoff, 1999, Pearce, 2007).

There were large numbers of nervous system drugs in this review comprising mostly anaesthetics, analgesics and ADHD drugs. Anti-epileptics only account for slightly over 10% of the nervous system drugs studied despite reported figures that state 60-90% of people with epilepsy worldwide are untreated or inadequately treated, including vast numbers of children (Scott RA, 2001, Meinardi et al., 2001). This is also discussed in further detail in chapter 6.

5. CONCLUSION

This review has elucidated several important characteristics of paediatric drug RCTs published in 2007. There appear to be more RCTs involving children performed and reported than ever before. Most are conducted in rich and developed countries, but RCTs are increasingly globalised. The RCTs appear to study the appropriate clinical areas to improve treatments for important childhood diseases such as infectious illness and asthma. Several aspects of the RCTs need more attention. Concerns include reporting standards especially concerning mixed age group studies, small sample sizes relating to questionable statistical power of the studies and the dearth of studies involving neonates despite the high rates of adverse drug reactions and off label and unlicensed prescriptions in neonates. Greater cooperation between paediatric researchers worldwide, as well as constructive dialogue involving industry and regulators, promises to ensure continued advancement in paediatric RCTs to improve medicines in children.

CHAPTER 4: METHODOLOGICAL & REPORTING QUALITY

The collective effort to generate evidence for drugs used by the paediatric population is steadily gaining momentum, as seen in the previous chapter. However to assist clinical decisions made by health professionals, the evidence generated needs to be of sufficient quality, meaning that the results of RCTs need to be internally and externally valid. This would depend on the design and conduct of RCTs, but moreover health workers and policy makers need to be able to access such information. This chapter describes the assessment of methodological and reporting aspects of paediatric RCTs published in 2007. The main aim is to advance the process of translating evidence generated from paediatric RCTs into informed health care decisions.

1. INTRODUCTION

1.1 Methodological and Reporting Quality

Evidence based medicine is about the judicious use of current best evidence, in combination with clinical expertise, to make decisions on individual patients or on policies in public health (Sackett et al., 1996). This idea has long been embraced by the medical fraternity and there is a great effort ongoing to compile, analyse and synthesise evidence from the multiple types of clinical research, most prominently by the Cochrane Collaboration. As the highest level of evidence (see section 2.2.1), RCTs are the cornerstone of this work of systematically reviewing and meta-analysing numerous research to provide the best current evidence (Higgins and Green, 2009).

RCTs can be considered the 'foundation' of clinical evidence; their quality impacts greatly on the reliability of the reviewed evidence, and by extension directly on the health of patients. Thus the findings of a RCT need to be valid. There are two components involved; internal and external validity. Internal validity means that in a study where different groups of patients are given different drugs, the difference seen in the outcome can be fully attributed to the drug being studied (only apart from the unlikely occurrence of random error). External validity or generalisability relates to whether the results are applicable to the population where the drug is going to be used (Juni et al., 2001). Therefore the internal validity of a RCT depends on avoiding the introduction of biases (selection bias, performance bias, detection bias and attrition bias) while external validity closely relates to how well the RCT has been reported.

Studies have confirmed that methodological characteristics, for example the concealment of treatment allocation, affect results of clinical trials as well as the overall assessment of treatment effects. Schulz et al. (1995) and Moher et al. (1998) found that inadequate concealment of treatment allocation leads to a significant overestimation of treatment effect. Consequently the assessment of trial quality has been accepted as an important part of systematic reviews by the Cochrane Collaboration (Higgins and Green, 2009).

There have been many studies examining the quality of RCTs in various fields. In child health, Anttila et al. (2006) assessed the quality of reporting of 15 RCTs involving children with cerebral palsy and found that the reporting quality was largely inadequate. Thakur et al., (2001) reviewed all 642 papers published in two paediatric surgery journals in 1998 to examine methodological standards associated with quality reporting although the sample included only three RCTs. Moher et al., (2002) used three separate tools to assess a sample of 251 reports of complementary and alternative medicine RCTs involving children, and again found reporting quality to be insufficient.

The work mentioned above highlights two important points. Firstly that in most cases, the assessment of the methodological quality of a RCT is closely intertwined with the quality of reporting. Secondly that there seems to be a paucity of studies investigating the quality of RCTs of medicines involving the paediatric population. Therefore, this chapter aims to scrutinise the quality of RCTs of a broad range of drug treatments involving the paediatric population.

1.2 Protection of the Rights of Participants

The protection of the rights of participants is fundamental in modern clinical research as prescribed by the Declaration of Helsinki and is especially relevant when the research involves the vulnerable paediatric population (Goodyear et al., 2008). There is considerable interest in the ethical aspects of paediatric clinical research (Sammons, 2009, see also section 1.3.1) going back many years (Steinbrook, 2002).

Despite the presence of solid guidelines on the ethical conduct of paediatric clinical research (AAP, 1995, RCPCH, 2000), there have been concerns with the relatively low proportions of reports of child health research that document ethical approval and informed consent, as raised by Weil et al. (2002). Nevertheless, Bauchner and Sharfstein (2001) found that RCTs specifically had almost universally documented (97%) that ethical approval was obtained. On the other hand, the documentation of assent has been mostly ignored (Sifers et al, 2002) although there is growing opinion that it is an important ethical and regulatory requirement of RCTs (Ungar et al., 2006).

In addition to the quality aspects of the trials mentioned earlier, I also investigate the documentation of these important characteristics relating to the protection of trial participants, within RCTs in the database.

1.3 Formulation Information

Another unsatisfactory situation in paediatric pharmacology is the lack of suitable oral dosage forms particularly liquid forms and especially for younger children and infants (Nahata, 1999). Schirm et al. (2003) found that although approximately half of all paediatric prescriptions in the community were for oral medicines, paediatric formulations were often inadequate.

This problem closely relates to the large proportions of unlicensed and off label medicines used in paediatrics (see section 1.4). Frequently pharmacists are forced to resort to prepare extemporaneous formulations of drugs for children, with accompanying issues of excipients, dosing accuracy i.e. bioequivalence and bioavailability as well as efficacy, amongst others (Standing and Tuleu, 2005, Krause and Breitkreutz, 2008). Significant effort is under way to improve the availability of appropriate formulations for paediatric medicines (Knoppert, 2009).

Unfortunately, formulation information is often neglected in published reports of paediatric clinical trials. Standing et al. (2005) found that only 37% of reports of paediatric oral drug trials in 10 high impact medical journals gave adequate formulation information for the study to be replicated, and more than a quarter (26%) did not even state the formulation used. This is surprising considering that this information is needed for the findings to be valid. Dosage forms may vary for each drug being studied and different formulations can have different bioavailability.

Therefore, reports of the paediatric RCTs of oral medicines in this systematic review are analysed to determine whether appropriate formulation information has been documented.

2. METHODS

The overall comparison method of each RCT in the database was determined. The number of cross-over studies was also noted. The number of treatment arms in each study was identified.

2.1 Methodological and Reporting Quality

There have been numerous studies looking at the assessment of trial quality, specifically the tools used to measure quality. Moher et al. (1995) reported that there were 9 checklists and 25 scales available in the literature for assessing trial quality. With ongoing work this number has at least doubled (Jadad and Enkin, 2007). On the other hand, few of these tools have actually undergone validation to be used by reviewers. The most frequently used validated tool appears to be the Jadad scale (Jadad et al., 1996).

For this review, the Jadad scale has been selected for several reasons. Firstly the large numbers of reports require a scale that can be used effectively. Secondly the Jadad scale is numerical, allowing statistical analyses to be performed on findings from the review. Thirdly all the items in the Jadad scale can be incorporated into the CONSORT Statement (see later) so that RCT reports can be analysed efficiently for both methodological and reporting quality.

On the other hand, the Cochrane Collaboration explicitly discourages the use of the Jadad scale solely, seemingly due to apparent omission of the assessment of allocation concealment. They recommend the use of a 'domain-based' assessment of six specific domains of a certain RCT report developed between 2005 and 2007 (Higgins and Green, 2009). However this tool is much more complex and subjective compared to the Jadad scale despite admittedly providing a more rigorous assessment of the risk of bias.

Early in the course of the review, trial runs using the Cochrane Collaboration's tool revealed that they were time-consuming and perhaps more appropriate for smaller systematic reviews of a specific clinical research question. Consequently the decision was made to use the Jadad scale with a slight modification to enable a quick assessment of allocation concealment to be made.

This alteration entails that the fourth point of the Jadad scale, involving whether the randomisation sequence generation was adequate, to be conferred only if allocation was felt to be adequately concealed (for example using central allocation, sequentially numbered sealed envelopes or sequentially numbered sealed drug containers). Jadad scale items were identified using the data extraction form (see Chapter 2). Each RCT report was scored out of five. The following table details the Jadad scale items.

No	Item	Scoring
1	Was the study described as randomised?	1 point for 'yes' 0 point for 'no'
2	Was the study described as double-blind?	1 point for 'yes' 0 point for 'no'
3	Was there a description of withdrawals?	1 point for 'yes' 0 point for 'no'
4	The sequence for generating the randomisation was appropriate **and allocation of intervention was adequately concealed**	1 point for 'yes' 0 point for 'no'
5	The method of double blinding was appropriate	1 point for 'yes' 0 point for 'no'
	Total	Scored out of 5

Table 1: Validated Jadad 5-point scale, adapted from Assessing the Quality of Reports of Randomised Clinical Trials: Is Blinding Necessary? (Jadad et al., 1996).

The Consolidated Standards of Reporting Trials (CONSORT) statement was the culmination of a major effort by a group of trial investigators, methodology researchers and journal editors to improve reporting of RCTs (Altman et al., 2001). It is a checklist of 22 important items that must be included in a report of a RCT. In addition to the Jadad scale items, all of which are incorporated in the statement, several items of the statement have been adapted to assess reporting quality of the RCTs in this review specifically relating to methodology (some statement items are covered in the previous as well as the next chapter as they relate to the specific topics covered). The items were assessed using the overall data collection form for this systematic review. They are described in the following table.

Paper section and topic	Descriptor
Title and Abstract	Whether there was any description that the study involved the paediatric population
Methods: Interventions	Whether the dosages of the drug were mentioned Whether the dosages were described solely as mass for example in milligrams (mg) or other parameters were included for example scaled to bodyweight (mg/kg) or surface area (mg/m^3)
Methods: Outcomes	Whether a primary outcome measure was clearly defined
Methods: Sample size or power calculations	Whether sample size or power calculations were performed *a priori*
Results: Participant flow	Flow of participants through each stage The CONSORT flowchart must be included

Table 2: Reporting quality items adapted from the CONSORT statement (Altman et al., 2001)

2.2 Documentation of the Protection of Trial Participants

Each RCT report was carefully read to check that approval from ethical committees or institutional review boards was obtained and documented. It was also determined whether the trial reported that informed consent was obtained from the participants or care givers. RCTs that mentioned that assent of the eligible paediatric participant was noted, except in trials where this was not possible for instance in trials involving infants, emergency situations or where the participants were unconscious.

2.3 Formulation Information

For each report of a RCT of an oral drug, it was determined whether the dosage forms and the manufacturer of the drug used in the RCT was mentioned. When both were present, the formulation information was considered adequate and appropriate for paediatric use. For all oral drug RCTs where participants included children below 12 years of age, liquid formulations were judged to be appropriate. When solid formulations were used such as tablets or capsules, formulation information was considered adequate when an accompanying account of whether children were able to swallow the dose whole or how the dose was administered was given (Standing et al., 2005).

2.4 Statistical Analysis

As mentioned, all data were retrieved using the standardised collection form as detailed in Chapter 2. Statistical descriptors used included proportions, means and percentages. The Student's t-test was used in hypothesis testing for the differences between means arising from the analyses.

3. RESULTS

From the 604 RCTs identified, 242 (40%) were active-comparator trials where the main drug treatment studied was compared to another drug or other drugs. Thirty-five percent (213 trials) were placebo-controlled trials. A further 79 (13%) were trials comparing different dosing regimens or formulations of the same drug. The remainder consisted of RCTs with untreated controls, comparing different routes of administration or comparing to non-pharmacological interventions. The comparisons made by the RCTs are described in the following table.

Type of Comparison	Number (n)	Percent (%)
Drug vs drug	242	40
Drug vs placebo	213	35
Different dose/regimen/formulation	79	13
Untreated controls or vs withdrawal of treatment	46	8
Different route of administration	12	2
Compared to non-drug interventions	12	2
Total	604	100

Table 3: Types of comparison used by the RCTs

The majority, 441 (73%) trials, compared two parallel groups while the remaining 27% compared more than two intervention groups. There were 54 (9%) studies that used a cross-over design.

3.1 Methodological and Reporting Quality

Out of the 604 RCTs in the database, assessments for quality were made for the 582 RCTs with their full text in English. The remaining 22 RCTs were reported in several other languages and the limited access to translation resources precluded the analysis of these papers.

The mean Jadad score for the RCTs was 3.22 (Standard Deviation, SD=1.31). Sixty-six percent (383) studies scored 3 or more out of 5, 10% (58 RCTs) and 24% (141 RCTs) scored just 1 and 2 points respectively. The final Jadad scores for the RCTs can be seen in the following table.

Jadad Score (out of 5)	Number of trials (n)	Percent (%)
1	58	10
2	141	24
3	134	23
4	112	19
5	137	24
Total	582	100

Table 4: Jadad scores of the RCTs

*non-English language reports were not scored due to limited resources for translation

There was no significant difference in the mean Jadad scores of RCTs involving neonates compared to RCTs of older children (two tailed p-value=0.8410).

Group	Neonatal RCTs	Non-neonatal RCTs
Mean Jadad Score	3.268	3.218
Number of trials (N)	41	541

Only RCTs were included in this systematic review, therefore all the reports scored the first point on the Jadad scale. Looking at the other four items on the Jadad scale, scoring rates ranged between 49% and 67%. Scoring rates of individual items can be seen in the next table.

Jadad Score Item	Studies scoring point (n)	Item absent (n)	Percent of studies scoring point (%)
Was the study described as randomised?	582	0	100
Was the study described as double blind?	309	273	53
Was there a description of withdrawals and dropouts?	391	191	67
Was the method to generate the sequence of randomisation described and appropriate?*	316	266	54
Was the method of double blinding described and appropriate?	282	300	49

Table 4: Individual items of the Jadad scoring system

**and allocation of intervention was adequately concealed*

In almost one-fifth (111, 19%) of the RCT reports, there was no indication in either the title or abstract that the study involved the paediatric population. All were mixed age group studies that recruited both adults and patients 16 years old and below. Except for 10 (2%) reports, all of the trials (572, 98%) documented the dosages used. Almost half (285, 49%) of the studies scaled the dose according to body weight, while a further 25 trials (4%) reported that doses were scaled according to body surface area. The remaining 262 trials described doses in singular mass, volume or concentration units.

Description of dose	Number (n)	Percent (%)
Bodyweight included e.g. mg/kg	285	49
Mass/volume/concentration only	262	45
Surface area included	25	4
Not described	10	2
Total	582	100

Table 5: Description of doses in the RCTs

It was felt that the primary outcome measure or measures were clearly defined in 354 (61%) of the RCT reports. An almost identical number of trials (358, 62%) documented that *a priori* sample size or power calculations were performed. A diagram or chart describing the flow of participants through each and every stage of the RCT (as recommended by the CONSORT statement) was available in 223 (38%) of the reports.

3.2 Ethical Approval and Informed Consent

From the 582 reports examined, 528 (91%) described that the study obtained approval from an ethics committee or an institutional review board. Ninety-seven percent (537 reports) declared that informed consent was received. In 128 (22%) of the reports, it was mentioned that assent from the child was obtained or that consent was obtained directly from the participants aged 16 and below. Looking specifically at studies recruiting adolescents aged 12 to 16 years, 109/366 (30%) RCTs documented that assent was sought.

3.3 Formulation information

Out of 226 RCTs of oral drugs, 145 (64%) included information regarding the formulation used, while only 86 (38%) described the manufacturer of the drug used. Thus information on drug formulation was judged to be adequate in 86 out of 226 (38%) of the oral drug RCTs.

4. DISCUSSION

High quality RCTs form the foundation of scientific evidence for the use of paediatric medicines. This review has found that overall, drug RCTs involving the paediatric population published in 2007 are of good quality, scoring a mean of 3.22 points on the Jadad scale.

RCTs scoring 3 points and above are regarded as being of good quality as it has been shown previously that studies that score 2 points and below produce exaggerated treatment effects of up to 35% beyond those of good quality studies (Moher et al., 1998). Unfortunately over one-third of the RCTs in this systematic review scored less than 3 points on the Jadad scale, representing a significant proportion of trials that may provide sub-optimal evidence for paediatric medicines. Furthermore when the key components of methodological quality are examined individually, several areas were identified where improvements are needed.

Just slightly over half of the RCTs were described as being double blind. Double blinding involves ensuring RCT participants, investigators as well as the treatment providers and outcome assessors are unaware of the assigned intervention (Boutron et al., 2006). This is needed to prevent major biases from being introduced; such as performance bias when there may be unequal care provided apart from the drug being evaluated (Juni et al., 2001), and ascertainment bias where the results of the trial are influenced by the knowledge of which intervention each participant is receiving (Jadad and Enkin, 2007).

Although not all RCTs are appropriate to be double-blinded, this result echoes that of Schulz et al. (1996), where only half of trials in obstetrics and gynaecology that could have been double-blinded were actually double-blinded. Schulz et al. (1996) also found that the studies that were double blind reported their blinding methods poorly and did not evaluate the success. Further evidence to this effect came from Boutron et al. (2005).

Thus it is felt that there should be greater awareness of the need for double blinding by investigators and sponsors of RCTs involving paediatric participants, considering there exists empirical evidence that double blinding affect estimates of treatment effect (Schulz et al., 1995).

In fact double blinding may be needed to prevent wrong conclusions being made following a RCT (Noseworthy et al., 1994). In addition, blinding techniques for RCTs have been well documented for both drug trials (Boutron et al., 2006) and non-drug trials (Boutron et al., 2007). Nevertheless, it was found that in the large majority of the RCTs that were double blind, the method of double blinding was described appropriately, with 282/309 or 91% of the double blind trials scoring the final point on the Jadad scale.

Two-thirds of RCTs in the database described patient withdrawals and dropouts. By knowing how many participants withdrew and the reasons for withdrawal, readers can assess whether the randomisation procedure has been conducted properly as imbalances in these occurrences between treatment groups can point to bias (Altman et al., 2001). This information is also important for the 'intention-to-treat' analysis to be made. This analysis basically entails including all randomised patients irrespective of whether they completed the treatment protocol (Hollis and Campbell, 1999).

Thus ‘intention-to-treat’ impacts on external validity by allowing the effects of a drug treatment to be estimated in the general population instead of the idealised situation of a clinical trial. On the other hand, only just over one-third of the RCTs included a full chart of patient flow through the trial as recommended by the CONSORT statement. Such a flowchart guarantees transparency to allow ‘intention-to-treat’ analyses where descriptions in the text have been often be found to be inadequate (Egger et al., 2001).

A major criticism of the Jadad score that has been used here is that it neglects to assess the concealment of treatment allocation during the randomisation process (Higgins and Green, 2009). The landmark study by Schulz et al. (1995a) discovered that studies with inadequate allocation concealment yielded significantly larger treatment estimates of up to 41% compared to studies where allocation concealment was concealed adequately. This finding supported the hypothesis that significant bias can be introduced into trials that do not conceal treatment allocation. For example, selection bias can be a distinct possibility, either as a result of deliberate subversion (despite being well intentioned) or unintentionally (Schulz, 1995a). This results from trial investigators who are aware of treatment allocations. They may channel participants with a better prognosis to the experimental group and poorer prognosis to the control group, by delaying a patient’s entry until the desired allocation, or by excluding or refusing entry to eligible participants (Schulz et al., 1995b).

Therefore the decision was made to assess the concealment of treatment allocation of RCTs in this systematic review and incorporate the assessment into the fourth item on the Jadad scale. Allocation concealment is also an important item on the CONSORT checklist, being item 9 out of the 22 point checklist.

As with double blinding, only just over half of the RCTs were deemed to have an appropriate randomisation sequence that was adequately concealed. Again, this requires attention so that the estimated effects of drug treatments being studied are not exaggerated, thus yielding inaccurate evidence.

Another criticism with the Jadad scale is that it is more a reflection of reporting quality rather than methodological quality. This has been a long-standing argument and it was felt that many of the tools described by Moher et al. (1995) that are used to assess trial quality, were liable to confuse reporting and methodological quality (Higgins and Green, 2009). A study by Huwiler-Muntener et al. (2002) assessed 60 RCTs and found that studies with similar reporting quality can have important differences in methodological quality. On the other hand, other authorities are of the opinion that methodological quality of a trial is intertwined with the quality of reporting (Juni et al., 2001).

Rather than dwelling on the arguments, I have taken a pragmatic view for this study. For health professionals, the reports of RCTs (and resulting systematic review or meta-analyses) are usually the only way of learning the results of the trials conducted, for the evidence to be used in clinical practice. It is felt that both methodological quality and reporting quality are essential. Furthermore with the ongoing efforts of medical journal editors to improve reporting quality for example the CONSORT statement (Altman et al., 2001) as well as the increasing oversight of RCTs through trial registers (Sammons et al., 2005, Pandolfini and Bonati, 2009), reporting quality should move closer to reflect methodological quality. Thus no separate analysis of the two was attempted for this systematic review.

This systematic review has found that paediatric-specific reporting is another area that requires improvement, particularly for RCTs that recruited both from the adult and paediatric populations. In chapter 3, it was seen that these mixed age group RCTs did not describe paediatric participant numbers nor their age group categories appropriately. In this chapter it was found that in almost one-fifth or 111 of the RCTs in the database, there was no indication in either the title or abstract that the trial recruited from the paediatric population. This represents a significant body of evidence that may be missed by busy health care professionals.

It was found that 61% of RCTs from the database designated a clear primary outcome measure. The primary outcome measure is the pre-specified outcome measure considered to be the most important to patients, clinicians, policymakers and trial sponsors (Moher et al., 2010). For many diseases, there may be a multitude of ways to measure the effects of a treatment. When a primary outcome measure is described in a RCT report, it allows the reader to determine the appropriateness or accuracy of the outcome measure being used. More importantly, findings from the RCT can then be compared to other trials within the disease area or using related treatments (Altman et al., 2001).

The documentation of *a priori* power or sample size calculations is closely related to having a designated primary outcome measure, as power calculations are based on the primary outcome. It was found that a similar number, less than two-thirds of the RCTs in the database, documented the calculations. Thus it seems an important characteristic of RCTs regarding statistical significance is inadequately reported in paediatric RCTs.

This problem is lamented across numerous medical specialities (Halpern, 2005, Charles et al., 2009). With sample size calculations being neglected, compounded with the generally low number of participants in paediatric RCTs (see chapter 3), there is a significant possibility of underpowered trials. In underpowered trials, patients endure the burden as well as the risk of clinical experimentation, but without being able to provide valid and generalisable evidence for better healthcare. Needless to say this situation is regarded as being unethical (Halpern et al., 2002).

As would be expected, the reporting of dosages used was nearly universal. Nearly half of the trials reported doses scaled to body weight and several more scaled according to body surface area. This use of allometric technique probably indicates the situation in which many drug doses used in paediatric populations are based on incomplete or no pharmacokinetic data (Abernethy and Burckart, 2010). No single allometric technique has proven to be the most appropriate (Mahmood, 2006, Johnson, 2010). Nonetheless despite the many complexities of conducting pharmacokinetic studies in the paediatric population (Anderson et al., 2007), it is hoped that ongoing pharmacokinetic work will continue to contribute to the growing initiatives aiming to improve drug treatment for children (MacLeod, 2009).

The findings on formulation information from this study almost mirror those of Standing et al. (2005). Formulation information appropriate for the paediatric population is largely neglected in clinical trials, highlighting a much wider problem with the inadequacy of paediatric oral dosage forms in general (Mulla et al., 2007).

Examples can be severe; such as when toxic excipients led to the deaths of many children in Nigeria during the Mypikin tragedy (Bonati, 2009) to the 4 children under 36 months who died from choking on albendazole tablets during a deworming campaign in Ethiopia (WHO, 2007). The 'Make medicines child size' campaign by the WHO (Knoppert, 2009) promises to make significant strides in the effort to change this reality.

It was encouraging that except for a tiny minority, RCTs in the database documented that informed consent was obtained and that 91% received ethical or institutional review board approval. This agrees with the findings by Bauchner and Sharfstein (2001). There should be a greater effort by medical journal editors to require all paediatric RCTs to document that informed consent and ethical approval was attained. This is in concert with Bauchner's (2002) opinion that structured reporting of ethical committee or institutional review board approval would further the protection of paediatric participants in clinical trials. However less than one-third of studies involving adolescents appear to document that assent was received. There is now a greater recognition of the autonomy of the paediatric participant in trials (John et al., 2007, Ungar et al., 2006, see also Chapter 1) and future work will need to explore whether there is increased awareness amongst investigators and sponsors regarding assent especially among older children.

5. CONCLUSION

The work done for this chapter has made several discoveries that deserve highlighting. Most paediatric drug RCTs published in 2007 seemed to be of good methodological quality. However several important design characteristics of the trials need further attention so that the resulting evidence is valid as well as generalisable to improve the use of medicines in the paediatric population. These include double blinding, adequate concealment of treatment allocation, as well as appropriate power or sample size calculations. Furthermore, it is felt that more effort is required to ensure that these RCTs report paediatric specific information for example the inclusion of paediatric age groups, formulation information appropriate for children and the documentation of assent in trials where older children are involved. The evidence based use of medicines in children requires high quality, ethical and well reported RCTs involving the paediatric population.

CHAPTER 5: SAFETY

The preceding chapters have highlighted that appropriate, high quality paediatric randomised controlled trials (RCTs) are needed to provide the evidence base for medicines used by children so that they benefit from, and are not harmed, by the medicines. In this chapter, paediatric RCTs published in 2007 are analysed to document adverse events experienced by the participants and assess whether adverse drug reactions occurred. In addition I attempt to ascertain whether adequate measures were taken to safeguard RCT participants from harm. Therefore this chapter explores the following aspects of RCTs involving the paediatric population; toxicity occurring within the RCTs, the protective measures put in place, and implications of the safety information obtained from the RCTs to the paediatric population in general. The objective is not only to identify areas of improvements so that paediatric participants are less at risk of toxicity in RCTs, but also to determine whether adequate safety information is contributed by the RCTs for the safe use of medicines in children.

1. INTRODUCTION

As mentioned in preceding chapters, changes in US and European drug regulation have created a stimulatory environment for paediatric drug trials to be performed (Smyth, 2007, Hoppu, 2008, Saint-Raymond and Seigneuret, 2009). As a result larger numbers of paediatric RCTs have been conducted (Sammons et al., 2008); providing valuable information for the judicious use of medicines in children (Roberts et al., 2003, Rodriguez et al., 2008). However when participating in clinical drug trials, paediatric patients are exposed to a risk of experiencing adverse drug reactions (ADRs) (Sammons et al., 2008, Turner et al., 1999). This risk is a concern for parents, clinicians, investigators, trial sponsors and regulatory agencies. This is especially important considering the vulnerable nature of the paediatric participants and that their participation in a clinical trial is by proxy consent of their caregivers (Caldwell et al., 2004, Smyth and Weindling, 1999, Sammons et al., 2007, Kodish, 2003).

There have been a good number of studies looking at ADRs occurring in the paediatric population. For instance, Bourgeios et al. (2009) reported on paediatric ADRs in the outpatient setting throughout the US. Clavenna and Bonati (2009) reviewed prospective studies of paediatric ADRs following on from Impicciatore et al.'s (2001) earlier meta-analysis of paediatric ADRs. Choonara and Conroy (2002) and Neubert et al. (2004) reviewed paediatric ADRs in relation to unlicensed and off label drugs. There have been many pharmacovigilance studies (Choonara, 2006) by other research groups (Horen et al., 2002, Cohen et al., 2008, Le et al., 2006, Kaushal et al., 2001, Moore et al., 2002, Jha et al., 2007, Fattahi et al., 2005 – see section 5 of chapter 1).

However to my knowledge, the only major effort to characterise toxicity experienced by paediatric patients in *clinical trials* was performed by Sammons et al. (2008). This landmark study reviewed more than 700 clinical trials of oral or intravenous drugs over a 7 year period between 1996 and 2002. Adverse events (AEs) were common and were found in 71% of the trials while 1 in 5 (20%) trials reported serious adverse events. Adverse drug reactions (ADRs) were determined to have occurred in more than 1/3 (36.5%) of the trials, with severe ADRs judged to have occurred in 5%.

Six of the trials were halted by independent oversight bodies after severe ADRs were experienced. These bodies are usually termed as safety monitoring committees, SMCs (EMEA, 2005) or data safety monitoring boards, DSMBs (DeMets et al., 1999) and their important role was clearly demonstrated. Yet a major finding of Sammons et al. (2008) was that only 2% of all the trials had a SMC/DSMB in place. This was in contrast to the significant proportions of trials with AEs or ADRs. Another major finding was the high rates of ADRs and mortalities seen in neonatal trials.

Therefore I aim to provide an update on drug toxicity and reappraise the presence of SMCs/DSMBs in paediatric RCTs. By analysing a wider set of RCTs including HIV/Oncology RCTs as well as including RCTs of drugs administered other than through the oral or IV routes, this review hopes to build upon Sammons et al.'s (2008) work in characterising ADRs occurring within the RCTs. Furthermore, this chapter also looks at the reporting of AEs and ADRs by paediatric RCTs, in the context of the growing concern with the apparently inadequate reporting of information on safety or harms in RCTs overall (Ioannidis, 2009).

2. METHODS

The definitions used for this study largely follow on from those used by Sammons et al. (2008). However several additions were made to the analysis.

2.1 SAFETY CHARACTERISTICS

Each paediatric RCT report from my database was analysed to evaluate the following safety aspects:

1. Safety Monitoring

It was assessed whether safety monitoring was mentioned in the methods section of each. Any mention of the words ‘safety’, ‘adverse effect/event/experience/reaction’, ‘side/unwanted effect’, ‘toxicity’ or any indication that adverse events were monitored for was noted.

2. SMC/DSMB and Terminated or Amended Trials

Each paper was then checked to determine whether a safety monitoring committee (SMC), data safety monitoring board (DSMB) or an independent safety evaluator was present to oversee the trial. In addition, it was determined whether any interim analysis (Fossa and Skovlund, 2000) was performed or whether stopping rules (Hedenmalm et al., 2008) for the trials were designated. These were assumed to be present whenever a SMC/DSMB is mentioned.

Any trial that was discontinued was also noted and the reason for discontinuation was determined. Any RCT that reported an alteration to the study protocol arising from an interim analysis or from new information/alerts arising from newly published reports or from the SMC/DSMB of the RCT itself was recorded.

3. Adverse Events (AEs) and Mortalities

Whether any adverse events were detected were determined from carefully reading the results section. The definition and classification of adverse events (AEs) used in this study was based on guidelines produced by the European Agency for the Evaluation of Medicinal Products (EMEA, 2001) in compliance with the International Conference for Harmonisation (ICH).

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (EMEA, ICH topic E2A, 1995). AEs are classified as serious, significant or mild according to the following groupings:

i) Serious AE - any untoward medical occurrences at any dose that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

ii) Significant AE - defined as haematological and other laboratory abnormalities and any AE that led to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

iii) Mild AE - defined as any AE occurring that did not need any intervention.

The most serious AE in each report was determined and used to stratify the trials. The number of papers reporting any mortality was recorded. In particular, any RCTs which indicated a positive trend in mortality in the intervention group or non-placebo comparator groups were noted.

4. Adverse Drug Reactions (ADRs)

An ADR is defined as an adverse event that is thought to be linked in either time or dose to a drug given to that patient (Turner et al., 1999, Sammons et al., 2008). Each randomised trial included in this study was assessed as to whether a possible ADR had occurred and were classified according to the highest severity of ADR in the report.

The classification used for ADRs are as follows:

1. Severe: fatal or potentially life threatening or causing permanent disability
2. Moderate: requiring treatment or prolonging stay in hospital
3. Mild: no treatment required and no effect on length of stay in hospital.

All trials reporting a serious AE (SAE) were further reviewed by two paediatric clinical pharmacologists, Professor Imti Choonara and Associate Professor Helen Sammons, independently to judge whether any of the serious AEs were possible ADRs. The decision by each reviewer was noted and all differing ratings were discussed at a meeting to obtain a consensus expert opinion.

2.2 ANALYSIS

1. ATC Drug Categories

The proportion of RCTs that reported an SAE, mortality or where a severe or moderate ADR was judged to have occurred, was calculated for each ATC drug category. This was done to assess whether certain types of drugs (or disease categories) were associated with a higher incidence of toxicity within RCTs involving children.

The proportions of RCTs reporting SAEs were cross tabulated to the median sample size of paediatric participants from RCTs in each ATC category. This was done to determine whether an artefactual relationship existed due to chance, in the assumption where a higher number of SAEs would occur naturally with greater participant numbers. For example if a certain ATC category consisted of mostly large trials, the hypothesis would be that this category would contain a higher number of SAEs due to the larger population sizes thus confounding the effect of the drug type.

2. Age Group Categories

The above comparison was also performed for each ICH age group category to assess whether a certain age group (especially neonates) experienced a higher incidence of toxicity or mortality within the RCTs.

3. SMCs/DSMBs

Trials reporting serious AEs, mortalities or that were determined to have encountered severe or moderate ADRs, were compared to the rest of the RCTs in the database in terms of whether SMCs/DSMBs were documented.

4. Statistical Analysis

Data from each report were retrieved using a standardised data extraction form (provided in chapter 2) then stored and analysed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were described with frequencies, percentages and 95% confidence intervals. The degree of agreement between reviewers was described by the Kappa coefficient (κ). Fisher's exact test was used to calculate p-values for differences in proportions. The Spearman's rank correlation coefficient rho (r_s) was used to check whether there were any associations between the safety characteristics and sample size populations of the RCTs.

3. RESULTS

582 paediatric randomised drug trials were analysed. The 22 RCT reports in the database that had an English abstract but where the main text was not in English were excluded.

3.1 SAFETY CHARACTERISTICS

1. Safety Monitoring

More than a third (207, 36%) lacked any description of how safety was observed during the study while the other 375 (64%) trials mentioned safety monitoring in the methods section.

In the results section 463 (80%) of the trials reported on adverse events including studies reporting that no adverse events had occurred, while 119 (20%) of the trials had no description of adverse events.

2. SMCs/DSMBs and Terminated or Amended Trials

Only 69 out of the 582 (12%) reports documented that a SMC, DSMB or independent safety evaluator was designated to oversee the trial. An additional eight trials mentioned either termination rules or that interim analysis was done but without specifically mentioning the presence of a SMC/DSMB.

SMCs terminated three RCTs due to toxicity and changed the protocol of one trial after an episode of toxicity. Another trial was halted for administrative reasons. Details of these terminated trials or where SMCs/DSMBs took action can be seen in table 1.

Author	Drug studied	Comparator	Disease	Age group	N	Action Taken by SMC/DSMB
Lands et al.	Ibuprofen high-dose	Placebo	Cystic Fibrosis	6-18 yrs	142	Protocol changed by SMC/DSMB H2-antagonists recommended after 1 patient had gastrointestinal (GI) bleed
Van Meurs et al.	Inhaled nitric oxide	Placebo	Preterms with severe respiratory failure >1500g	<34 weeks Gest	29	Terminated due to risk of grade 3 or 4 intraventricular haemorrhage (IVH), in conjunction with other evidence in the literature In trial 2 patients in placebo arm had IVH
Lorch et al.	Seq high-dose chemotherapy	Single. high-dose chemo	Relapsed/ refractory germ cell tumour	16-59 yrs	211	Terminated due to excess toxicity in comparator arm Treatment-related deaths was 4% in study arm vs 16% in comparator arm, p=0.01
Sullivan et al.	Recombinant human epidermal growth factor 1-48	Placebo	Severe Necrotizing Enterocolitis	neonates <12 weeks	8	Terminated due to "administrative reasons unrelated to the conduct of the trial"
Bonsante et al.	Low-dose hydrocortisone	Placebo	Prevention of chronic lung disease in preterms	Preterms 24-30 weeks	50	Terminated due to emerged external evidence of risk of GI perforation In trial 2 neonates in treatment arm & 1 in placebo arm developed GI perforation

Table 1: Teminated trials and where SMCs/DSMBs altered the protocol

3. Adverse Events and Mortalities

From the 463 RCTs that reported on AEs, 41 (7%) reported that no AEs occurred within the trial. These were overwhelmingly small and short duration RCTs. The remaining 422 RCTs that did document AEs, were then categorised according to the most serious AE described within the RCT.

Thus 210 (36%) RCTs reported serious AEs occurring within the trial (table 2). 87 (15%) RCTs reported mortality occurring within the trial (table 2).

Category of most serious Adverse Event (AE)	Number (n)	Percent (%)
SERIOUS	210	36.1
Significant	70	12.0
Mild	142	24.4
No AEs experienced	41	7.0
AEs NOT DOCUMENTED BY REPORT	119	20.4
TOTAL	582	100.0

Table 2: Grade of AEs documented in the trials

4. Adverse Drug Reactions (ADRs)

Of the total of 582 trials, ADRs were considered to have occurred in 305 (52%) of the studies. A further 141 (24%) were determined to have experienced no ADRs. In the remaining 136 (23%) RCTs, it was impossible to judge whether ADRs were suffered by the participants, these were mostly where the report did not describe AEs.'Most of the trials were judged to contain mild ADRs (160, 28%). However either moderate or severe ADRs were determined to have occurred in 79 (14%) and 66 (11%) of trials respectively (table 3).

Category of Adverse Drug Reactions (ADRs) judged to have occurred	Number (n)	Percent (%)
SEVERE	66	11.3
MODERATE	79	13.6
Mild	160	27.5
None	141	24.2
UNABLE TO ASSESS	136	23.4
Total	582	100.0

Table 3: ADRs judged to have been suffered by participants in the RCTs

Independent examination of 210 reports containing serious AEs (SAEs) demonstrated ‘moderate’ agreement between the two paediatric clinical pharmacologists as to whether ADRs had occurred ($\kappa = 0.49$, 95% CI 0.31-0.59). Several meetings resulted in a concensus opinion for each RCT that was initially rated differently. The remaining 372 were rated by myself. Back-testing of my own ratings revealed an agreement level of 83.8% (differing in 34/210 or 16.2% of the ratings) in the judgement of whether an ADR had been experienced, compared with the joint expert opinion.

The severe ADRs detected in the RCTs included most of the major organ systems. Chemotherapy-related toxicities were the most prominent (table 4). Other severe ADRs detected were cardiotoxicity, nephrotoxicity, psychiatric symptoms including suicidal ideation, haematotoxicity including neutropaenia, thrombocytopaenia and leucopaenia, steroid related ADRs, gastrointestinal bleeding and infections (tables 5 – 7).

Table 4: Paediatric RCTs where severe ADRs were detected (ATC Group L: antineoplastic and immunomodulating agents)

No	Drug	Control/Comparator	Disease	Age	Severe ADRs
946	Doxo,Bleo,Vinb,Dacarbazine + RT	No Rx RT only	Hodgkin's Lymphoma	16-75yrs recruited	Leucopaenia, cardiotoxicity, inadequate details on events
1001	Invasive chemo with high-dose cytarabine & methotrexate (ONCO)	Std post-remission rx	ALL	12 months & below	Sepsis, nephrotoxicity, hepatotoxicity, neurotoxicity
1169	Seq high-dose chemo (ONCO)	Single. high-dose chemo	Relapse/ refractory germ cell tumours	16-59 yrs	Multiple chemotherapy related toxicities, trial terminated due to excess mortality in arm B
1238	Intensified maintenance chemo. (ONCO)	No treatment	Post-remission Acute Promyelocytic Leukaemia	15-70yrs	Excess death rate in treatment arm, 15%v3%
1286	ChemoRT with carboplatin (ONCO)	ChemoRT with cisplatin	Locoregionally advanced Ca nasopharyngeal	16-70 yrs	Sepsis
1493	Different chemo regimes (ONCO)	As noted	B-cell non-Hodgkin lymphoma	2.5-20.5 yrs	Multiple chemotherapy related toxicities and deaths
1494	8-course CHOP regimen (ONCO)	6-course intensified CHOP regimen	Agressive non-Hodgkin lymphoma	16-65 yrs	Multiple chemotherapy related toxicities and deaths
1496	Reduced intensity chemo (ONCO)	Standard intensity FAB chemo	High-risk CNS non-Hodgkin B lymphoma and B acute lymphoblastic leukaemia	6 mo – 21 yrs	Sepsis and haemorrhages
1897	ABX-CBL hybridoma-gen. murine IgM monoclocal antibody (ONCO)	Antithymocyte globulin	Steroid-resistant acute graft-vs-host disease	2-65 yrs	Neutropaenia, pneumonia
1956	Etoposide-Ifosfamide + HD MTX (ONCO)	Doxorubicin + HD MTX	Osteosarcoma	3.1-19.5 yrs	Multiple chemotherapy related toxicities
1988	GM-CSF (ONCO)	No Rx	Priming for Induction regime for ALL	15-50 yrs	Multiple chemotherapy related toxicities and deaths
2180	High Dose Methotrexate Intrathecal (ONCO)	Low dose Methotrexate intrathecal	Chemotherapy for acute lymphoblastic leukaemia	1.5-15 yrs	Neurotoxicity
2233	Chemo regimen (ONCO)	Chemo regimen	Osteosarcoma	4-41 yrs	Chemotherapy related toxicities and deaths

2245	Vincristine pulses + dexamethasone (ONCO)	Untreated controls	ALL continuation rx	Younger than 18	Chemotherapy related toxicities and deaths
99912	Chemo regimens (ONCO)	Other chemo regimens	Early-stage Hodgkins	15-70 yrs	Cardiotoxicity and second malignancies
8882108	Cyclophosphamide + antithymocyte globulin	Cyclo alone	Conditioning regimen for bone marrow transplant	<10-60 years	Chemotherapy related toxicities and deaths

Table 5: Paediatric RCTs where severe ADRs were detected (ATC Groups J&P: antiinfectives for systemic use and antiparasitic drugs)

No	Drug	Control/Comparator	Disease	Age	Severe ADRs
317	Liposomal AmB + Caspofungin	Lipo AmB (hi-dose)	Invasive Aspergillosis – haem. Malignancies	16-75 years	Nephrotoxicity – inadequate details of event
575	Nifurtimox-eflornithine	Eflornithine	Sleeping sickness Trypanosoma brucei gambiense	15-70 years	Neutropaenia 1v6
957	Amphotericin B 1mg/kg vs 0.75mg/kg alt day vs 1mg/kg vs 0.75mg/kg daily		Indian visceral leishmaniasis	2-65 yrs	Nephrotoxicity, hepatotoxicity, thrombocytopaenia
1228	Paromomycin	Amphotericin B	Visceral leishmaniasis	5-55 yrs	Hepatotoxicity, ototoxicity, nephrotoxicity
1262	Anidulafungin	Fluconazole	Invasive candidiasis	16-91 yrs	Convulsions
1409	Amodiaquine+SP OR Amo+artesunate	Artemether-lumefantrine	Uncomplicated falciparum malaria	1-10 yrs	Convulsions
1908	Artemether-lumefantrine	Dihydroartemisin-piperaquine	Drug resistant falciparum and vivax malaria	1-60 years	Sudden death, ?cause
2178	Posaconazole	Fluconazole/Itraconazole OR Fluconazole OR Itraconazole	Prophylaxis of fungal infection in neutropaenic patients	13-82 yrs	Cardiac arrhythmias
888147	Gatifloxacin	Cefixime	Uncomplicated Enteric fever	2-65 yrs	Thrombocytopaenia
888507	Human rotavirus vaccine	Placebo	Rotavirus gastroenteritis	6-14 weeks	Possible intussusceptions
888839	Hep A vax + hexavalent combi vax	Hep A vax + separate vax	Prophylaxis	Infants	Serum sickness
888950	Inhaled Zanamivir	Placebo	Prophylaxis of influenza	12 yrs & above	Bronchitis
8881448	4 groups : Choroquine (CQ) 50mg vs Amodiaquine (AQ) 15mg vs AQ 30 mg v CQ 25 mg		Uncomplicated malaria	2-177 months	Convulsions
8881482	Live Att. rotavirus vaccine	3 different virus concentrations VS placebo	Prophylaxis	6-12 weeks	Intussusception
8881788	HPV vaccine	Hep A vax	Prophylaxis	15-25 years	Infectious events and abnormal pregnancy

Table 6: Paediatic RCTS where severe ADRs were judged to have occurred (ATC Group N: nervous system drugs)

No	Drug	Control/Comparator	Disease	Age	Severe ADRs
161	Levetiracetam	Placebo	Idiopathic generalised epilepsy	4 to 65 years	Suicidal ideation
298	Venlafaxine ER	Placebo	Paed Social Anxiety Disorder	8-18 years	Suicidal ideation
521	IV Valproate	IV Diazepam	Status epilepticus	5-144 months	Respiratory depression
593	Bupropion X 2 doses	Placebo	Smoking cessation	14-17 yrs	Depression, suicidal ideation
710	IV Valproate	IV Phenytoin	Status epilepticus	2-17 yrs	Hypotension and respiratory depression
754	Fluoxetine	Placebo	Adolescent depression	12-17 yrs	Suicidal ideation and events
766	Olanzapine	Placebo	Bipolar Mania	13-17 yrs	Neutropaenia, possible suicidal ideation and exacerbation of bipolar disorder
771	Idebenone X 3 doses	Placebo	Friedreich's Ataxia	9-17 yrs	Neutropaenia
1793	Lamotrigine OR Topiramate (SANAD trial)	Valproate	Gen and unclassifiable epilepsy	5 years & above	Severe psychiatric symptoms
1794	Carbamazepine OR Gabapentin OR Lamotrigine (SANAD trial)	Oxcarbazepine OR Topiramate	Partial epilepsy	5 yrs & above	Severe psychiatric symptoms
2130	Venlafaxine	Placebo	Generalised Anxiety Disorder	6-17 yrs	Suicidal ideation
888587	Multidrug Intravenous Anaesthesia (Midazolam, Ketamine, Propofol)	General Endotracheal Anaesthesia(Propofol,Vecuronium,Isoflurane)	MRI scanning	1-7 years	Respiratory depression

Table 7: Paediatric RCTs where severe ADRs were detected (remaining ATC drug groups)

No	Drug	Control/Comparator	Disease	Age	Severe ADRs
78	Deferiprone PO Desferrioxamine IV	Deferiprone PO	Thalassemia major	5-24.5 Years	Cardiotoxicity & neutropaenia
244	Continuous Subcut Insulin Infusion	Multiple Daily Injections	Type 1 DM	3.1 to 5.3 years	Hypoglycaemia
723	Dexa. IV vs Dexa+Glycerol PO vs Glycerol PO	Vs Placebo IV + PO 4 arms Double dummy for all	Bacterial meningitis	2-184 months	Gastrointestinal bleeding
799	Continuous SC Insulin Inj. (Aspart/Lispro Insulin – quick acting)	Multiple Daily Inj. (Glargine OD + human Insulin)	Type 1 DM	9-18 years	Hypoglycaemia
873	Ibuprofen high-dose	Placebo	Cystic Fibrosis	6-18 yrs	Gastrointestinal bleeding
894	Amifostine	No treatment	Chemo for Osteosarcoma (toxicity protection)	7-15 years	Nephrotoxicity
965	Levocetirizine	Placebo	Atopic children	12-24 months	Possible convulsions
1253	IV Terbutaline	Placebo (NSaline)	Status asthmaticus	2-17 yrs	Cardiac arrhythmia
1772	Glimepiride	Metformin	Type 2 DM	8-17 yrs	Hypoglycaemia, ketoacidosis
2001	Idursulfase	Placebo	Mucopolysaccharidosis II (Hunter Syndrome)	6-20 yrs	Respiratory depression
2076	Mometasone inh 400mic vs 800 mic vs Placebo		Severe persistent asthma	13-83 yrs	Steroid related ADRs
2078	Dexrazoxane	No Dexrazoxane	Prevention of cardio-pulmonary toxicity during chemo of paed Hodgkins	21 yrs and younger	Higher risk of second malignancy
2328	Magnesium sulphate	Placebo	Neuroprotection after traumatic brain injury	14 above	Excess mortality in treatment group
888217	Steroid for 3 days + Tacrolimus, mycophenolate, basiliximab induction	Steroid maintenance	Immuno Suppression for live-donor renal transplant	5-60 years	Steroid related ADRs

888476	Budesonide/formoterol	Salmeterol/fluticasone	Uncontrolled asthma	12 above	Sepsis steroid-related
888928	Dexa OR glycerol OR dexa+glycerol	Placebo	Bacterial meningitis	2mo – 12 yrs	Gastrointestinal bleeding

Severe ADRs were considered to have occurred in seven of the RCTs that involved neonates. As seen in table 1, two of these RCTs were terminated by their respective SMCs (Van Meurs et al., 2007, Bonsante et al., 2007). The other severe ADRs seen in the neonatal studies were necrotising enterocolitis (NEC), growth retardation, pulmonary and CNS haemorrhages and hypertension (table 8).

Table 8: Paediatric RCTs involving neonates where severe ADRs were considered to have occurred

Record No	Drug studied	Comparator	Disease	Age group	Severe ADRs
675	Ibuprofen PO	Indomethacin PO	Patent Ductus Arteriosus	Preterms	NEC
1330	Prednisolone PO daily	IV methypred monthly	Infantile haemangioma	<4 months	Growth retardation and hypertension
1396	Ibuprofen PO	Indomethacin IV	Patent Ductus Arteriosus	<35 weeks gest	Pulmonary haemorrhage
1401	Inhaled nitric oxide	Placebo	Preterms with severe resp failure	<34 weeks gest	Grade 3 or 4 IVH/PVL – trial terminated
1865	Drotrecogin alfa	Placebo	Severe sepsis	38 weeks to 17 years	Fatal CNS bleeding
8881295	IV immune globulin IHN-A21	Placebo	Prevention of Late Onset Sepsis in LBW neonates	Prem. Neonates	Multiple SAEs considered possible ADRs
8881837	Low-dose hydrocortisone	Placebo	Prevention of chronic lung disease in preterms	Preterms 24-30 weeks	Gastrointestinal perforation – trial terminated due to risk

3.2 ANALYSIS RESULTS

1. ATC Drug Categories

The RCTs were evaluated in relation to SAEs and the type of drugs studied. Cardiovascular drug RCTs had the highest proportion of trials reporting SAEs with 69% (9/13) of the trials documenting SAEs occurring (table 9). This was followed by the antineoplastic and immunomodulating drug category, 68% (28/41) reporting SAEs occurring within their RCTs. Systemic anti-infective drugs had the third highest proportion of RCTs reporting SAEs occurring with over half (58/101, 57%) of the RCTs mentioning SAEs.

WHO ATC Drug Class	Proportion reporting SAE (n/total)	Percent (%)
Cardiovascular system	9/13	69
Antineoplastic and immunomodulating agents	28/41	68
Anti-infectives for systemic use	58/101	57
Blood and blood forming organs	7/15	47
Systemic hormonal preparations,excl. sex hormones and insulins	18/42	43
Respiratory system	25/74	34
Antiparasitic products,insecticides and repellents	15/45	33
Alimentary tract and metabolism	12/41	29
Musculo-skeletal system	5/20	25
Genito urinary system and sex hormones	1/4	25
Nervous system	24/155	16
Dermatologicals	5/40	13
Sensory organs	1/10	10
Various[#]	2/3	67
Total	210/582	36

Table 9: Proportion of RCTs in each ATC class reporting SAE(s)

[#]2 out of 3 were oncology RCTs – amifostine in osteosarcoma and dexrazoxane in AML/MDS (amifostine and dexrazoxane are not classified as antineoplastic or immunomodulating agents)

When looking at RCTs reporting deaths occurring within RCTs, the same three drug classes predominate (table 10). RCTs of antineoplastic drugs and immunomodulators carried the highest proportion of mortality occurring with 23 out of 41 (56%) reporting deaths during the trial. Almost half of cardiovascular drug RCTs (6/13, 46%) and a quarter of systemic anti-infective RCTs (25/101, 25%) reported deaths during the trial period.

One of the four RCTs (25%) in the genitourinary and sex hormones category reported SAEs and deaths occurring. This was a RCT of oestradiol and progesterone replacement on extremely preterm neonates where the median birth weight of the neonates was just 670g and the median gestational age was 25 weeks (Trotter et al., 2007).

WHO ATC Drug Class	Proportion reporting mortality (n/total)	Percent (%)
Antineoplastic and immunomodulating agents	23/41	56
Cardiovascular system	6/13	46
Anti-infectives for systemic use	25/101	25
Genito urinary system and sex hormones*	1/4	25
Blood and blood forming organs	3/15	20
Antiparasitic products,insecticides and repellents	8/45	18
Systemic hormonal preparations, excl. sex hormones and insulins	6/42	14
Sensory organs	1/10	10
Alimentary tract and metabolism	3/41	7
Respiratory system	4/74	5
Nervous system	5/155	3
Dermatologicals	-	-
Musculo-skeletal system	-	-
Various[#]	2/3	67
Total	87/582	15

Table 10: Proportion of RCTs in each ATC class recording death(s) in the trials

*Effect of oestradiol and progesterone replacement on bronchopulmonary dysplasia in extremely preterm infants (Trotter et al., 2007)

[#]2 out of 3 were oncology RCTs – amifostine in osteosarcoma and dexrazoxane in AML/MDS (see chapter 3)

SAEs and mortality may not be drug related. The ATC drug class in relation to severe and moderate ADRs is shown in table 11. Drugs used in the treatment of malignancies were considered the most toxic in the paediatric RCTs. Of the 41 RCTs of antineoplastic and immunomodulating drugs, 17 (42%) were judged to have severe ADRs and a further 6 (15%) were judged to have moderate ADRs experienced by participants. In RCTs of other drug categories rates of severe ADRs were markedly lower, with 15% (2/13) of cardiovascular drug RCTs judged to have severe ADRs followed by antiparasitic agents and blood products, both with 13% (6/45 and 2/15) considered to have severe ADRs.

WHO ATC Drug Class	Severe ADR (n/total)	Percent (%)	Moderate ADR (n/total)	Percent (%)
Antineoplastic and immunomodulating agents	17/41	42	6/41	15
Cardiovascular system	2/13	15	1/13	8
Antiparasitic products,insecticides and repellents	6/45	13	1/45	2
Blood and blood forming organs	2/15	13	2/15	13
Alimentary tract and metabolism	5/41	12	5/41	12
Systemic hormonal preparations,excl. sex hormones and insulins	5/42	12	5/42	12
Anti-infectives for systemic use	9/101	9	20/101	20
Nervous system	12/155	8	15/155	10
Musculo-skeletal system	1/20	5	2/20	10
Respiratory system	5/74	7	10/74	14
Dermatologicals	-	-	9/40	23
Genito urinary system and sex hormones*	-	-	2/4	50
Sensory organs	-	-	1/10	10
Various[#]	2/3	67	-	-
Total	66/582	11	79/582	14

Table 11: Proportion of RCTs where severe & moderate ADRs were detected

*Effect of oestradiol and progesterone replacement on bronchopulmonary dysplasia in extremely preterm infants (Trotter et al., 2007)

[#]2 out of 3 were oncology RCTs – amifostine in osteosarcoma and dexrazoxane in AML/MDS (see chapter 3)

2. Crosstabulating to Sample Size

The percentage of trials reporting SAEs in each ATC class was crosstabulated with the median number of patients in each ATC class (table 12). This was done to detect whether the size of the study populations in the ATC categories is associated with the number of SAEs reported by the trials. The median was chosen over the mean of the sample population sizes as large ranges in the study sizes can skew the mean, for instance the mean of 5 trials with the following sample sizes: 5, 17, 21, 43, 3005 would be 618 which does not reflect the actual distribution.

WHO ATC Drug Category	Median Sample Size	Proportion reporting SAE (%)
Anti-infectives for systemic use	240	57
Antiparasitic products,insecticides and repellents	202	33
Sensory organs	200	10
Dermatologicals	174	13
Genito urinary system and sex hormones	117	25
Antineoplastic and immunomodulating agents	103	68
Systemic hormonal preparations,excl. sex hormones and insulins	68	43
Nervous system	67	16
Respiratory system	64	34
Cardiovascular system	51	69
Musculo-skeletal system	54	25
Alimentary tract and metabolism	46	29
Blood and blood forming organs	46	47
Various*	478	67

Table 12: Mean and Median Sample Sizes of RCTs in each ATC category

*treated as outlier but included in calculations for Spearman's rho (r_s)

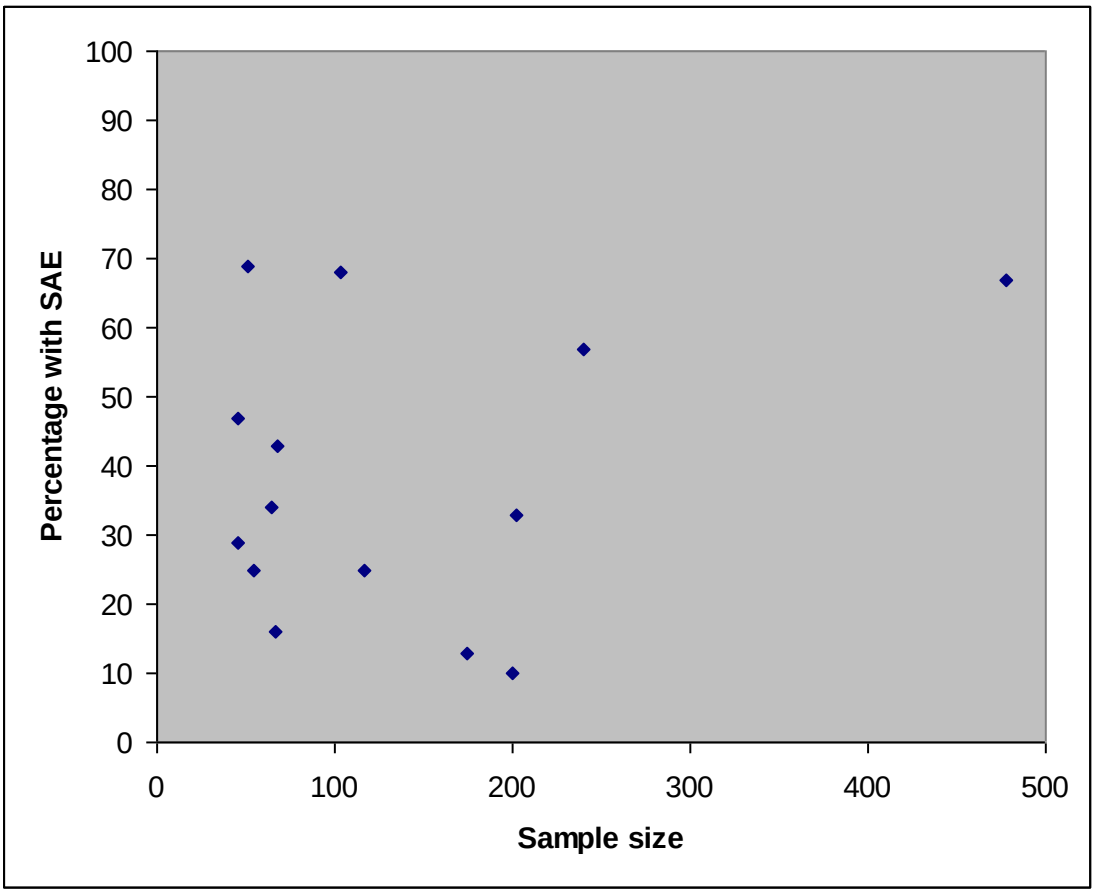


Chart 1: Scattergraph plotting median sample size and percentage reporting SAE of each ATC drug category

Following crosstabulation, the Spearman's rank correlation coefficient rho (r_s) was found to be -0.0529 with a two-tailed p-value of 0.860156 (N=14, df=12). This value is far from r_s=1 or -1 which would indicate perfect correlation between the two variables. Therefore there appears to be no correlation between the sample sizes of RCTs in each ATC category and the proportion of SAEs reported in the trials. Where more RCTs of certain ATC classes such as antineoplastic, cardiovascular and anti-infective drug classes were seen to report SAEs, the results show that this could not to be due to the confounding effect that these RCTs were larger, and therefore more likely due to probability alone to encounter SAEs.

3. Age Group Categories

Overall, 41 trials included neonates (both preterm and term) while 541 trials did not involve neonates. Analysis of data from table 13 show that significantly more RCTs involving neonates reported that SAEs (51% vs 35%, p=0.043) occurred, compared to trials that did not involve neonates.

ICH age group*	Trials reporting SAEs (n)	Total no. of trials involving age group (n)	Percent (%)
Preterm	18	25	72
Term	7	22	32
Infant	59	151	39
Child	121	389	31
Adolescent	132	357	37

Table 13: Proportion of RCTs involving each age group reporting SAEs

*Age groups of participants in many trials overlap the ICH categories

This was also seen for trials that reported deaths (table 14). A significantly higher percentage of trials that involved neonates reported mortality occurring within the trial (39% vs 13%, p<0.01).

ICH age group*	Trials reporting mortality	Total no. of trials involving age group	%
Preterm	16	25	64
Term	3	22	14
Infant	23	151	15
Child	47	389	12
Adolescent	56	357	16

Table 14: Proportion of trials in each ICH age group where deaths were recorded

*Age groups of participants in many trials overlap the ICH categories

Severe ADRs were detected in a higher proportion of RCTs involving neonates compared to trials that did not involve neonates, although this difference was not statistically significant (15% vs 12%, p=0.4475). Studies involving neonates had a lower median number of patients participating in the RCTs compared to the trials that did not involve neonates (60 vs 90).

ICH age group*	Trials with severe & moderate ADRs detected (n)	Total no. of trials involving age group (n)	Percent (%)
Preterm	7	25	28
Term	2	22	9
Infant	16	151	11
Child	38	389	10
Adolescent	51	357	14

Table 15: Proportion of trials in each ICH age group where severe and moderate ADRs were detected

*Age groups of participants in many trials overlap the ICH categories

RCTs involving both paediatric and adult patients reported significantly more SAEs and deaths occurring (table 16). Significantly more severe and moderate ADRs were also detected in these mixed-age population trials.

Trial type	RCTs with deaths	RCTs with SAEs	Severe & Moderate ADRs detected
Mixed	21%	41%	33%
Not mixed	12%	32%	20%
Significance	p<0.01	p=0.05	p<0.01

Table 16: AEs, mortality and severe and moderate ADRs in mixed-age population RCTs

4. SMCs/DSMBs

It was then evaluated whether SMC/DSMBs were more likely to be put in place if serious adverse events or significant toxicity were expected during the trial. It was found that significantly more trials that mentioned a SAE occurring, documented that a SMC/DSMB was present in comparison to trials that had no or non-serious AEs (55/210, 26% vs 14/372, 4%) (table 17).

	SMC/ DSMB present	No SMC/ DSMB	Total
RCTs with SAEs	55	155	210
RCTs without SAEs	14	358	372
Total	69	513	582

Fisher's exact test, $p<0.05$

Table 17: 2x2 table comparing RCTs with SMCs/DSMBs that reported SAEs

Similarly, significantly more trials in which severe or moderate ADRs were detected, mentioned that a SMC/DSMB was formed (41/145, 28% vs 28/437, 7%) (table 18) .

	SMC/ DSMB present	No SMC/ DSMB	Total
RCTs with severe & moderate ADRs	41	104	145
RCTs without mild or no ADRs	28	409	437
Total	69	513	582

Fisher's exact test, $p<0.05$

Table 18: 2x2 table comparing RCTs with SMCs/DSMBs where severe and moderate ADRs were detected

4. DISCUSSION

This work to characterise and analyse toxicity occurring in recent paediatric RCTs has revealed some interesting results. More than one-third of RCTs in the study report serious adverse events (SAEs) occurring and deaths occured in 15% of the trials. These SAEs and mortalities are not necessarily linked to the drug treatment being studied and may actually be a feature of the disease processes or background levels of risk unrelated to the therapy in the study. However when the adverse events were assessed to determine their relationship to the drugs being trialled, severe or moderate adverse drug reactions (ADRs) were considered to have occurred in a quarter of the RCTs. As pointed out by Sammons et al. (2008) previously, these findings do not indicate the risk of paediatric participants experiencing ADRs in RCTs, but merely the proportion of RCTs where ADRs were detected.

Put together, severe and moderate ADRs were seen in a quarter (24.9%) of the RCTs in this review. Severe ADRs were considered to have occurred in 11% of the RCTs, more than double the percentage from the Sammons review. This difference is likely to be due to the inclusion of oncology RCTs in this review, which were excluded in the Sammons review.

Severe ADRs were seen in many organ systems. Most have been documented in the literature such as the many chemotherapy related toxicities, steroid related ADRs and gastrointestinal bleeding related to high dose NSAIDs. Suicidal ideation relating to SSRIs in paediatrics have also been extensively discussed (Hammad et al., 2006, Bridge et al., 2007). An independent SMC/DSMB plays an important role by constantly reviewing and being alert to emerging toxicity evidence. This was exemplified in two of the four terminated RCTs in this review (Van Meurs et al., 2007 and Bonsante et al., 2007).

However only 12% of the RCTs documented that a SMC/DSMB was designated to oversee the trial. This result, in conjunction with Sammons et al.'s (2008) finding, further highlights the apparent absence of SMCs/DSMBs in RCTs involving children despite the evidence of toxicity described above. Occasionally in RCTs, initial data can suggest possible harmful effects i.e. toxicity rather than the beneficial effects being looked for. The interpretation and handling of these emerging harms is complicated and challenging, therefore a SMC/DSMB would be best suited to deal with this information (DeMets et al., 1999).

It was found that significantly more studies with SAEs had independent SMCs/DSMBs, and this was also seen with studies where severe and moderate ADRs were detected. However this appears to be a 'the chicken or the egg' scenario; in which it was unclear whether RCTs with SMCs/DSMBs had more rigorous safety monitoring mechanisms, or that when toxicity was expected, investigators would be more likely to form SMCs/DSMBs to oversee the trial. Although more research is needed to explain this apparent association, there are many examples of previous clinical trials that attest to the important role of SMCs/DSMBs in protecting the safety of participants (Hillman and Louis, 2003, Pocock et al., 2004, Pocock et al., 2005, Hedenmalm et al., 2008).

The examples cited also describe the challenging situations faced by SMCs/DSMBs especially when trying to decide whether a trial should be stopped. On the other hand, there is presently extensive literature on the vital role of a SMC/DSMB and how it should function (Slutsky and Lavery, 2004, Pocock 2006). There is also a charter developed by the DAMOCLES Study Group (2005) as well as operational guidelines by the WHO (2005) to assist SMC/DSMBs in monitoring clinical trials. These guidelines as well as robust stopping rules are important as SMC/DSMBs would always need to be wary of false toxicity signals. As in the study by Sammons et al., (2008), this review has revealed several instances where SMCs/DSMBs acted to terminate potentially harmful RCTs or modified protocols in the interest of safety.

The low proportion of paediatric RCTs that document the presence of SMCs/DSMBs appear in stark contrast. There is a strong ethical argument that all clinical trials, except for the smallest and most straight-forward studies, should have SMCs/DSMBs in place (Cairns et al., 2001). This argument is even harder to dispute when paediatric populations are involved in clinical trials (Sammons, 2009). Furthermore, SMC/DSMBs are now becoming a regulatory requirement (EMEA, 2005). Hence it is felt that all RCTs involving vulnerable populations need SMCs/DSMBs (Lang et al., 2008), in this case all RCTs involving the paediatric population.

As expected, RCTs of drugs used in treating cancer were found to be associated with the most toxicity; with a much higher proportion of RCTs where severe ADRs were detected compared to RCTs of other drug classes. This finding probably relates to the more complex and aggressive disease processes as well as the use of more toxic pharmacotherapy being studied in the trials. Nevertheless, the valuable information gained from these trials has been demonstrated before, leading to a massive difference in survival outcomes (Mitchell, 2007 – see section 3.3 of Chapter 1). It was reassuring that severe ADRs were relatively infrequent overall in paediatric RCTs of other drug classes; ranging from zero to 15% of RCTs where severe ADRs were judged to have occurred.

Significantly more SAEs and mortalities were seen in RCTs where neonates were studied. This was also seen in Sammons et al.'s (2008) review. Interestingly when the adverse events were assessed, the difference in severe and moderate ADRs detected in trials involving neonates compared to older children were found to be non-significant. Perhaps this indicates the more vulnerable nature of neonates, especially preterm neonates, rather than higher toxicity in the drugs being used. More research is needed to elucidate ADRs in neonates. Previous reviews of ADRs occurring in hospitalised children have not detected any differences between the rates of ADRs in neonatal units compared to other wards (Turner et al., 1999, Impicciatore et al., 2001, Le et al., 2006). However this could be explained by the different ADR detection methods used. In fact the various ADR detection methods used in different studies make an accurate estimation of ADR prevalence in the paediatric population a challenging task (Clavenna and Bonati, 2009).

Information on toxicity obtained in paediatric trials can be extremely valuable to improve the safety of medicines prescribed to the paediatric population. From a review of paediatric clinical trials submitted to the US FDA to obtain paediatric exclusivity, it was found that out of the 33 studies reviewed, 9 (27%) resulted in significant new safety information that led to labelling changes. Safety data were collected from all of the 33 studies (Roberts et al., 2003).

However the effort to improve safety of paediatric medicines would benefit greatly from the adequate reporting of safety data from paediatric RCTs. In my review, more than one-third of the RCTs did not describe how safety was monitored in the trial and one-fifth did not even describe adverse events.

It was also found that significantly more adverse events, moderate and severe adverse drug reactions were experienced in RCTs with mixed age populations where both adult and paediatric patients were included. However, as commented upon in chapter 3, most of these studies do not adequately report the characteristics of the paediatric-aged participants such as numbers for each ICH age category of the participants.

In most of these reports, it was not possible to ascertain whether the adverse event was suffered by an adult patient or a paediatric patient. This is felt to be an important omission that needs to be highlighted, as adverse events or reactions suffered by a paediatric patient can bring different implications to those suffered by an adult. For instance during a drug RCT, a new occurrence of hypertension is viewed very differently if it is experienced by a 12 year old compared to a 60 year old. Additionally, metaanalysis of the findings at a later date may provide extra evidence on toxicity specifically for the paediatric population. If this information is not available, this opportunity would therefore be missed.

Journal publications are the 'public face' of RCTs conducted and when the two experts could only achieve a moderate agreement when rating the safety information, this might indicate more standardised and transparent reporting of safety data is needed (Ioannidis et al., 2004). However, the reasonably high rate of agreement of the consensus expert ratings with my own ratings for the 210 RCTs with SAEs provided a measure of confidence for the remaining 372 RCT without SAEs that I rated independently.

In more than 23% of the RCTs, whether ADRs had occurred was not able to be determined. This represents a large gap where important safety data is unavailable to be evaluated. In fact, this apparent disinterest with safety information from randomised trials points to a much wider trend. Adult RCTs are far more numerous than paediatric ones (Martinez-Castaldi et al., 2008, Cohen et al., 2006) and this trend has been lamented in all RCTs recently by Ioannidis (2009). He reviewed 11 empirical studies evaluating the reporting of harms in randomised trials and found that the reporting of harms occurring were mostly inadequate.

Randomised controlled trials are an important source of toxicity information, and in conjunction with non-randomised or observational studies (Smith et al., 2008), provide essential insights for the assessment of safety of medicines used in the paediatric population (Ashby, 2008). Thus in addition to providing the evidence base on the efficacy of drug treatments, RCTs are also important in large-scale evidence of the harms of interventions (Papanikolaou and Ioannidis, 2004, Papanikolaou et al., 2006). More research on the safety data or information on harms obtained from RCTs is needed to support recent efforts by regulators (Greener, 2008) as well as globally by the WHO (Choonara, 2008) to improve the safety of medicines used by children.

5. CONCLUSION

In conclusion, this chapter has revealed that although many paediatric RCTs report SAEs and mortalities occurring, drug toxicity is detected in a lesser portion of the trials. By far the greatest number of severe ADRs is seen in RCTs of drugs used to treat cancer, likely to be related to the toxic nature of chemotherapy. The findings from this work reiterate that more attention should be paid to the presence of SMCs/DSMBs; in fact it is felt that all paediatric clinical trials should be overseen by SMCs/DSMBs. Another area requiring more attention is the reporting of safety information from RCTs, especially in large RCTs where both adults and children are involved. Safer paediatric RCTs require better oversight and improved reporting of toxicity information from RCTs would allow better evaluation to make medicines safer for children.

CHAPTER 6:
THE GLOBAL SITUATION

Throughout the writing of this thesis, it became increasingly evident that despite exciting changes occurring in the field of paediatric clinical pharmacology to enhance the safe and judicious use of medicines in the paediatric population, a crucial discrepancy came steadily into focus. Overwhelmingly the world's sickest children, who stand to benefit the most from medicines to treat their diseases, live in poor countries. They live in very different circumstances and also suffer from different diseases to paediatric populations living in resource-rich nations, where the majority of health research is conducted. Concurrently another trend became apparent where there is a noticeable shift of clinical trials to low and middle income countries (LMIC), postulated to be due to increasingly higher costs and regulatory requirements in high income countries (HIC). This chapter discusses the situation of published paediatric RCTs in relation to paediatric health on a global level.

1. INTRODUCTION

The greatest burden of disease in the paediatric population lies overwhelmingly in low and middle income countries (LMIC). In 2003, the Bellagio Child Survival Study Group estimated that almost all of the more than 10 million deaths in children younger than five occurred in LMIC (Black et al., 2003). The largest proportion of deaths occurred in the first 28 days of life, with 3.9 million neonates dying. Another 51% of the deaths were caused by 5 diseases; pneumonia (19%), diarrhoea (17%), malaria (8%), measles (4%) and HIV/AIDS (3%) (Bryce et al., 2005).

More than half or about 6 million of these children died of preventable or treatable diseases (Anon., 2003). The Bellagio group concluded that even with the most conservative assumptions, 63% of these deaths could have been prevented with child survival interventions already available (Claeson et al., 2003). There have already been substantial improvements to the situation. The latest figures by UNICEF (2009) show that the overall annual under-five mortality rate has already fallen to 8.8 million in 2008. Nonetheless almost all these deaths still occur in LMIC, with Africa and Asia accounting for more than 90% of the deaths.

This situation reflects the absence or failure of healthcare infrastructure in these countries. A closely related discussion refers to the '10/90 gap' where the Global Forum for Health Research reported that only 10% of worldwide expenditure on health research and development is devoted to the problems that primarily affect the poorest 90% of the world's population (Global Forum for Health Research, 1999).

The ‘10/90 gap’ became the group’s catchphrase to demonstrate the continuing mismatch between the needs and investments, where health research applied to the needs of LMIC remains grossly underresourced, in areas that account for the greatest burden of preventable disease.

The Bellagio group estimated in 2003 that interventions needed to save the 6 million children from dying of preventable causes would cost US$5.1 billion or about US$887 per child life saved (Bryce et al., 2005a). The focus of the group is on scaling up delivery of existing interventions known to be effective rather than on health research development. Nevertheless, improving delivery systems of life-saving interventions to children and mothers as well as the development of clinical research would bring about synergistic effects to the overall health of the paediatric population living in these resource-poor areas.

Thus paediatric clinical pharmacology has the potential to make substantial contributions to the health and survival of children living in LMIC. The International Alliance for Better Medicines for Children (Macleod et al., 2007) has received support from numerous quarters including from the WHO with the passage of the World Health Resolution on Better Medicines for Children and the launch of the Make medicines child size campaign (MacLeod, 2009). A further indication of the relevance of the field is seen from recommendations made by the Copenhagen consensus (2008). This was an effort by the world’s leading economists to prioritise the world’s problems overall, not just related to health, in which MacLeod (2009) noted that from the 20 top measures considered most likely to be cost effective globally, nine directly relate to improving drug therapy for children.

There is now a rapidly evolving situation where clinical research is becoming increasingly globalised. Although commented on in some external literature, this trend has almost developed without being noticed in the medical literature with hardly any related publications documenting this growing trend in MEDLINE as described by Thiers et al., (2008). However their data shows that it is a real and growing phenomenon, largely caused by cost savings for the biopharmaceutical industry and also emerging research infrastructure in rapidly developing LMIC.

Further evidence supporting this changing situation came from Glickman et al. (2009). They discovered that for industry-sponsored phase 3 clinical trials conducted by the 20 largest U.S.based drug companies, about one-third were performed solely outside the United States and more than half of study sites were outside the U.S. They also found that from 300 reports of clinical trials published in the New England Journal of Medicine (NEJM), the Lancet and the Journal of the American Medical Association (JAMA); the proportion of trials conducted in the U.S. and Western Europe decreased, while the number of countries where trial sites were located, particularly developing countries, more than doubled between 1995 and 2005.

Profound questions are being asked about the ethical and scientific implications of this globalisation of clinical trials. Glickman et al. (2009) asks; who benefits from this trend? What is the potential for exploitation of research subjects? Are the resulting findings valid and generalisable to other settings?

All these issues build the context of work for this chapter. The aim is to examine paediatric drug RCTs in relation to the global health situation for the paediatric population and also the increasing globalisation of clinical trials.

2. METHODS

2.1 Setting the scene

For this chapter, the first step was to outline the global burden of disease in the paediatric population from the most recent data. Although under-five mortality features prominently in the literature, for example by the Bellagio study group and UNICEF, it was felt a wider view was needed to provide the background for the analysis of paediatric RCTs considering that this systematic review included older children as participants including adolescents. Furthermore, it was felt important to understand how non-fatal diseases contributed to the burden of disease and what differences can be seen between different country or regional groups.

The Global Burden of Disease project was initiated in 1990 and is a massive effort undertaken by several organisations including the WHO and the World Bank to provide estimates of morbidity and mortality data by age, sex and region, with the overall aim to guide health policy decisions (Murray and Lopez, 1996). The project collected comprehensive epidemiological data from each country on disease prevalences and causes of death; each country volunteered information from registries or health authorities and where information was scanty, modelling techniques were used to provide estimates on causes of death.

Mortality data regarding causes of death was categorised using the ICD-10 system into three broad groups by the project researchers, they were described as group I - communicable, maternal, perinatal and nutritional conditions, Group II – noncommunicable diseases and Group III – injuries.

In addition to reporting data on mortality, the project introduced a single parameter called the Disability-Adjusted Life Years (DALY) as a single measure to quantify the burden of diseases, injuries and risk factors. The DALY reflects both the potential years of life lost due to premature death and also the years of life lost due to being in poor health or disability. Therefore one DALY reflects one year of healthy life lost due to premature death or disease.

DALYs = The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.

Within the project, countries were classified according to gross national income per capita and analysed according to two major groups comparing high income countries (HIC) to low and middle income countries (LMIC). Four broad age categories were used; neonates and children younger than five (0-4 years of age), older children (5-14 year olds), adults (15-59 year olds) and the elderly (60 years and above).

To provide the background for comparisons of data from my systematic review, information regarding disease-related mortality and DALYs from the project was reviewed and summarised for the two paediatric age groups namely the 0-4 year olds and the 5-14 year olds. Mortality classified to be caused by Group III – injuries were excluded for these two age categories. Thus paediatric disease-related mortality and DALYs were obtained for the country income categories.

2.2 Review of paediatric RCTs published between 1996 and 2002

A previously constructed database of RCTs involving oral and intravenous medicines in children was reanalysed (Sammons et al., 2008). The method of identifying relevant RCTs for the Sammons database has already been described. Briefly, they used the Cochrane Collaborations highly sensitive search strategy to search MEDLINE for paediatric RCTs published between 1996 and 2002.

For this current study, the full journal articles of the published RCTs contained in the Sammons database were re-examined to determine the country setting, disease studied, and main therapy being trialled, as well as the funding source and ethical approval where mentioned. The main disease and the main drug being studied were recategorised according to ICD-10 and WHO ATC systems respectively.

Country locations of the RCTs were stratified according to the United Nation's Human Development Index (HDI) categories, sourced from the Human Development Report of 2002 (data from year 2000). The HDI is a composite of important indicators of human development comprising life expectancy, literacy rate, education enrolment and gross domestic product (see chapter 2). Countries are given a single score; 0.8 and above are classed as highly developed, 0.5-0.79 considered medium development and below 0.49 classed as low development.

Medium and low HDI countries were grouped as developing countries. In addition to the aforementioned characteristics of the trials, data on the presence of SMC/DSMBs and ADRs, were also compared between the developed and developing countries.

2.3 Paediatric drug RCTs published in 2007 according to country settings

Country settings of paediatric RCTs compiled in the current systematic review were previously categorised according to HDI (2007) and World Bank per capita income levels of the year 2007 (see section 3.2).

The following characteristics of the RCTs were compared between trials conducted in the different HDI and World Bank income categories:

i. sample population sizes

ii. types of disease areas of the trials according to the ICD-10 system

iii. types of drugs being studied according to the ATC system

iv. funding sources

v. Jadad score of the RCTs

vi. documentation of sample size or power calculations

vii. inclusion of a patient/CONSORT flowchart

viii. documentation of ethical approval, informed consent and assent

ix. mention of safety monitoring

x. presence of SMC/DSMBs

xi. occurrence of serious adverse events (SAEs) and mortality in the trial

xii. adverse drug reactions (ADRs) judged to have been experienced

2.4 Comparisons to burden of disease data

Characteristics of paediatric RCTs from both datasets namely those published from 1996 to 2002 and in 2007 were related to data obtained by the Global Burden of Disease project regarding disease prevalences as well as disease-related burden and mortality. For the first database of trials published between 1996 and 2002, the burden of disease report published in 2006 (Lopez et al., 2006 - data obtained up to 2001) was used while for the second database of trials published in 2007, the latest WHO report on the global burden of disease published in 2008 was used (WHO - data obtained from 2004).

The major comparisons made were between high income countries (HIC) versus low and medium income countries (LMIC) of the World Bank income groupings (World Bank, 2007), as well as between developed (high HDI) and developing countries (medium and low HDI).

2.5 Statistical Analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for storage and analysis of data. Means were compared using the unpaired t-test. The chi-squared test was used to examine the statistical significance of differences between multiple groups. Differences in proportions were compared using Fisher's exact text with two-tailed p values, which was also used when differences between multiple groups involved small numbers.

3. RESULTS

3.1 The Global Burden of Disease in Children

The latest report from the Global Burden of Disease project was published in 2008 utilising data collected from the year 2004 (WHO, 2008). When data from this report was analysed, it revealed that the vast majority of the paediatric population live in low and middle income countries (LMIC). More than 1.6 billion children live in LMIC while there are about 180 million children living in HIC (table 1).

Overall, almost 11 million children died of disease in LMIC in 2004. This compares dramatically to the 86,000 disease-related deaths in the paediatric population occurring in HIC.

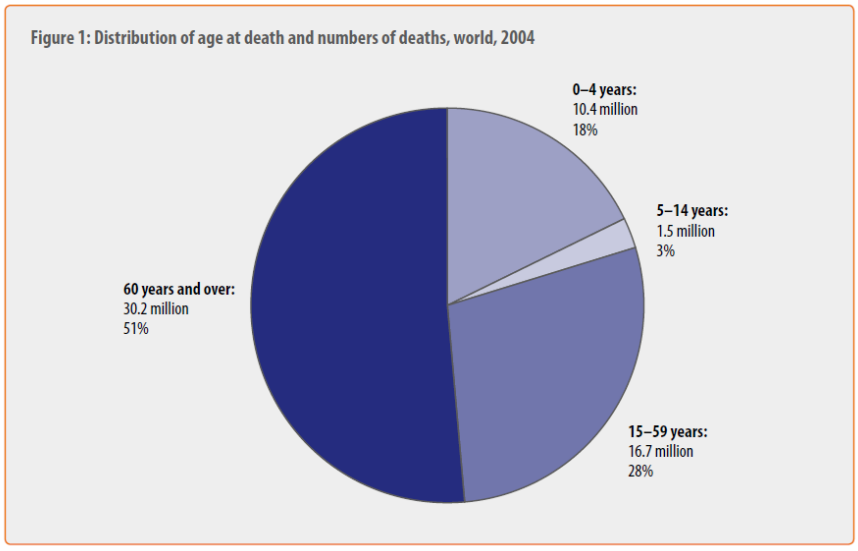
Children aged 0-14 years living in low income countries had a disease-related mortality rate of more than 20 times compared to those living in high income countries (100 vs 5 deaths, per 10,000 children). When considered as a group, children 0-14 years of age in LMIC had a disease-related mortality rate of more than 13 times over children in HIC (70 vs 5 deaths, per 10,000 children).

Deaths caused by injuries are a fraction of disease-related mortality overall, accounting for 7% of total mortality in the population aged 0-14 years old worldwide. The rate of injury-related deaths for 0-14 year olds was almost the same for middle income and low income countries, and were roughly twice above the rate in high income countries.

The data showed that the great majority of deaths in the paediatric population occur in children under five. Of the 11.9 million deaths occurring in 0-14 year olds, under-five mortality accounted for 10.4 million or 87% of the deaths (figure 1). Thus the attention paid by most organisations to under-five mortality is clearly justified.

Item	HIC	LMIC	
	High Income Countries	Middle Income Countries	Low Income Countries
Population of 0-14 year olds	179 million	773 million	894 million
Disease-related deaths (x 1000)	86	1948	8990
Injuries (x 1000)	17	393	449
Total Deaths (x 1000)	103	2341	9439

Table 1: Deaths occurring in the paediatric population 0-14 years, classified by income category



Source: The Global Burden of Disease Report: 2004 update. The WHO, 2008.

Children in HIC died of very different diseases compared to LMIC countries (table 2). The two major groups of diseases that accounted for two-thirds of deaths (57,000 deaths) in HIC were perinatal conditions and congenital abnormalities. In LMIC, infectious and parasitic diseases together with respiratory infections caused more than 60% of deaths of children up to 14 years of age. However, deaths related to perinatal conditions were also prominent, with a total of 3,142,000 neonates dying in LMIC due to prematurity, birth asphyxia and trauma as well as neonatal infections. A further 371,000 children died of congenital abnormalities in LMIC.

Major diseases causing death in children 0-14 years old (x 1000 children)	HIC	LMIC	
	High Income Countries	Middle Income Countries	Low Income Countries
Infectious and parasitic diseases	6	525	4055
Respiratory infections	4	284	1770
Perinatal conditions	37	745	2397
Congenital abnormalities	20	134	237

Table 2: Major disease-related causes of death in the global paediatric population

Analysis of data from Table A3, Annex A, page 66-68, The Global Burden of Disease: 2004 update (WHO, 2008)

To study the overall burden of disease in children including non-fatal illnesses and disability, the Disability-adjusted Life Years (DALYs) due to disease were examined for the paediatric population aged 0-14 years old (Table 3). Children in LMIC have approximately 6 fold more DALYs due to disease versus children in HIC (0.29 vs 0.05, per child). The paediatric population in LMIC also have 4 times more DALYs due to injuries compared to those in HIC (0.028 vs 0.007, per child). Overall, children in LMIC suffer from 6 times more DALYs compared to children in HIC (0.32 vs 0.05, per child).

Item	HIC	LMIC	
	High Income Countries	Middle Income Countries	Low Income Countries
Population of 0-14 year olds	179 million	773 million	894 million
DALYs* due to disease (x 1000)	8743	109,309	381,772
DALYs due to injuries (x 1000)	1199	19,088	28,045
Total DALYs (x 1000)	9942	128,397	409,816

Table 3: Comparison of DALYs in children 0-14 between income levels

Analysis of data from Table A4, Annex A, page 69-72, The Global Burden of Disease: 2004 update

* DALYs = The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability

Another major difference between HIC and LMIC emerged when causes of the DALYs were analysed. The majority of the burden of disease in the paediatric population of HIC arises from non-communicable diseases, contributing to more than 60% of their total DALYs. The three major noncommunicable conditions were neuropsychiatric disorders, congenital abnormalities and respiratory diseases particularly asthma (table 4).

Disease-related DALYs in children 0-14 years	HIC	LMIC	
	High Income Countries	Middle Income Countries	Low Income Countries
Total DALYs (x 1000 DALYs)	9942	128,397	409,816
Noncommunicable conditions (x 1000 DALYs)	6055	38,124	49,313
Neuropsychiatric disorders	2173	13,483	14,937
Congenital abnormalities	1419	7971	4679
Respiratory diseases	943	3911	4335

Table 4: Major noncommunicable diseases causing DALYs

Analysis of data from Table A4, Annex A, page 69-72, The Global Burden of Disease: 2004 update

In contrast, the biggest burden of disease suffered by children in LMIC is caused by communicable, maternal, perinatal and nutritional conditions, accounting for three-quarters or 75% of the total DALYs in LMIC (table 5). Infectious and parasitic diseases were the biggest causes of the DALYs in LMIC, followed by perinatal conditions, respiratory infections and nutritional deficiencies.

Disease-related DALYs in children 0-14 years	HIC	LMIC	
	High Income Countries	Middle Income Countries	Low Income Countries
Total DALYs (x 1000 DALYs)	9942	128,397	409,816
Communicable, maternal, perinatal and nutritional conditions (x 1000 DALYs)	2688	71,185	332,459
Infectious and parasitic diseases	477	21,558	154,384
Respiratory infections	250	11,433	64,480
Perinatal conditions	1768	31,290	93,331
Nutritional deficiencies	191	6804	19,835

Table 5: Major causes of disease burden in the paediatric population

Analysis of data from Table A4, Annex A, page 69-72, The Global Burden of Disease: 2004 update

3.2 Reanalysis of Paediatric RCTs published between 1996 and 2002

After omitting duplicate studies from the Sammons database, a total of 733 papers were analysed. 575 or 78% of the RCTs took place in high HDI countries, while 122 (17%) and 36 (5%) took place in medium and low HDI countries respectively.

Following ICD-10 classification, the majority of RCTs that took place in medium and low HDI countries studied infectious and parasitic diseases (Table 6). 57 out of 122 RCTs in medium HDI countries and 32 out of 36 RCTs in low HDI countries were in this category. Respiratory diseases were the second most common disease area studied (14 RCTs), followed by nervous system diseases (10 RCTs) and perinatal conditions (10 RCTs).

When the medicines trialled in the RCTs were categorised according to the ATC system, a similar trend was observed. 99 out of 158 (63%) RCTs were those of anti-parasitic or systemic anti-infective drugs. Next were nervous system drugs, accounting for 20 of the RCTs (13%) (Table 7).

On closer inspection of the antiparasitic and anti-infective groups, anti-malarial therapies (24 RCTs) were most frequently studied, followed by therapies for geohelminthic infection (23), schistosomiasis (8), leishmaniasis (6), typhoid (5), upper respiratory tract infections (5), giardia (4) and tuberculous infections (3).

ICD-10 classification	No (n)	Percent (%)
Certain infectious and parasitic diseases (A00-B99)	89	56
Diseases of the respiratory system (J00-J99)	14	9
Certain conditions originating in the perinatal period (P00-P96)	10	6
Diseases of the nervous system (G00-G99)	10	6
Diseases of the digestive system (K00-K93)	6	4
Diseases of the genitourinary system (N00-N99)	3	2
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	3	2
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	2	1
Endocrine, nutritional and metabolic diseases (E00-E90)	2	1
Mental and behavioural disorders (F00-F99)	2	1
Injury, poisoning and certain other consequences of external causes (S00-T98)	2	1
Diseases of the circulatory system (I00-I99)	1	1
Diseases of the musculoskeletal system and connective tissue (M00-M99)	1	1
Diseases of the eye and adnexa (H00-H59)	1	1
Diseases of the ear and mastoid process (H60-H95)	1	1
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	11	7
Total	158	100

Table 6: ICD-10 classes of paediatric RCTS in developing countries between 1996-2002

ATC drug classification	No (n)	Percent (%)
Antiparasitic products, insecticides and repellents (group P)	71	45
Anti-infectives for systemic use (group J)	28	18
Nervous system (group N)	20	13
Alimentary tract and metabolism (group A)	8	5
Antineoplastic and immunomodulating agents (group L)	7	4
Respiratory system (group R)	5	3
Systemic hormonal preparations, excl. sex hormones and insulins (group H)	5	3
Musculo-skeletal system (group M)	4	3
Dermatologicals (group D)	3	2
Blood and blood forming organs (group B)	3	2
Cardiovascular system (group C)	2	1
Various (group V)	2	1
Total	158	100

Table 7: ATC classes of paediatric RCTs in developing countries between 1996 and 2002

Fewer RCTs from medium and low HDI countries mentioned safety monitoring in their respective reports; 442/575 (77%) in high HDI, 83/122 (68%) in medium HDI, 22/36 (61%) in low HDI RCTs (p=0.02). In particular, there was practically no mention of SMCs from RCTs conducted in developing countries. Only one out of the 158 paediatric RCTs from medium and low HDI countries mentioned a SMC (compared to 12 out of 575 RCTs from high HDI countries, p=0.32). This Brazilian trial of G-CSF in preterm infants with early onset sepsis was terminated by the SMC, there was a flaw in the trial design and calculation of number of participants (Miura et al., 2001).

Looking at toxicity reporting, fewer RCTs from developing countries specified whether trial participants experienced adverse events. 113/575 (20%) of RCTs from high HDI countries lacked mention of toxicity data, whereas 31/122 (25%) paediatric RCTs from medium and 12/36 (33%) from low HDI countries had no mention of toxicity data (p=0.07). In terms of mortality occurring in the RCT participants, there was no significant difference found among the HDI categories.

Significantly fewer paediatric RCTs from developing countries mentioned that their study had obtained approval from an ethics committee or an institutional review board, compared to RCTs from developed or high HDI countries (61% vs 73%, p=0.0039).

The major source of stated funding for paediatric RCTs in developing countries appeared to come from academic or governmental sources. 63 (40%) of the RCTs stated that they were funded by academic/governmental institutions. In contrast, significantly more RCTs in high HDI countries acknowledged funding from pharmaceutical companies (27% vs 15%, p=0.0028). 67 (42%) of the 158 RCTs from developing countries did not mention their funding source at all. A similarly large percentage (43%) of RCTs from high HDI countries did not mention their funding source.

3.3 Characteristics of paediatric drug RCTs published in 2007 according to setting

1. Sample Sizes

Overall, RCTs performed in low income countries were larger compared to RCTs in medium and high income countries (table 8). As expected RCTs with study sites in multiple countries covering more than one income category (MSDI) were the largest on average.

World Bank income category*	Median number of participants in RCT	Mean number of participants
High income countries	75	185
Medium income countries	62	207
Low income countries	214	307
MSDI[#]	353	521

Table 8: Sample sizes of paediatric drug RCTs published in 2007

*sourced from World Bank, World Development Indicators 2007. Washington DC, USA.

[#]Multinational RCTs with study sites in different income categories

2. ICD-10 disease classes

In LMIC, a significantly higher proportion of RCTs studied infectious and parasitic diseases compared to HIC (39% vs 13%, $p<0.01$). In low income countries especially, 80% of the trials were in this class. Curiously, the most frequent ICD-10 category in high income countries was the non-specific 'symptoms, sign and abnormal clinical and laboratory findings, not elsewhere classified' (table 9). This was also the most frequent category in middle income countries when separated from low income countries. For MSDI RCTs, the respiratory disease category was most common followed by infectious and parasitic diseases.

World Bank income category	Most frequent ICD-10 category of disease studied		
High income countries	Symptoms, signs & abnormal clinical and laboratory findings, not elsewhere classified 17%	Respiratory diseases 14%	Certain infectious and parasitic diseases 13%
Medium income countries	Symptoms, signs & abnormal clinical and laboratory findings, not elsewhere classified 35%	Certain infectious and parasitic diseases 26%	Respiratory diseases 8%
Low income countries	Certain infectious and parasitic diseases 80%	Nervous system Diseases of skin and subcutaneous tissue Symptoms, signs, not elsewhere classified 4% each	
MSDI[#]	Respiratory diseases 33%	Certain infectious and parasitic diseases 21%	Endocrine diseases 12%

Table 9: Top three most common ICD-10 categories in paediatric RCTs published in 2007 by income level

[#]Multinational RCTs with study sites in different income categories

3. ATC drug classes

The ATC classes of the drugs studied in the RCTs revealed the explanation for large number of trials being classed in the non-specific 'symptoms and signs' ICD-10 disease category. There were large numbers of paediatric RCTs of anaesthetic and analgesic agents published in 2007. According to the ICD-10 system, these trials were classified in the 'symptoms and signs' category rather than the nervous system diseases category. These trials were mostly conducted in high income countries and can be seen in the nervous system class when the RCTs were categorised according to the ATC system (Table 10).

As seen earlier, antiparasitic products and anti-infectives for systemic use were the most common drugs studied in RCTs conducted in LMIC.

World Bank income category	Most frequent ATC category of drugs trialled		
High income countries	Nervous system 26%	Anti-infectives for systemic use 15%	Respiratory drugs 15%
Medium income countries	Nervous system 36%	Anti-infectives for systemic use 18%	Antiparasitic products 8%
Low income countries	Antiparasitic products 61%	Anti-infectives for systemic use 18%	Nervous system& Dermatologicals Both 6%
MSDI[#]	Respiratory drugs 36%	Anti-infectives for systemic use 26%	Nervous system 10%

Table 10: Top three most common ATC drug classes in paediatric RCTs published in 2007 by income level

[#] Multinational RCTs with study sites in different income categories

4. Funding sources

A large number of RCTs from medium income countries did not report their main funding source for the trials (Figure 2). The largest proportion of RCTs performed in low income countries acknowledged charitable organisations as the main study sponsor. In contrast, most of the large multinational trials with study sites crossing income categories (MSDI) reported pharmaceutical companies as their main sponsors. Industry sponsors were also the most commonly acknowledged in RCTs performed in high income countries.

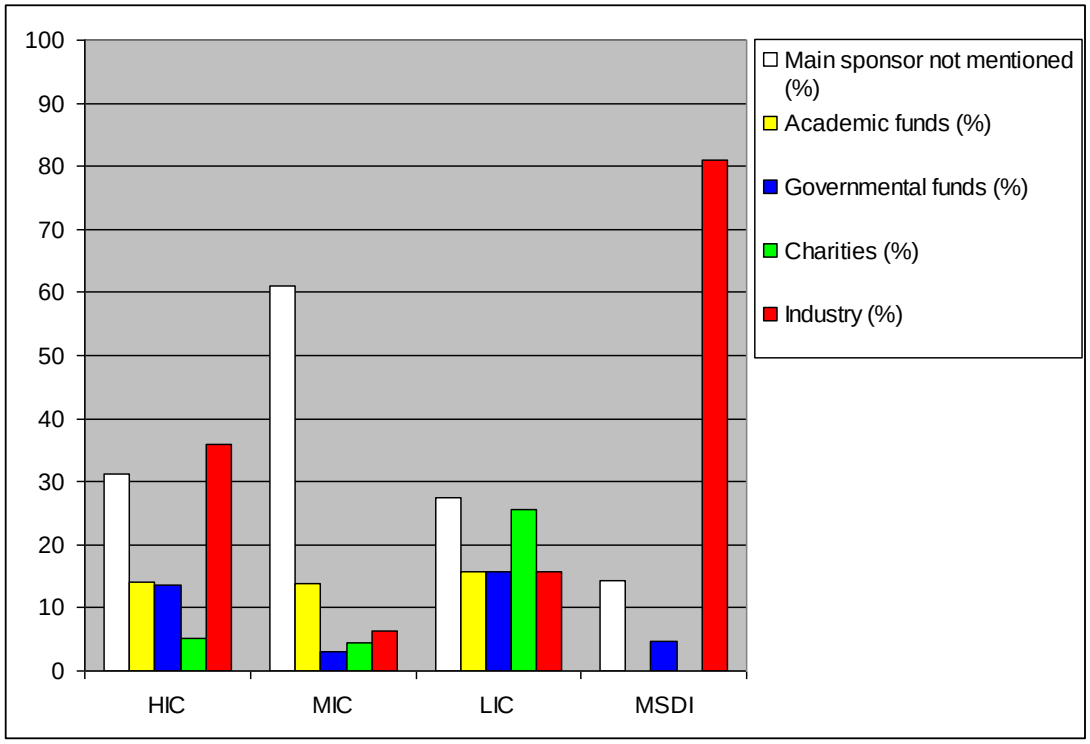


Figure 2: Main trial sponsors documented by paediatric RCTs published in 2007 by income level

5. Methodological quality

The mean Jadad score for studies conducted in LMIC were significantly lower than studies conducted in HIC (2.88 vs 3.33, p=0.05) (table 11).

Category	Mean Jadad	Standard deviation (SD)
HIC	3.33	1.265
MIC	2.77	1.371
LIC	3.24	1.242
MSDI[#]	3.83	1.208

Table 11: Mean Jadad score and standard deviation of the mean scores

[#] Multinational RCTs with study sites in different income categories

A significantly higher proportion of RCTs from HIC reported power or sample size calculations compared to LMIC trials (64% vs 52%, p<0.01). However there was no significant difference between HIC and LMIC in terms of RCTs that included a CONSORT participant flowchart (table 12).

	HIC	LMIC	p-value
a priori sample size /power calculation performed	64%	52%	<0.01
CONSORT participant flowchart	37%	35%	0.78

Table 12: Indicators of methodological/reporting quality in paediatric RCTs published in 2007

6. Documentation of ethical aspects

All 42 of the MSDI RCTs documented that ethical approval and informed consent was obtained (Figure 3). About one-third reported that assent was obtained from the paediatric participant.

A significantly higher percentage of RCTs conducted in HIC reported that ethical or institutional review board approval was obtained compared to RCTs in LMIC (93% vs 85%, $p<0.01$). However there was no significant difference relating to the documentation of informed consent (93% vs 90%, $p=0.32$).

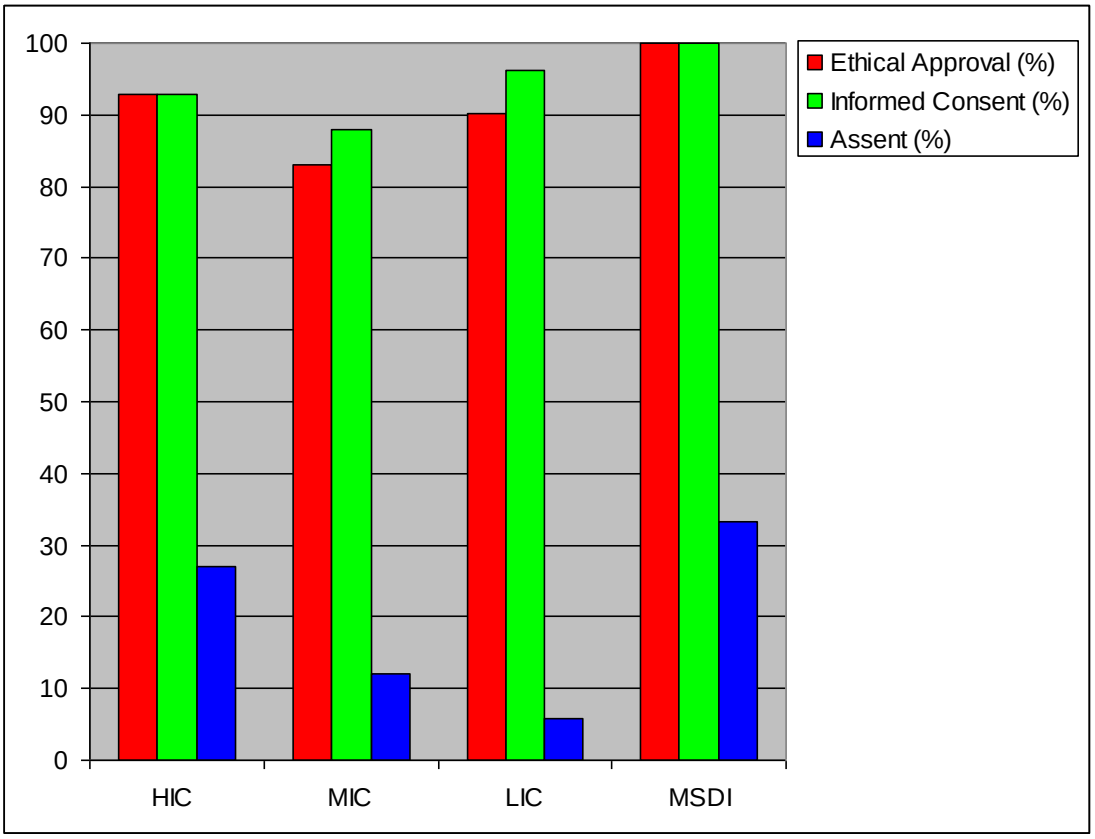


Figure 3: Percentages of paediatric RCTs published in 2007 documenting ethical aspects by income level

7. Safety and toxicity characteristics

A significantly higher proportion of trials conducted in HIC reported on their safety monitoring methods compared to RCTs performed in LMIC (65% vs 36%, p<0.01), while 93% of MSDI RCTs reported on safety monitoring (table 13).

Income Group		RCTs reporting safety monitoring (N/total)	Percent (%)	RCTs reporting SMC/ DSMB	Percent (%)
HIC		229/352	65	40/352	11
LMIC	MIC	46/159	29	7/159	4
	LIC	30/51	59	10/51	20
MSDI		39/42	93	12/42	29

Table 13: RCTs reporting safety monitoring and presence of SMC/DSMB, by income level of study setting

Similar proportions of HIC and LMIC trials reported that a SMC/DSMB was formed (11% vs 8%, p=0.25). However a significantly higher percentage of MSDI RCTs reported on safety monitoring (93% vs 56%, p<0.01), and documented the designation of a SMC/DSMB to oversee the trials (29% vs 11%, p<0.01), compared to RCTs in HIC and LMIC.

A substantial number of the RCT reports neglected to mention the occurrence of adverse events (including when no adverse events occurred). LMIC RCT reports were significantly worse compared to HIC in this aspect. Seventy nine percent (79%, 275/352) of reports of RCTs performed in HIC included adverse events compared to 70% of RCT reports from LMIC (147/210), p=0.03. MSDI RCTs almost universally reported on adverse events occurring within the trials (figure 4).

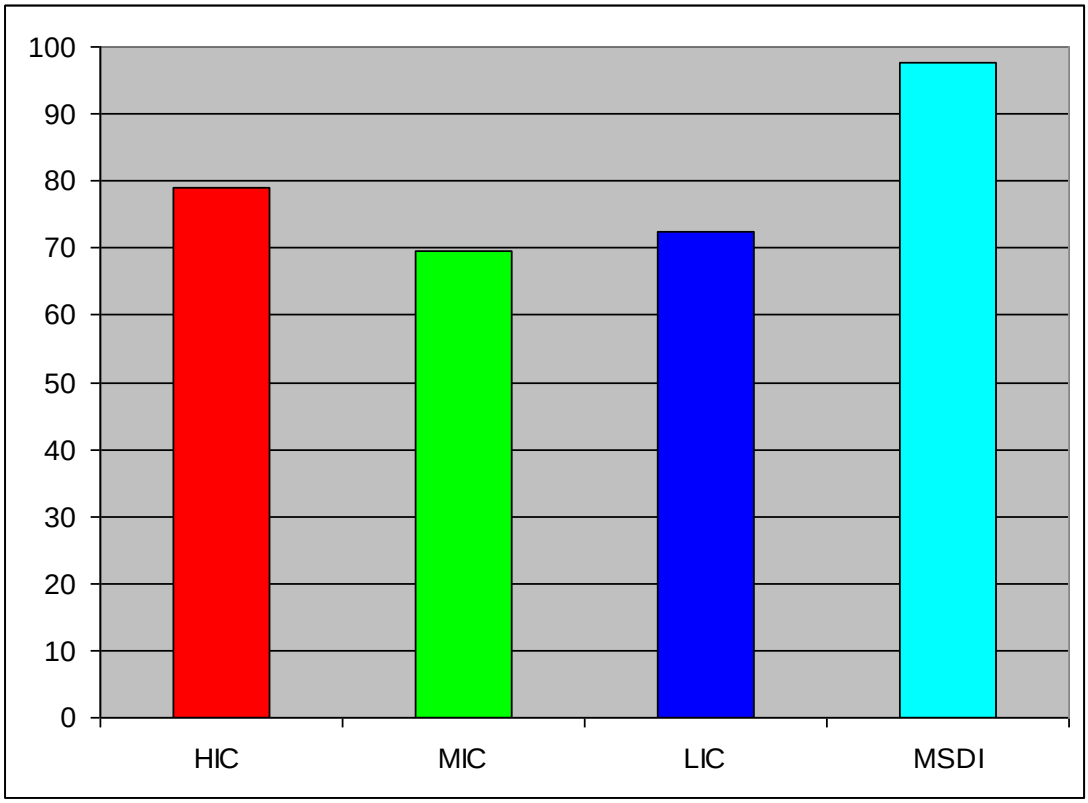


Figure 4: Reporting of adverse events in paediatric RCTs from each category of setting (%)

RCTs conducted in HIC reported a significantly higher rate of serious adverse events (SAEs). Thirty six percent (128/352) of the HIC trials reported a SAE compared to 24% of trials conducted in LMIC ($p<0.01$). Similar proportions of RCTs conducted in HIC and LMIC reported mortalities (13% in both) (table 14).

Income Group		Median sample size (N)	Proportion with SAEs	Percent (%)	Proportion with mortality	Percent (%)
HIC		75	128/352	36	46/352	13
LMIC	MIC	62	35/159	22	19/159	12
	LIC	214	16/51	31	9/51	18
MSDI		353	31/42	74	13/42	31

Table 14: Paediatric RCTs published in 2007 reporting SAEs and mortality, by income level of setting

Severe and moderate ADRs were detected in a significantly higher proportion of RCTs conducted in HIC compared to LMIC (25% vs 16%, $p=0.01$). However, the largest percentages of trials reporting SAEs, severe and moderate ADRs as well as mortalities were seen in the big MSDI RCTs (table 15).

Income Group		Median sample size (N)	Severe & Moderate ADRs detected	Percent (%)
HIC		75	88/352	25
LMIC	MIC	62	26/159	16
	LIC	214	7/51	14
MSDI		353	24/42	57

Table 15: Paediatric RCTs published in 2007 where severe and moderate ADRs were detected, by income level of setting

The possible mechanisms for these differences between RCTs conducted in the different income level settings were explored by cross tabulating with the categories of trials that had the highest toxicities (table 16). There were no significant differences in the proportions of cardiovascular, chemotherapy, neonatal or mixed-age population trials from those conducted in HIC compared to LMIC.

MSDI RCTs had much larger sample populations (see table 8 previously). The MSDI RCTs also were found to contain a significantly higher percentage of mixed-age trials compared to the other income categories (50% vs 29%, $p<0.01$).

Income level of study setting	Cardio vascular RCTs (N)	Chemotherapy RCTs (N)	RCTs involving neonates (N)	RCTs of both adult and paediatric patients (N)	Total no of trials (N)
HIC	7	28	21	92	352
MIC	6	10	18	46	159
LIC	0	0	0	17	51
MSDI	0	3	2	21	42
Total	13	41	41	176	604

Table 16: Cardiovascular, chemotherapy, neonatal and mixed-age population paediatric RCTs published in 2007, by income level of study setting

4. DISCUSSION

The great majority of the paediatric population worldwide live in LMIC. They suffer and die from different diseases, and at much higher rates compared to those children living in HIC. Thus there is a very large difference in mortality rates between paediatric populations in HIC and LMIC. It was found that the relatively few child deaths in HIC occur perinatally and the paediatric population are mostly burdened by neuropsychiatric illnesses, congenital abnormalities and asthma. These diseases contribute significantly to the disease burden in HIC, as seen in the smaller discrepancy between DALYs of children in HIC and LMIC. Nevertheless the fact remains that far greater numbers of children are afflicted by disease and die in LMIC, particularly due to infections, in addition to the large number of deaths during the neonatal period.

Encouragingly both databases of paediatric RCTs show that infectious and parasitic diseases was the most commonly studied area in LMIC. Nevertheless it is apparent that the majority of RCTs were performed in developed countries, with 78% of trials in the Sammons database and 65% of RCTs in this review of 2007 publications, conducted in high HDI countries. There also seems to be evidence suggesting an overall shift of paediatric RCTs from HIC to LMIC country settings.

There appears to be significant differences between paediatric RCTs conducted in HIC and LMIC. Paediatric RCTs performed in LMIC were found to have lower methodological and reporting quality. Fewer of these RCTs were seen to document important aspects of RCTs in their published reports, including ethical approval, safety monitoring and the occurrence of adverse events. On the contrary, more RCTs from HIC were found to report SAEs and were judged to have severe and moderate ADRs.

Interestingly, closer analysis suggests that HIC and LIC RCTs were more similar compared to MIC RCTs. A possible explanation is indicated by the funding information volunteered by the RCT reports. More LIC RCTs were funded by drug companies compared to MIC RCTs. It is postulated that the methodological and reporting standards used by industry-sponsored investigators in LIC would be more similar to the HIC RCTs that are also mostly sponsored by the pharmaceutical industry.

This review of paediatric RCTs published in 2007 also identified many RCTs with study settings located in countries that were in different HDI and World Bank income categories. These MSDI RCTs appear to have unique characteristics. They are much larger and are more likely to recruit both adult and paediatric populations to the study. The great majority identify drug companies as their main sponsors. These RCTs also appear to have exceptional methodological and reporting quality, scoring the highest on the Jadad scale. All of them documented that ethical approval and informed consent were obtained, moreover almost one-third recorded assent from paediatric participants.

However, these cross category RCTS had the highest percentage of studies reporting serious adverse events, mortality and where severe and moderate adverse drug reactions were detected. This could be due to the large and heterogeneous sample populations, many of these trials recruited elderly patients as well as those with comorbidities. Another explanation is the possible application of better detection methods, as well as more transparent and organised reporting of adverse events in these MSDI RCTs.

When findings from this review were compared directly to data from the Burden of Disease project (WHO, 2008), a mere 35% (see chapter 3) of paediatric RCTs published in 2007 were performed in LMIC with a population of 1.6 billion below 15 years of age, from which there were 10.9 million deaths due to disease. The remainder, including most of the studies in the cross category class of RCTs, involved the paediatric population of HIC which numbered 180 million in total.

This corresponds with the mismatch referred to by the Global Forum for Health Research (1999). There are other literature that document this apparent discrepancy as well. Isaakidis et al. (2002) evaluated the amount of randomised clinical evidence in relation to the burden of disease in sub-saharan Africa. They identified only slightly over 1000 RCTs performed over a 50 year period. In relation to child health, UNICEF states that around half of global child deaths occur in sub-saharan Africa.

This is also in contrast to the hundreds of thousands of RCTs currently archived in the Cochrane register (see section 2.3.1.2). Gluud and Nikolova (2007) also show that most of the RCTs published since 1946 originated from North American and Western European countries, with Scandinavian countries the most productive in terms of RCTs per population. Rochon et al. (2004) also commented that RCTs published in high impact, international journals in 1999 had little relevance to international health especially the burden of disease in poor countries.

Swingler et al. (2003) estimated the correlation between systematic reviews in two major databases; namely the Cochrane database of systematic reviews (CDSR) and the database of abstracts of reviews of effects (DARE), and the global burden of disease. They found that the contents of both databases were both geared towards the priorities of established market economies or high income countries rather than global health concerns.

On a broader scope, Pecoul et al. (1999) lamented on the lack of effective treatment for many diseases endemic in poor countries due to the lack of research and development for these diseases. Trouiller et al. (2002) analysed global drug development over the past 25 years and found that of the 1393 new drugs granted market authorisation, considerably fewer targeted infectious and parasitic diseases which accounted for the majority of the global disease burden but were minor in high income countries.

All this points to a 'morally uncomfortable global drug gap' affecting poor populations where Cohen-Kohler (2007) suggests that there is not only a lack of access to essential drugs but also an apparent absence of effort to address this problem. There is further relevance to paediatric populations in LMIC when additional issues are included in the consideration. It is recognised that there has been inadequate research on medicines for children (Klassen et al., 2008, Choonara, 2000). This is also reflected in the lack of high quality published evidence in the literature compared to those of adults (Cohen et al., 2007, Martinez-Castaldi et al., 2008).

Therefore the paediatric population in poor countries may suffer from a three-fold inadequacy – firstly the overall lack of scientific evaluation of medicines given to children, secondly the lack of research and development to provide safe and effective medicines appropriate for the illnesses that affect them and finally the lack of delivery infrastructure and mechanisms to allow them access to essential drugs.

There are exciting efforts to tackle the situation. In 2007 WHO launched the 'Make medicines child size' campaign, calling for more research and development of safe, effective, child-specific medicines with a heavy emphasis on global child health needs. The major infectious diseases such as malaria, TB and HIV/AIDS afflicting children in poor countries are targeted as well as the tropical diseases that have long been neglected (O'Connell, 2007).

The argument made here is not simply for more RCTs to involve paediatric populations in LMIC. As previously mentioned, the Bellagio study group estimates that millions of child deaths annually can be prevented by improved delivery of readily available interventions. However looking at the bigger picture, it is felt that improved delivery and access to healthcare should go hand-in-hand with high quality, ethical research to benefit child health. In themselves high quality, ethical clinical trials has the potential to bring numerous benefits to the population being studied.

Yusuf (2002) suggests that RCTs in developing countries allow the evaluation of treatments specifically accounting for the environmental and genetic factors that may be very different to those affecting populations in developed countries, as well as that for diseases that are common in developing countries. He adds that by being involved in randomised trials, health professionals from poor countries may develop and spread the practice of evidence-based medicine thus improving healthcare provision.

On the other hand, there are multiple concerns and challenges that require addressing regarding performing randomised trials in the paediatric population of poor countries. The same bioethical principles apply when involving children in experimental situations (see section 3.1 chapter 1).

Beyond the ethical challenges of paediatric studies, there are serious ethical issues specifically relating to the conduct of clinical trials in poor or developing regions. Emanual et al. (2004) discusses an ethical framework with specific benchmarks so that clinical trials in developing countries are ethical; the primary objective is to minimise exploitation of the populations involved in these randomised trials (Brody, 2002).

This and many other discussions (Angell, 2000, Koski and Nightingale, 2001) arose from previous ethical quandaries relating to clinical trials in developing countries. For example, the question on what to use as the 'standard of care' as seen in the zidovudine controversy. In several trials of zidovudine used to prevent perinatal HIV transmission in African and Asian countries, the use of a placebo group when an effective treatment was available, was widely regarded as unethical despite the 'standard of care' in the local situation being no treatment (Angell, 1997, Lurie and Wolfe, 1997, Lallemant et al., 1998). Furthermore, the local 'standard of care' was applied where in most cases, no medical care at all was made available to the trial participants.

Both of the databases here show that documentation of ethical approval were significantly lower in paediatric RCTs performed in developing or LMIC countries. This is concerning since it may indicate a lower level of ethical oversight in RCTs in poor or developing areas. Further evidence is seen from Zhang et al.'s (2008) recent review of randomised controlled trials conducted in China where only 18% of the studies documented informed consent and less than 10% reported that ethical approval was obtained.

The trovafloxacin saga in Nigeria (Ahmad, 2001) highlights the vital importance of adhering to ethical principles; by obtaining and documenting both informed consent and ethical approval from the necessary parties. The drug was trialled in a group of severely ill children during a meningitis epidemic in Nigeria; without the authorisation of the local health authorities nor the informed consent of the parents. Thus it is felt appropriate to repeat the call made in chapter 4; that the protection of the rights of participants should be adequately maintained and documented. Ethical approval and informed consent (Annas, 2009) must be universally reported for paediatric RCTs.

A related and equally important concern is with the safety oversight in paediatric trials in poor countries. Again, both reviews of RCTs found that significantly a lower proportion of studies performed in poor and developing countries described safety monitoring. Sammons et al.'s (2008) database revealed an almost total absence of SMC/DSMBs in trials conducted in developing countries, while slightly fewer LMIC paediatric RCTs published in 2007 designated SMC/DSMBs. The situation is still evolving up to the present. A recent inquiry by the Indian government into a vaccine clinical trial after the death of an infant (Mudur, 2009) suggests ineffective oversight could be at fault.

Conversely, a higher proportion of paediatric RCTs from high income countries seem to report SAEs. The analysis shows that a significantly higher proportion of HIC paediatric RCTs were judged to have had severe and moderate ADRs compared to RCTs conducted in LMIC. The reasons for this are unclear, as the most toxic types of trials such as chemotherapy RCTs and those that involve neonates appear to be equally spread out between HIC and LMIC trials in the database.

Another significant discrepancy between HIC and LMIC may offer some clues to the difference mentioned in the preceding paragraph. From the 1996 to 2002 period, more reports of paediatric RCTs conducted in developing countries did not include toxicity reporting i.e. adverse events occurring within the trial. This finding was repeated in paediatric RCTs published in 2007.

Therefore, there is the suggestion that the apparently lower proportion of RCTs conducted in LMIC found to have toxicity relates to the gaps in safety reporting rather than a true difference in ADRs experienced by the patients. This is supported by the mean Jadad scores; RCTs conducted in HIC scored significantly higher compared to LMIC RCTs. The Jadad score include aspects of both methodological and reporting quality. Nevertheless, more research is needed to elucidate this apparent difference in adverse events and toxicity between paediatric RCTs in HIC and LMIC.

Although Sterckx (2005), Cohen-Kohler (2007) and many others argue that access to effective medicines is accepted as an inalienable human right, the reality is that pharmaceuticals are a commercial product. Their development and supply is governed by commercial interests (Rose, 2009). This brings us to a significant new trend seen recently where the clinical research sponsored by the pharmaceutical industry is increasingly being conducted in developing countries (Glickman et al., 2009).

According to Thiers et al. (2008), the reasons contributing to this shift include cheaper costs, greater recruitment capability, the growth of contract research organisations (CROs), expanding markets and the rapid development that is experienced by newly emerging countries with the corresponding strengthening of health research capabilities.

This trend is also observed in the two databases in this review. Of the paediatric RCTs published between 1996 to 2002, 78% were performed in high HDI countries. This percentage was found to have substantially decreased to 65% in RCTs published in 2007. Furthermore, there was a dramatic increase in multinational paediatric RCTs from just 1% in publications between 1996 and 2002, to 16% in 2007.

Thus the globalisation of clinical trials also applies to paediatric RCTs. On the whole this trend promises to confer welcome benefits to ensure better medicines for children on a global level (MacLeod, 2009). Nevertheless paediatric clinical pharmacologists, parents, regulators and industry must continue to remain dedicated to the effort of providing children worldwide with safe and effective medicines supported by sound scientific evaluation.

5. CONCLUSION

The vast majority of the paediatric population of the world live in poor and developing countries. They suffer markedly higher morbidity and mortality compared to children in rich countries, caused by very different diseases. Improved access to health care interventions are needed to alleviate their heavy burden of disease, however it is felt that high quality and ethical clinical trials should go hand-in-hand with efforts to improve delivery of preventative and therapeutic measures. As expected, most RCTs involving the paediatric population are conducted in rich and developed nations but the situation is rapidly changing, corresponding with the rising trend of globalisation in clinical trials. Paediatric RCTs performed in resource-poor populations has the potential to confer many benefits. However it is essential to avoid the possibility of exploitation and harm to the participants. All involved parties need to pay attention to the ethical, methodological, safety and reporting aspects of these trials to obtain the best evidence in the interest of the world's children.

CHAPTER 7: CONCLUSION

This final chapter provides an overview of the findings and discussions from the thesis. The background of this work is the changing situation concerning the evidence base for medicines used in children. Consequently it is important to describe the recent overall situation of paediatric randomised controlled trials (RCTs) of medicines involving children, as RCTs are regarded as the highest level of evidence. Many aspects regarding these RCTs have been encouraging. However this review has also identified many areas that require attention to ensure paediatric RCTs are appropriately conducted and reported. The safeguarding of participants must be prioritised but when adverse drug reactions occur, accurate and transparent reporting is needed so that useful information is gained. The primary conclusion of this thesis is the idea that clinical research (including RCTs) should respond to the health needs of children worldwide, the vast majority of whom live (and die) in poor or developing areas.

1. CONTRIBUTION TO KNOWLEDGE AND FUTURE WORK

The situation with medicines used in children is evolving rapidly (Hoppu, 2008, MacLeod, 2009) . Previously paediatric involvement in the testing of drugs was largely avoided (Steinbrook, 2002, Shirkey, 1999). This was attributed to the intention of protecting the under-aged from the risks of experimentation. In fact, the real reason may have been economic (Caldwell et al., 2004, Smyth, 2001). In the free market economy, the pharmaceutical industry is the main sponsor of research and development for drugs (Li et al., 2007, Rose, 2009). To my knowledge, this study is the first to look at declared funding of published paediatric RCTs. The results show that half of paediatric RCTs published in 2007 declared drug companies as the main source of funding; this is likely to be a substantial underestimation, when indirect funding and trials that did not declare their sponsors are considered.

The rise of evidence-based medicine coupled with a much greater understanding that the paediatric population differed from adults in many ways other than just physical size (Klassen et al., 2008), have triggered major changes at the turn of the millennium. The widespread use of unlicensed and off label drugs in children accompanied by data suggesting greater risks of toxicity, not to mention being scientifically unjustifiable, has captured the attention of the medical community as well as the public (Conroy et al., 1999, McIntyre et al., 2000, Conroy et al., 2000a, Choonara and Conroy, 2002).

As a result, new legislation first in the United States and then in the European Union was enacted to help ensure medicines used in children will be supported by rigorous scientific evaluation, which can only be obtained with the involvement of the paediatric population in clinical trials (Choonara, 2007, Greener, 2008, Roberts et al., 2003).

Randomised controlled trials (RCTs) are regarded as the highest level of clinical evidence since they are the least prone to bias. There has been a great effort in recent years by organisations chiefly the Cochrane Collaboration to compile and analyse RCTs. The refined information gained is then used to assist in clinical decision-making as well as to guide wider policy developments in the best interest of patients. In the background of aforementioned changes to the situation of paediatric medicines, the meticulously developed and validated tools used by bodies such as the Cochrane Collaboration are used here and the resulting work has elucidated many characteristics of RCTs involving the paediatric population.

It is heartening that there have been far more RCTs involving the paediatric population conducted and then published in 2007 compared to the period between 1996 and 2002 from Sammons et al.'s (2008) review. From the reports, more than 100,000 children were involved in the RCTs with trials seen to be larger compared to those reviewed in previous studies.

An issue highlighted by this review is the low number of RCTs involving neonates. Research shows that drugs used in neonatal units are frequently unlicensed and off label (Conroy et al., 1999). The neonatal population also experiences high rates of adverse drug reactions (Kaushal et al., 2001, Moore et al., 2002, Sammons et al., 2008). Moreover neonatal diseases form a large proportion of the burden of disease in developed countries (WHO, 2008). More work is therefore needed to shed light on this area; including what amount of clinical trials should involve neonates and how to install the mechanisms to do as such, if more randomised evidence relevant to neonates is required.

An important feature of this review was the use of both the ATC and ICD-10 classification systems. This method provides an accurate and reproducible categorisation of RCTs. Therefore future work can quickly use the data obtained here for analysis and correlations, along with other health statistics available within the WHO domain.

The study identified many trials of anti-infectives, respiratory as well as anti-parasitic products. Again this was reassuring as these agents correspond to the bulk of the disease burden in children overall. There have been previous concerns raised that the pharmaceutical industry often conduct paediatric clinical trials in areas where there is potential profits to be gained in the adult market, rather than areas where paediatric evidence is most needed (Jong et al., 2001). Studies submitted for paediatric exclusivity indicate this as well (Rodriguez et al., 2008). A further indication of such a tendency is seen in this review. The highest number of RCTs is in the nervous systems drugs category but when the ICD-10 disease area is observed, the majority of these studies fell into the 'symptoms, signs and abnormal findings' category, reflecting on the large number of analgesic and anaesthetic agents being studied. Further research is needed to explore whether certain disease areas or drug types should be paid more or less attention. Also more work should be done to clarify the motivations behind paediatric RCTs as well as the funding sources for these studies as referred to earlier.

The assessment of quality of paediatric RCTs is another original contribution made by my work. Although an integral component of specific systematic reviews by the Cochrane Collaboration, the methodological or reporting quality of paediatric RCTs in general has not been documented previously. Overall, paediatric RCTs published in 2007 appear to be of good quality, with the mean Jadad score exceeding the threshold of 3 points usually regarded by reviewers to indicate good methodology or reporting (Jadad and Enkin, 2007). Nevertheless, deeper analysis revealed many areas where reporting of paediatric RCTs need improvement to allow readers to interpret the findings accurately in addition to forming appropriate conclusions. Good reporting is essential as it can affect the ability to assess and apply evidence in clinical situations.

Mixed age group RCTs were found to generally overlook reporting important characteristics of the paediatric participants. Many did not volunteer the exact number of participants 16 year olds or under and also lacked mentioning the specific age or age ranges of the paediatric patients. Such information is needed for many reasons, for example considering the developmental processes undergone by the different age groups. Furthermore, these basic characteristics are required to assess the generalisability of the findings of the trial to the actual healthcare setting in paediatrics.

This study also contributes to the accumulating body of evidence that RCTs in general often disregard the adequate reporting of safety characteristics including adverse events and especially possible adverse drug reactions suffered by paediatric participants (Ioannidis, 2009). The assessment of potential toxicities is already complicated in view of their infrequent occurrence in small sample populations and further made to be extremely difficult when basic characteristics such as those mentioned above are missing.

Thus it is hoped that this work should continue towards the development and implementation of a consolidated set of reporting standards of RCTs involving the paediatric population to supplement the CONSORT statement already in place (Moher et al., 2001). Important aspects of paediatric RCTs mentioned earlier as well as other items such as adequate formulation information for oral drugs (Standing et al., 2005) would then be crystallised into a checklist of items that must be included when reporting the studies. Such a checklist can also be associated with the ongoing effort to register all clinical trials involving children worldwide (Pandolfini et al, 2009).

The main original contribution of this thesis is felt to be the comprehensive assessment and description of paediatric RCTs in relation to the global health burden for the paediatric population. Clinical drug trials have traditionally been centred in highly developed or affluent nations due to a combination of factors; including existence of industry or academic initiative as well as availability of healthcare infrastructure and expertise. However as the world hurtles into the era of globalisation, commentators such as Annas (2009), Thiers et al., (2008) and Glickman et al., (2009) have noticed a steadily growing shift towards having trial settings in lower-cost locations in developing countries.

This review has found evidence that paediatric RCTs are undergoing the same changes. Paediatric RCTs located in developing countries as well as multinational trials appeared to be steadily increasing in number. However the results suggest that paediatric RCTs conducted in LMIC lag behind RCTs from high income countries (HIC); in areas such as reporting, methodology used and also the documentation of ethical characteristics of the studies.

Fortunately there are ongoing high profile discussions on the oversight and ethical conduct of clinical trials in developing countries (Angell, 2000, McCarthy, 2001, Pandolfini et al., 2003, Hyder et al., 2004). Most promisingly, there appears to be a greater desire for collaboration in the field of paediatric pharmacology as demonstrated by the Alliance for Better Medicines in Children (Koren et al., 2009), as well as a greater awareness of the importance of paediatric medicines shown by the WHO in launching campaigns such as 'Make medicines child size' (Choonara and Bauchner, 2008) and safer medicines for children (Watts, 2007).

In summary, this was an in-depth study of published RCTs which are the highest level of clinical evidence for medicines used in the paediatric population. It is original in its breadth, currency and relevance to children overall.

2. LIMITATIONS AND JUSTIFICATIONS

This systematic review of paediatric RCTs published in 2007 has some limitations, mostly by virtue of its nature. Although highly sensitive search strategies were used (chapter 2), admittedly some relevant RCTs may be missed. However the sheer number of RCTs compiled and analysed has provided useful information consistent with the initial aims of this study. The large volume of reports yielded by the search strategies has also precluded the inclusion of further years in the interest of manageability of the database. Further work should follow looking at more recent publications of RCTs involving children, to illuminate on the changing situation mentioned earlier.

Research by Hartling et al., (2004) and Benjamin et al., (2006) has found that large numbers of paediatric clinical trials fail to reach publication and consequently are 'lost' from the public field. Surprisingly the main reason was found to be that the results were never submitted for publication by the investigators themselves.

This problem is discouraging, as investigators have an ethical commitment to their patients to publish their findings. Hence even the large number of studies compiled by this review may be an underrepresentation of the overall situation with paediatric drug RCTs. The effort to register paediatric clinical trials internationally within the WHO registry holds great promise for greater accessibility of RCTs involving children (Pandolfini et al., 2009).

The main limitation of this review is felt to be the dependence on just the literature as many aspects of the reporting quality of the paediatric RCTs were found to be wanting. There was no attempt to contact the study authors. This was not felt to be feasible mainly due to the large number of trials contained in the database.

Furthermore an earlier stated goal of the study was to examine reporting quality of paediatric RCTs. The rationale is that although contacting authors is a luxury afforded to systematic reviewers, it would not be a realistic proposition for busy clinicians and policymakers. It is felt that the onus should be on the trial investigators or authors themselves to accurately and transparently describe paediatric RCTs conducted. Also important is the role of peer reviewers and journal editors, especially with the availability of guidelines such as the CONSORT statement.

Another limitation is the restriction of this review to the English language literature. Some information has been extracted from the 22 non-English RCT reports. However there are large gaps in the data that could not be analysed. Both the search strategies and the medical literature databases are heavily focussed on English language scientific reports, therefore it is plausible that many paediatric RCTs conducted in non-English speaking settings and reported in languages other than English would be missed by this review. Furthermore, existing non-English, local or country-specific trial databases were not included in the search. Future collaborative studies should provide more insights on non-English RCTs and thus more clearly describe the overall situation of paediatric RCTs.

Another factor that cannot be discounted is human error. All abstracts yielded by the search strategies were reviewed by me in regards to the suitability for inclusion. Most of the trial characteristics were also reviewed and designated to the relevant categories by myself. However, both my supervisors were closely involved in reviewing the reports that contained serious adverse events. Hence in effect, more than one-third of the RCTs in the database were reviewed by both supervisors. Moreover, I kept in close contact with both supervisors over the period of data collection and referred any unclear items to them during the supervisory meetings.

It is acknowledged that many types of nonrandomised studies also involve the paediatric population (Martinez-Castaldi et al., 2008) as well as non-drug studies. Future collaborations should shed more light on the overall situation with clinical studies involving children. Although RCTs are regarded by many as the highest quality of evidence, there are also those who question the hierarchical approach to evidence for medical interventions (Rawlins, 2008). It is acknowledged that this thesis has not looked at any alternative study types (observational studies in particular) for paediatric medicines that are perhaps equally relevant. Nevertheless, it is hoped that the insights offered by this thesis into the characteristics of paediatric drug RCTs may lead to useful discussions, as well as improvements, regarding the conduct and reporting of paediatric RCTs on a global level.

3. CLOSING WORDS

In closing, paediatric RCTs are seen to be increasingly globalised. Such a shift brings with it the potential for causing harm especially exploitation contrary to the principles outlined in the Declaration of Helsinki (Ahmad, 2001, Goodyear et al., 2008, Kimmelman et al., 2009), and especially vulnerable children. However these RCTs can also bring direct and ancillary benefits to the health of the paediatric populace of such locales.

In LMIC, the greatest benefits can be obtained from improving access to basic health interventions such as vaccines, clean water, perinatal care, but RCTs can and should go hand-in-hand with such measures. Benefits include allowing assessments of treatment efficacy specific to the health needs of the population thereby allowing the most cost-effective treatments to be delivered, the development of safe and effective treatments for diseases causing heavy morbidity and mortality as well as ancillary benefits. These include providing basic standards of care, improvements to local health facilities as well as expertise, and building collaborations between researchers from both rich and poor regions (Yusuf, 2002).

The argument is not merely advocating RCTs involving paediatric populations in poor countries. It is the wider argument that healthcare research should focus more on the health needs of the global children, and thus must attempt to shrug off the underlying influence of financial rewards and profits as the primary motivator. After significant advancements seen recently, yet another paradigm shift of paediatric clinical research is required, towards being motivated by altruistic and beneficient reasons, rather than driven ultimately by the pursuit of returns denominated in currency. The main issue should be the health of the world's children.

REFERENCES

1. ABERNETHY, D.R., BURCKART, G.J. (2010) Pediatric Dose Selection. *Clinical Pharmacology & Therapeutics*, 87(3), 270–271.

2. AHMAD, K. (2001) Drug company sued over research trial in Nigeria. *Lancet*, 358, 815.

3. AKOBENG, A. K. (2005a) Understanding randomised controlled trials. *Archives of Disease in Childhood*, 90, 840-4.

4. AKOBENG, A. K. (2005b) Understanding systematic reviews and meta-analysis. *Archives of Disease in Childhood*, 90, 845-8.

5. ALTMAN, D. G., SCHULZ, K. F., MOHER, D., EGGER, M., DAVIDOFF, F., ELBOURNE, D., GOTZSCHE, P. C., LANG, T. & CONSORT, G. (2001) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Annals of Internal Medicine*, 134, 663-94.

6. AMERICAN ACADEMY OF PAEDIATRICS (AAP), COMMITTEE ON DRUGS (1995) Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. *Pediatrics*, 95, 286-294.

7. ANNAS, G. J. (2009) Globalized Clinical Trials and Informed Consent. *New England Journal of Medicine*, 360, 2050-2053.

8. ANDERSON, B.J., POTTS, A.L., HERD, D.W. (2007) Problems and pitfalls performing pharmacokinetic studies in children. *Paediatric and Perinatal Drug Therapy*, 8: 4–17.

9. ANGELL, M. (1997) The ethics of clinical research in the Third World. *New England Journal of Medicine*, 337, 847-9.

10. ANGELL, M. (2000) Investigators' responsibilities for human subjects in developing countries. *New England Journal of Medicine*, 342, 967-9.

11. ANONYMOUS (2003) The world's forgotten children. *Lancet*, 361(9351):1.

12. ANONYMOUS (2007) Medicines for children: safety as an afterthought. *Lancet*, 370, 1190-1190.

13. ANTTILA, H., MALMIVAARA, A., KUNZ, R., AUTTI-RAMO, I., MAKELA, M. & MAKELA, M. (2006) Quality of reporting of randomized, controlled trials in cerebral palsy. *Pediatrics*, 117, 2222-30.

14. ASSADI, M., CAMPELLONE, J. V., JANSON, C. G., VELOSKI, J. J., SCHWARTZMAN, R. J., LEONE, P. (2007) Treatment of spinocerebellar ataxia with buspirone. *Journal of the Neurological Sciences*, 260, 143-6.

15. ASHBY, D. (2008) Establishing causality in the assessment of safety of medicines for children. *Acta Pædiatrica*, 97, 1611-1616.

16. BAUCHNER, H. (2002) Protecting research participants. *Pediatrics*, 110, 402-4.

17. BAUCHNER, H., SHARFSTEIN, J. (2001) Failure to report ethical approval in child health research: review of published papers. *British Medical Journal*, 323, 318-9.

18. BELAY, E. D., BRESEE, J. S., HOLMAN, R. C., KHAN, A. S., SHAHRIARI, A. & SCHONBERGER, L. B. (1999) Reye's Syndrome in the United States from 1981 through 1997. *New England Journal of Medicine*, 340, 1377-1382.

19. BELSHE, R. B., EDWARDS, K. M., VESIKARI, T., BLACK, S. V., WALKER, R. E., HULTQUIST, M., KEMBLE, G. & CONNOR, E. M. (2007) Live attenuated versus inactivated influenza vaccine in infants and young children. *New England Journal of Medicine*, 356, 685-696.

20. BENJAMIN, D. K., JR., SMITH, P. B., MURPHY, M. D., ROBERTS, R., MATHIS, L., AVANT, D., CALIFF, R. M. & LI, J. S. (2006) Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *Journal of the American Medical Association*, 296, 1266-73.

21. BLACK, R. E., MORRIS, S. S. & BRYCE, J. (2003) Where and why are 10 million children dying every year? *Lancet*, 361, 2226-2234.

22. BONATI, M. (2009) Once again, children are the main victims of fake drugs. *Archives of Disease in Childhood*, 94, 468-.

23. BONATI, M., CHOONARA, I., HOPPU, K., PONS, G., SEYBERTH, H. (1999) Closing the gap in drug therapy. *Lancet*, 353, 1625.

24. BONATI, M., BREITKREUTZ, J., CHOONARA, I., HOPPU, K., JACQZ-AIGRAIN, E., LANGHENDRIES, J.-P., PONS, G., RANE, A., SEYBERTH, H., RG, VAN DEN ANKER, J. & EUROPEAN NETWORK FOR DRUG INVESTIGATION IN CHILDREN, E. (2006) Paediatric clinical pharmacology in Europe. *Paediatric and Perinatal Drug Therapy*, 7, 134-137

25. BONSANTE, F., LATORRE, G., IACOBELLI, S., FORZIATI, V., LAFORGIA, N., ESPOSITO, L. & MAUTONE, A. (2007) Early low-dose hydrocortisone in very preterm infants: A randomized, placebo-controlled trial. *Neonatology*, 91: 217-221.

26. BOURGEOIS, F. T., MANDL, K. D., VALIM, C. & SHANNON, M. W. (2009) Pediatric Adverse Drug Events in the Outpatient Setting: An 11-Year National Analysis. *Pediatrics*, 124, e744-750.

27. BOUTRON, I., GUITTET, L., ESTELLAT, C., MOHER, D., HROBJARTSSON, A., RAVAUD, P. (2007) Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Medicine,* 4(2):e61.

28. BOUTRON, I., ESTELLAT, C., RAVAUD, P. (2005) A review of blinding in randomized controlled trials found results inconsistent and questionable. *Journal of Clinical Epidemiology*. 58(12):1220-6.

29. BOUTRON, I., ESTELLAT, C., GUITTET, L., DESCHARTRES, A., SACKETT, D.L., HROBJARTSSON, A., RAVAUD, P. (2006) Methods of blinding in reports of randomized controlled trials assessing pharmacologic treatments: a systematic review. *PLoS Medicine.* 3(10):e425.

30. BRIDGE, J.A., IYENGAR, S., SALARY, C.B., BARBE, R.P., BIRMAHER, B., PINCUS, H.A., REN, L., BRENT, D.A. (2007) Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials. *Journal of the American Medical Association*, 297:1683-1696.

31. BRODY, B. A. (2002) Ethical issues in clinical trials in developing countries. *Statistics in Medicine*, 21, 2853-8.

32. BROWN, J.K. (1988) Valproate toxicity. *Developmental Medicine and Child Neurology*, 30, 115-125.

33. BRYCE, J., BLACK, R.E., WALKER, N., BHUTTA, Z., A., LAWN, J.E, STEKETEE, R.W. (2005) Can the world afford to save the lives of 6 million children each year? *Lancet* 1;365(9478):2193-200.

34. BRYCE, J., BOSCHI-PINTO, C., SHIBUYA, K. & BLACK, R. E. (2005) WHO estimates of the causes of death in children. *Lancet*, 365, 1147-1152.

35. BUCHELER, R., SCHWAB, M., MORIKE, K., KALCHTHALER, B., MOHR, H., SCHRODER, H., SCHWOERER, P. & GLEITER, C. H. (2002) Off label prescribing to children in primary care in Germany: retrospective cohort study. *British Medical Journal*, 324, 1311-1312.

36. BUDETTI, P. P. (2003) Ensuring safe and effective medications for children. *Journal of the American Medical Association*, 290, 950-1.

37. CAIRNS, J. A., HALLSTROM, A. & HELD, P. (2001) Should all trials have a data safety and monitoring committee? *American Heart Journal,* 141, 156-63.

38. CALDWELL, P. H., MURPHY, S. B., BUTOW, P. N., CRAIG, J. C. (2004) Clinical trials in children. *Lancet*, 364, 803-11.

39. CAMPBELL, H., SURRY, S. A. M. & ROYLE, E. M. (1998) A review of randomised controlled trials published in Archives of Disease in Childhood from 1982-96. *Archives of Disease in Childhood*, 79, 192-197.

40. CALDWELL, P. H. Y., BUTOW, P. N. & CRAIG, J. C. (2002) Pediatricians' attitudes toward randomized controlled trials involving children. *The Journal of Pediatrics*, 141, 798-803.

41. CALDWELL, P. H. Y., BUTOW, P. N. & CRAIG, J. C. (2003) Parents' attitudes to children's participation in randomized controlled trials. *The Journal of Pediatrics*, 142, 554-559.

42. CHALUMEAU, M., TRELUYER, J. M., SALANAVE, B., ASSATHIANY, R., CHERON, G., CROCHETON, N., ROUGERON, C., MARES, M., BREART, G. & PONS, G. (2000) Off label and unlicensed drug use among French office based paediatricians. *Archives of Disease in Childhood*, 83, 502-505.

43. CHAN, A.-W. & ALTMAN, D. G. (2005) Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*, 365, 1159-1162.

44. CHARLES, P., GIRAUDEAU, B., DECHARTRES, A., BARON, G., RAVAUD, P. (2009) Reporting of sample size calculation in randomised controlled trials: review. *British Medical Journal*, 338:b1732.

45. CHOONARA, I. (2000) Clinical trials of medicines in children. *British Medical Journal*, 321, 1093-4.

46. CHOONARA, I. (2006) Improving children's medicines. *Archives of Disease in Childhood*, 91, 550-1.

47. CHOONARA, I. (2006) Paediatric pharmacovigilance. *Paediatric and Perinatal Drug Therapy*, 7, 50-53.

48. CHOONARA, I. (2007) Regulation of drugs for children in Europe. *British Medical Journal*, 335, 1221-2.

49. CHOONARA, I. (2008) WHO wants safer medicines for children. *Archives of Disease in Childhood*, 93, 456-7.

50. CHOONARA, I. & BAUCHNER, H. (2008) Publishing the evidence for children's medicines. *Archives of Disease in Childhood*, 93, 815.

51. CHOONARA, I., CONROY, S. (2002) Unlicensed and off-label drug use in children: implications for safety. *Drug Safety*, 25, 1-5.

52. CHOONARA, I., DUNNE, J. (1998) Licensing of medicines. *Archives of Disease in Childhood*, 78, 402-3.

53. CHOONARA, I., GILL, A., NUNN, A. (1996) Drug toxicity and surveillance in children. *British Journal of Clinical Pharmacology*, 42, 407-10.

54. CHOONARA I, DEWIT O, HARROP E, HAWORTH S, HELMS P, KANABAR D, LENNEY W, RYLANCE G, and VALLANCE P (2004). Training in paediatric clinical pharmacology in the UK. *British Journal of Clinical Pharmacology*. 58(2): 217–218.

55. CHOONARA, I. & RIEDER, M. J. (2002) Drug Toxicity and Adverse Drug Reactions in Children - A Brief Historical Review. *Paediatric and Perinatal Drug Therapy*, 5, 12-18.

56. CLAESON, M., GILLESPIE, D., MSHINDA, H., TROEDSSON, H., VICTORA, C., G. (2003) The Bellagio Study Group on Child Survival: Knowledge into action for child survival. *Lancet*, 362:323-27.

57. CLAVENNA, A. & BONATI, M. (2009) Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Archives of Disease in Childhood*, 94:724-728.

58. COHEN-KOHLER, J. C. (2007) The morally uncomfortable global drug gap. *Clinical Pharmacology & Therapeutics*, 82, 610-4.

59. COHEN, E., ULERYK, E., JASUJA, M. & PARKIN, P. C. (2007) An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. *Journal of Clinical Epidemiology*, 60, 118-123.

60. COHEN, A. L., BUDNITZ, D. S., WEIDENBACH, K. N., JERNIGAN, D. B., SCHROEDER, T. J., SHEHAB, N. & POLLOCK, D. A. (2008) National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events in Children and Adolescents. *The Journal of Pediatrics*, 152, 416-421.e2.

61. COMMISSION ON HEALTH RESEARCH FOR DEVELOPMENT (1990) *Health Research: Essential link to equity in development*. New York. Oxford University Press.

62. COMMITTEE ON DRUGS, AMERICAN ACADEMY OF PEDIATRICS. (1995) Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. *Pediatrics*, 95, 286-294.

63. CONROY, S., CHOONARA, I., IMPICCIATORE, P., MOHN, A., ARNELL, H., RANE, A., KNOEPPEL, C., SEYBERTH, H., PANDOLFINI, C., RAFFAELLI, M. P., ROCCHI, F., BONATI, M., JONG, G., DE HOOG, M., VAN DEN ANKER, J. (2000a) Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *British Medical Journal*, 320, 79-82.

64. CONROY, S., MCINTYRE, J., CHOONARA, I., (1999) Unlicensed and off label drug use in neonates. *Archives of Disease in Childhood Fetal & Neonatal Edition*, 80, F142-4; discussion F144-5.

65. CONROY, S., MCINTYRE, J., CHOONARA, I., STEPHENSON, T.(2000b) Drug trials in children: problems and the way forward. *British Journal of Clinical Pharmacology*, 49, 93-7.

66. COOPER, K. J. (2002) Pediatric marketing exclusivity--as altered by the Best Pharmaceuticals for Children Act of 2002. *Food & Drug Law Journal*, 57, 519-44.

67. COPENHAGEN CONSENSUS (2008) The ranked list of solutions. Available at http://www.copenhagenconsensus.com/Home.aspx. Accessed 12-12-2009.

68. CRAMER, K., WIEBE, N., MOYER, V., HARTLING, L., WILLIAMS, K., SWINGLER, G. & KLASSEN, T. (2005) Children in reviews: Methodological issues in child-relevant evidence syntheses. *BMC Pediatrics*, 5, 38.

69. DAMOCLES STUDY GROUP, N. H. S. H. T. A. P. (2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*, 365, 711-22.

70. DELL'AERA, M., GASBARRO, A., PADOVANO, M., LAFORGIA, N., CAPODIFERRO, D., SOLARINO, B., QUARANTA, R. & DELL'ERBA, A. (2007) Unlicensed and off-label use of medicines at a neonatology clinic in Italy. *Pharmacy World & Science*, 29, 361-367.

71. DeMETS, D., L., POCOCK, S.J., JULIAN, D., G. The agonizing negative trend in monitoring of clinical trials. *Lancet*. 1999;354:1983–1988.

72. DICKERSIN, K., MANHEIMER, E., WIELAND, S., ROBINSON, K. A., LEFEBVRE, C., MCDONALD, S. & CENTRAL DEVELOPMENT, G. (2002) Development of the Cochrane Collaboration's Central Register of Controlled Clinical Trials. *Evaluation and the Health Professions*, 25, 38-64.

73. DICKERSIN, K., SCHERER, R. & LEFEBVRE, C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *British Medical Journal*, 309, 1286-1291.

74. DIMASI J.A., HANSEN R.W., GRABOWSKI H.G. The price of innovation (2003) : New estimates of drug development costs. *Journal of Health Economics*, 22 (2), pp. 151-185.

75. DI PAOLO E.R.; STOETTER, H.; COTTING, J., FREY, P., GEHRI, M., BECK-POPOVIC, M., TOLSA, J., FANCONI, S., PANNATIER, A (2006) . Unlicensed and off-label drug use in a Swiss paediatric university hospital. *Swiss medical weekly*; 136(13-14):218-22.

76. EDEN, O. B. (1994) Consent difficult in paediatric oncology. *British Medical Journal*, 308, 272-.

77. EGGER, M., JUNI, P., BARTLETT, C. (2001) Value of flow diagrams in reports of randomized controlled trials. *Journal of the American Medical Association*, 285:1996-9.

78. EKIN-DAUKES, S., HELMS, P.J., TAYLOR M.W., MCLAY, J. (2005) Off-label prescribing to children: attitudes and experience of general practitioners. *British Journal of Clinical Pharmacology*. 60(2): 145–149.

79. ELSEVIER (2010) Embase. Biomedical Answers. Available at http://www.embase.com/. Accessed 16-1-2010.

80. EMEA (2001) ICH Topic E11 Clinical Investigation of Medicinal Products in the Paediatric Population. NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION (CPMP/ICH/2711/99). London, EMEA.

81. EMEA COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) (2005) Guideline on data monitoring committees. Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr. London, EMEA. Available at: http://www.emea.europa.eu/pdfs/human/ewp/587203en.pdf. Accessed 10-11-2009.

82. EMEA (1995) ICH Topic E 2 A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. CPMP/ICH/377/95. Available at: http://www.emea.europa.eu/pdfs/human/ich/037795en.pdf. Accessed 12-11-2009.

83. FATTAHI, F., POURPAK, Z., MOIN, M., KAZEMNEJAD, A., KHOTAEI, G. T., MAMISHI, S., SIADATI, A. & TABATABAEI, P. (2005) Adverse Drug Reactions in Hospitalized Children in a Department of Infectious Diseases. *Journal of Clinical Pharmacology*, 45, 1313-1318.

84. FEDERAL REGISTER (1983). Additional protections for children involved as subjects in research.43:786.

85. FEDERAL REGISTER. (1978) Protection of human subjects – proposed regulations on research involving children. 43:786.

86. FEDERAL REGISTER (1994). Specific requirements on content and format of labeling for human prescription drugs; revision of "pediatric use" subsection in the labeling. 59: 64240–50.

87. FEDERAL REGISTER (1998). Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients; Final Rule. 63: 66632–72.

88. FEDERAL REGISTER (2002). Best pharmaceuticals for children act 2002. Available at : http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049876.htm. Accessed August 2009.

89. FEDERAL REGISTER (2003). Pediatric Research Equity Act 2003. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf. Accessed August 2009.

90. FELMET, K., NGUYEN, T., CLARK, R. S., ORR, D., CARCILLO, J., CORNFIELD, D. N., NELSON, M. D., MILLA, C. E., SWEENEY, M. & TEGTMEYER, K. (2003) The FDA Warning Against Prolonged Sedation With Propofol in Children Remains Warranted. *Pediatrics*, 112, 1002-1003.

91. FOOD & DRUG ADMINISTRATION, H. H. S. (2000) International Conference on Harmonisation; guidance on E11 clinical investigation of medicinal products in the pediatric population; availability. Notice. Federal Register, 65, 78493-4.

92. FOSSA, S. D. & SKOVLUND, E. (2000) Interim analyses in clinical trials: why do we plan them?[comment]. *Journal of Clinical Oncology*, 18, 4007-8.

93. GALLEGOS-CASTORENA, S., MARTINEZ-AVALOS, A., MOHAR-BETANCOURT, A., GUERRERO-AVENDANO, G., ZAPATA-TARRES, M., MEDINA-SANSON, A. (2007) Toxicity prevention with amifostine in pediatric osteosarcoma patients treated with cisplatin and doxorubicin. *Pediatric Hematology & Oncology*, 24, 403-8.

94. GAZARIAN, M (2009). Training Pediatric Clinical Pharmacology and Therapeutics Specialists of the Future. *Pediatric Drugs*, 11(1):63-4.

95. GIDDING, S. S. (2007) The Importance of Randomized Controlled Trials in Pediatric Cardiology. *Journal of the American Medical Association*, 298, 1214-1216.

96. GILMAN, J.T., GAL P. (1992). Pharmacokinetic and pharmacodynamic data collection in children and neonates. *Clinical Pharmacokinetics*. 23:1-9.

97. GLANVILLE, J. M., LEFEBVRE, C., MILES, J. N., CAMOSSO-STEFINOVIC, J., (2006) How to identify randomized controlled trials in MEDLINE: ten years on.[erratum appears in J Med Libr Assoc. 2006 Jul;94(3):354]. *Journal of the Medical Library Association*, 94, 130-6.

98. GLASGOW, J. F. (2006) Reye's syndrome: the case for a causal link with aspirin. *Drug Safety*, 29, 1111-21.

99. GLICKMAN, S. W., MCHUTCHISON, J. G., PETERSON, E. D., CAIRNS, C. B., HARRINGTON, R. A., CALIFF, R. M., SCHULMAN, K. A. (2009) Ethical and scientific implications of the globalization of clinical research. *New England Journal of Medicine,* 360, 816-23.

100. GLOBAL FORUM FOR HEALTH RESEARCH (1999) 10/90 Report on Health Research 1999. Geneva. Available online at: http://www.globalforumhealth.org/Media-Publications/Publications/10-90-Report-on-Health-Research-1999. Accessed 3-7-2008.

101. GLOBAL HEALTH FORUM. http://www.globalforumhealth.org/ . Accessed 31-8-2009.

102. GLUUD, C. A., NIKOLOVA D. (2007) Likely country of origin in publications on randomised controlled trials and controlled clinical trials during the last 60 years. *Trials*, 8.

103. GOODYEAR, M. D., ECKENWILER, L. A. & ELLS, C. (2008) Fresh thinking about the Declaration of Helsinki. *British Medical Journal*, 337, a2128.

104. HALPERN, S.D. (2005) Adding nails to the coffin of underpowered trials. *Journal of Rheumatology*, 32:2065-2066.

105. GREENER, M. (2008) Bitter medicine. New regulations aim to address the dearth of clinical safety trials for drugs used in children. *EMBO reports*, 9, 505-508.

106. HALPERN, S.D., KARLAWISH, J.H.T., BERLIN, J.A. (2002) The continuing unethical conduct of underpowered clinical trials. *Journal of the American Medical Association*, 288:358-62.

107. HAMMAD, T.A., LAUGHREN, T., RACOOSIN, J. (2006) Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*, 63:332-339.

108. HARGRAVE, D. R., HANN, I. M., RICHARDS, S. M., HILL, F. G., LILLEYMAN, J. S., KINSEY, S., BAILEY, C. C., CHESSELLS, J. M., MITCHELL, C. & EDEN, O. B. (2001) Progressive reduction in treatment-related deaths in Medical Research Council childhood lymphoblastic leukaemia trials from 1980 to 1997 (UKALL VIII, X and XI). *British Journal of Haematology*, 112, 293-299.

109. HAUTALAHTI, O., RENKO, M., TAPIAINEN, T., KONTIOKARI, T., POKKA, T., UHARI, M. (2007) Failure of xylitol given three times a day for preventing acute otitis media. *Pediatric Infectious Disease Journal*, 26, 423-7.

110. HEDENMALM, K., MELANDER, H. & ALVAN, G. (2008) The conscientious judgement of a DSMB--statistical stopping rules re-examined. *European Journal of Clinical Pharmacology*, 64, 69-72.

111. HIGGINS, J. P. T., GREEN, S., (EDITORS) (2009) Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration.

112. HILLMAN, D. W. & LOUIS, T. A. (2003) DSMB case study: decision making when a similar clinical trial is stopped early. *Controlled Clinical Trials*, 24, 85-91.

113. HOLLIS, S., CAMPBELL, F. (1999) What is meant by intention to treat analysis? Survey of published randomised controlled trials. *British Medical Journal* 1999;319:670-674.

114. HOPPU, K. (2008) Paediatric clinical pharmacology - at the beginning of a new era. *European Journal of Clinical Pharmacology*, 64, 201-205.

115. HOREN, B., MONTASTRUC, J.-L. & LAPEYRE-MESTRE, M. (2002) Adverse drug reactions and off-label drug use in paediatric outpatients. *British Journal of Clinical Pharmacology*, 54, 665-70.

116. HORTON, R. (2003) Medical journals: evidence of bias against the diseases of poverty. *Lancet*, 361, 712-713.

117. HUWILER-MUNTENER, K., JUNI, P., JUNKER, C. & EGGER, M. (2002) Quality of reporting of randomized trials as a measure of methodologic quality. *Journal of the American Medical Association*, 287, 2801-4.

118. HYDER, A. A., WALI, S. A., KHAN, A. N., TEOH, N. B., KASS, N. E. & DAWSON, L. (2004) Ethical review of health research: a perspective from developing country researchers. *Journal of Medical Ethics*, 30, 68-72.

119. IMPICCIATORE, P., CHOONARA, I., CLARKSON, A., PROVASI, D., PANDOLFINI, C., BONATI, M. (2001) Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *British Journal of Clinical Pharmacology*, 52, 77-83.

120. IOANNIDIS, J. P., EVANS, S. J., GOTZSCHE, P. C., O'NEILL, R. T., ALTMAN, D. G., SCHULZ, K., MOHER, D., GROUP, C. (2004) Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine*, 141, 781-8.

121. IOANNIDIS, J. P. A. (2009) Adverse Events in Randomized Trials: Neglected, Restricted, Distorted, and Silenced. *Archives of Internal Medicine*, 169, 1737-1739.

122. IOANNIDIS, J. P. A. & LAU, J. (2001) Completeness of Safety Reporting in Randomized Trials: An Evaluation of 7 Medical Areas. *Journal of the American Medical Association*, 285, 437-443.

123. ISAAKIDIS, P., SWINGLER, G. H., PIENAAR, E., VOLMINK, J., IOANNIDIS, J. P. (2002) Relation between burden of disease and randomised evidence in sub-Saharan Africa: survey of research. *British Medical Journal*, 324, 702.

124. JADAD, A. R., ENKIN, M. (2007) Randomized Controlled Trials: Questions, Answers and Musings Blackwell Publishing. Oxford, United Kingdom.

125. JADAD, A. R., MOORE, R. A., CARROLL, D., JENKINSON, C., REYNOLDS, D. J., GAVAGHAN, D. J. & MCQUAY, H. J. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*, 17, 1-12.

126. JHA N, B. O., NAMGYAL T (2007) Prevalence of adverse drug reactions with commonly prescribed drugs in different hospitals of Kathmandu valley. *Kathmandu University Medical Journal*, 5, 504-510.

127. JOHN, T., HOPE, T., SAVULESCU, J., STEIN, A. & POLLARD, A. J. (2008) Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research? *Archives of Disease in Childhood*, 93, 379-383.

128. JOHNSON, T.N. (2008) The problems in scaling adult drug doses to children. *Archives of Disease in Childhood*, 93:207-211.

129. JONG, G. W., VAN DEN ANKER, J. N., CHOONARA, I. (2001) FDAMA's written request list: medicines for children. *Lancet*, 357, 398.

130. JUNI, P., ALTMAN, D. G. & EGGER, M. (2001) Systematic reviews in health care: Assessing the quality of controlled clinical trials. *British Medical Journal*, 323, 42-6.

131. KAM, P. C., CARDONE, D. (2007) Propofol infusion syndrome. *Anaesthesia*, 62, 690-701.

132. KASTNER, M., WILCZYNSKI, N. L., WALKER-DILKS, C., MCKIBBON, K. A., HAYNES, B. (2006) Age-specific search strategies for Medline. *Journal of Medical Internet Research*, 8, e25.

133. KAUFFMAN, R. E. (2000) Clinical trials in children: problems and pitfalls. *Paediatric Drugs*, 2, 411-8.

134. KAUSHAL, R., BATES, D. W., LANDRIGAN, C., MCKENNA, K. J., CLAPP, M. D., FEDERICO, F. & GOLDMANN, D. A. (2001) Medication errors and adverse drug events in pediatric inpatients. *Journal of the American Medical Association*, 285, 2114-20.

135. KIMMELMAN, J., WEIJER, C. & MESLIN, E. M. (2009) Helsinki discords: FDA, ethics, and international drug trials. *Lancet*, 373, 13-4.

136. KLASSEN, T. P., HARTLING, L., CRAIG, J. C., OFFRINGA, M. (2008) Children are not just small adults: the urgent need for high-quality trial evidence in children. *PLoS Medicine / Public Library of Science*, 5, e172.

137. KNOPPERT, D. C. (2009) Pediatric formulations: International issues and potential solutions. *Pediatric Drugs*, 11, 55-56.

138. KODISH, E. (2003) Informed consent for pediatric research: Is it really possible? *Journal of Pediatrics*, 142, 89-90.

139. KOREN, G., RIEDER, M. & MACLEOD, S. M. (2009) The global alliance for pediatric pharmacology: The future is here and now. *Pediatric Drugs*, 11, 4-5.

140. KOSKI, G. & NIGHTINGALE, S. L. (2001) Research involving human subjects in developing countries. *New England Journal of Medicine*, 345, 136-8.

141. KRAUSE, J., BREITKREUTZ, J. (2008) Improving Drug Delivery in Paediatric Medicine. *Pharmaceutical Medicine*, 22(1): pp 41-50.

142. KUMAR, P., WALKER, J. K., HURT, K. M., BENNETT, K. M., GROSSHANS, N. & FOTIS, M. A. (2008) Medication Use in the Neonatal Intensive Care Unit: Current Patterns and Off-Label Use of Parenteral Medications. *Journal of Pediatrics*, 152, 412-415.e1.

143. KUPST, M. J., PATENAUDE, A. F., WALCO, G. A. & STERLING, C. (2003) Clinical Trials in Pediatric Cancer: Parental Perspectives on Informed Consent. *Journal of Pediatric Hematology/Oncology*, 25, 787-790.

144. LALLEMANT, M., MCINTOSH, K., JOURDAIN, G., LE COEUR, S., VITHAYASAI, V., LEE, T. H., HAMMER, S., PRESCOTT, N. & ESSEX, M. (1998) Ethics of placebo-controlled trials of zidovudine to prevent the perinatal transmission of HIV in the Third World. *New England Journal of Medicine*, 338, 839-40.

145. LANDS, L. C., MILNER, R., CANTIN, A. M., MANSON, D., COREY, M. (2007) High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. *Journal of Pediatrics*, 151, 249-54.

146. LANG, T., CHILENGI, R., NOOR, R. A., OGUTU, B., TODD, J. E., KILAMA, W. L. & TARGETT, G. A. (2008) Data safety and monitoring boards for African clinical trials. *Transactions of the Royal Society of Tropical Medicine & Hygiene*, 102, 1189-94.

147. LAZAROU, J., POMERANZ, B. H. & COREY, P. N. (1998) Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies. *Journal of the American Medical Association*, 279, 1200-1205.

148. LE, J., NGUYEN, T., LAW, A. V. & HODDING, J. (2006) Adverse Drug Reactions Among Children Over a 10-Year Period. *Pediatrics*, 118, 555-562.

149. LEFEBVRE, C., & MCDONALD, S. (1996) Development of a sensitive search strategy for reports of randomised controlled trials in EMBASE. Proceedings of the 4th Annual Cochrane Colloquium, A-28.

150. LEVENE, M., WRIGHT, I. & GRIFFITHS, G. (1996) Is informed consent in neonatal randomised controlled trials ritual? *Lancet*, 347, 475-475.

151. LI, J. S., EISENSTEIN, E. L., GRABOWSKI, H. G., REID, E. D., MANGUM, B., SCHULMAN, K. A., GOLDSMITH, J. V., MURPHY, M. D., CALIFF, R. M. & BENJAMIN, D. K., JR. (2007) Economic return of clinical trials performed under the pediatric exclusivity program. *Journal of the American Medical Association*, 297, 480-8.

152. LOPEZ A.D., MATHERS, C.D., EZZATI, M., JAMISON, D.T., MURRAY, C.J.L. Eds (2006) Global burden of disease and risk factors. Oxford University Press, New York. Available at: http://www.dcp2.org/pubs/GBD. Accessed 20-8-2008.

153. LORCH, A., KOLLMANNSBERGER, C., HARTMANN, J. T., METZNER, B., SCHMIDT-WOLF, I. G., BERDEL, W. E., WEISSINGER, F., SCHLEICHER, J., EGERER, G., HAAS, A., SCHIRREN, R., BEYER, J., BOKEMEYER, C., RICK, O., GERMAN TESTICULAR CANCER STUDY GROUP. (2007) Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. *Journal of Clinical Oncology*, 25, 2778-84.

154. LURIE, P. & WOLFE, S. M. (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine*, 337, 853-6.

155. MACKWAY-JONES K, J. M., WYLIE K, GREEN C (2002) BestBETS: Pediatric Filter. Poster presented at the 8th European Conference of Medical and Health Libraries, Cologne, 16-21 September 2002.

156. MACLEOD, S. M. (2009) Improving drug treatment for children: Are we making an impact? *Pediatric Drugs*, 11, 1-3.

157. MACLEOD, S., PETERSON, R., WANG, Y., et al. (2007) Challenges in international pediatric pharmacology: a milestone meeting in Shanghai. *Pediatric Drugs*, 9:215-8.

158. MAHMOOD, I. (2006) Prediction of drug clearance in children from adults: a comparison of several allometric methods. *British Journal of Clinical Pharmacology*. 61(5): 545–557.

159. MARTINEZ-CASTALDI, C., SILVERSTEIN, M., BAUCHNER, H. (2008) Child versus adult research: the gap in high-quality study design. *Pediatrics*, 122, 52-7.

160. MASON, S. A. & ALLMARK, P. J. (2000) Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. *Lancet*, 356, 2045-2051.

161. MCCARTHY, M. (2001) US ethics guidelines for trials in the developing world. *Lancet*, 357, 1506.

162. MCINTYRE, J., CONROY, S., AVERY, A., CORNS, H., CHOONARA, I. (2000) Unlicensed and off label prescribing of drugs in general practice. *Archives of Disease in Childhood*, 83, 498-501.

163. MCKECHNIE, L. & GILL, A. B. (2006) Consent for neonatal research. *Archives of Diseases in Childhood Fetal Neonatal Edition*, 91, F374-376.

164. MEINARDI, H., SCOTT, R. A., REIS, R. & ON BEHALF OF THE ILAE COMMISSION ON THE DEVELOPING WORLD, J. W. A. S. S. (2001) The Treatment Gap in Epilepsy: The Current Situation and Ways Forward. *Epilepsia*, 42, 136-149.

165. MENON, V., MEHROTRA, A., SAXENA, R., JAFFERY, N. F. (2007) Comparative evaluation of megadose methylprednisolone with dexamethasone for treatment of primary typical optic neuritis. *Indian Journal of Ophthalmology*, 55, 355-9.

166. MITCHELL, C. (2007) Clinical trials in paediatric haematology-oncology: are future successes threatened by the EU directive on the conduct of clinical trials? *Archives of Diseases in Childhood*, 92, 1024-1027.

167. MOHER, D., COOK, D. J., EASTWOOD, S., OLKIN, I., RENNIE, D. & STROUP, D. F. (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*, 354, 1896-900.

168. MOHER, D., DULBERG, C.S., WELLS, G.A. (1994) Statistical power, sample size, and their reporting in randomized controlled trials. *Journal of the American Medical Association*, 272:122-4.

169. MOHER, D., HOPEWELL, S., SCHULZ, K.F., MONTORI, V., GOTZSCHE, P.C., DEVERAUX, P.J., ELBOURNE, D., EGGER, M., ALTMAN, D.G., (2010) CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *British Medical Journal*, 340:c869.

170. MOHER, D., JADAD, A.R., NICHOL, G., PENMAN, M., TUGWELL, P., WALSH, S.(1995) Assessing the quality of randomized controlled trials: An annotated bibliography of scales and checklists. *Controlled Clinical Trials*.16(1):62-73.

171. MOHER, D., PHAM, B., JONES, A., COOK, D. J., JADAD, A. R., MOHER, M., TUGWELL, P. & KLASSEN, T. P. (1998) Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*, 352, 609-13.

172. MOHER, D., SCHULZ, K. F., ALTMAN, D. & GROUP, C. (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Journal of the American Medical Association*, 285, 1987-91.

173. MOHER, D., SOEKEN, K., SAMPSON, M., BEN-PORAT, L. & BERMAN, B. (2002) Assessing the quality of reports of randomized trials in pediatric complementary and alternative medicine. *BMC Pediatrics*, 2, 2.

174. MOORE, T. J., WEISS, S. R., KAPLAN, S. & BLAISDELL, C. J. (2002) Reported adverse drug events in infants and children under 2 years of age. *Pediatrics*, 110, e53.

175. MUDUR, G. (2009) Inquiry into vaccine trial in India suggests ineffective oversight. *British Medical Journal*, 338, b1418-.

176. MULLA, H., TOFEIG, M., BU'LOCK, F., SAMANI, N., PANDYA, H.C. (2007) Variations in captopril formulations used to treat children with heart failure: a survey in the United Kingdom. *Archives of Disease in Childhood*, 92:409-411.

177. MURRAY, C.J.L., LOPEZ, A.D. (Ed) (1996) The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge: Harvard University Press.

178. NAHATA, M. C. (1999) Lack of Pediatric Drug Formulations. *Pediatrics*, 104, 607-609.

179. NEUBERT, A., DORMANN, H., WEISS, J., EGGER, T., CRIEGEE-RIECK, M., RASCHER, W., BRUNE, K., HINZ, B.(2004) The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Safety*, 27, 1059-67.

180. NEUBERT, A., WONG, I. C. K., BONIFAZI, A., CATAPANO, M., FELISI, M., BAIARDI, P., GIAQUINTO, C., KNIBBE, C. A. J., STURKENBOOM, M. C. J. M., GHALEB, M. A. & CECI, A (2008). Defining off-label and unlicensed use of medicines for children: Results of a Delphi survey. *Pharmacological Research*, 58, 316-322.

181. NIEMINEN, P. & ISOHANNI, M. (1999) Bias against European journals in medical publication databases. *Lancet*, 353, 1592-1592.

182. NOLAN, M. L., GREENBERG, A. E. & FOWLER, M. G. (2002) A review of clinical trials to prevent mother-to-child HIV-1 transmission in Africa and inform rational intervention strategies. *AIDS*, 16, 1991-1999.

183. NOSEWORTHY, J.H., EBERS, G.C., VANDERVOORT, M.K., FARQUHAR, R.E., YETISIR, E., ROBERTS, R. (1994) The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. *Neurology*, 44:16-20.

184. NUNN, T. (2009) The National Institute for Health Research Medicines for Children Research Network. *Pediatrics Drugs*, 11, 14-15.

185. O'CONNELL, D. (2007) Neglected diseases. *Nature* 449:157.

186. ONDRUSEK, N., ABRAMOVITCH, R., PENCHARZ, P. & KOREN, G. (1998) Empirical examination of the ability of children to consent to clinical research. *Journal of Medical Ethics*, 24, 158-165.

187. PANDOLFINI, C. & BONATI, M. (2005) A literature review on off-label drug use in children. *European Journal of Pediatrics*, 164, 552-8.

188. PANDOLFINI, C., BONATI, M. (2008) European paediatric research and children's therapeutic needs. A trial review. *Acta Paediatrica*, 97, 1232-7.

189. PANDOLFINI, C. & BONATI, M. (2009) Children's presence in research. A review of online registers. *European Journal of Clinical Pharmacology*, 65, 873-880.

190. PANDOLFINI, C., BONATI, M., REGGI, V. & FIGUERAS, A. (2003) Regulatory assessment of new drugs in developing countries. *Lancet*, 362, 249-50.

191. PANDOLFINI, C., BONATI, M., SAMMONS, H.M. (2009) Registration of trials in children: update of current international initiatives. *Archives of Disease in Childhood* ;94:717-719.

192. PAPANIKOLAOU, P. N., CHRISTIDI, G. D. & IOANNIDIS, J. P. (2006) Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *Canadian Medical Association Journal*, 174, 635 - 641.

193. PAPANIKOLAOU, P. N. & IOANNIDIS, J. P. A. (2004) Availability of large-scale evidence on specific harms from systematic reviews of randomized trials. *The American Journal of Medicine*, 117, 582-589.

194. PATEL, P., MULLA, H., TANNA, S., PANDYA, H. (2010) Facilitating pharmacokinetic studies in children: a new use of dried blood spots. *Archives of Disease in Childhood*, 95:484-487

195. PEARCE, N., AÏT-KHALED, N., BEASLEY, R., MALLOL, J., KEIL, U., MITCHELL, E., ROBERTSON, C. (2007) Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*, 62, 758-766.

196. PECOUL, B., CHIRAC, P., TROUILLER, P. & PINEL, J. (1999) Access to Essential Drugs in Poor Countries: A Lost Battle? *Journal of the American Medical Association*, 281, 361-367.

197. PERMANAND, G., MOSSIALOS, E. & MCKEE, M. (2007) The EU's new paediatric medicines legislation: serving children's needs? *Archives of Diseases in Childhood*, 92, 808-811.

198. PIRMOHAMED, M., JAMES, S., MEAKIN, S., GREEN, C., SCOTT, A. K., WALLEY, T. J., FARRAR, K., PARK, B. K. & BRECKENRIDGE, A. M. (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *British Medical Journal*, 329, 15-19.

199. PITROU, I., BOUTRON, I., AHMAD, N. & RAVAUD, P. (2009) Reporting of Safety Results in Published Reports of Randomized Controlled Trials. *Archives of Internal Medicine*, 169, 1756-1761.

200. POCOCK, S., WANG, D., WILHELMSEN, L., HENNEKENS, C. (2005) The data monitoring experience in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *American Heart Journal*, 149(5), 939-943.

201. POCOCK, S., WILHELMSEN, L., DICKSTEIN, K., FRANCIS, G., WITTES, J. (2004) The data monitoring experience in the MOXCON trial. *European Heart Journal*, 25(22): 1974-1978.

202. PRITCHARD-JONES, K. & PRITCHARD, J. (2004) Success of clinical trials in childhood Wilms' tumour around the world. *Lancet*, 364, 1468-1470.

203. RAWLINS, M. (2008) De testimonio: on the evidence for decisions about the use of therapeutic interventions. *Lancet*, 372(9656): 2152-61.

204. RERKASEM, K., ROTHWELL, P.M. (2010) Meta-analysis of small randomized controlled trials in surgery may be unreliable. *British Journal of Surgery*, 97, 466-469.

205. RICKERT, V. I., TIEZZI, L., LIPSHUTZ, J., LEON, J., VAUGHAN, R. D. & WESTHOFF, C. (2007) Depo Now: Preventing Unintended Pregnancies among Adolescents and Young Adults. *Journal of Adolescent Health*, 40(1):22-8.

206. ROBERTS, R., RODRIGUEZ, W., MURPHY, D. & CRESCENZI, T. (2003) Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *Journal of the American Medical Association*, 290, 905-11.

207. ROBINSON, K. A. (2005) Should meta-analysts search Embase in addition to Medline? *Journal of Clinical Epidemiology*, 58, 320-320.

208. ROCHON, P. A., MASHARI, A., COHEN, A., MISRA, A., LAXER, D., STREINER, D. L., DERGAL, J. M., CLARK, J. P., GOLD, J. & BINNS, M. A. (2004) Relation between randomized controlled trials published in leading general medical journals and the global burden of disease. *Canadian Medical Association Journal*, 170, 1673-1677.

209. RODRIGUEZ, W., SELEN, A., AVANT, D., CHAURASIA, C., CRESCENZI, T., GIESER, G., DI GIACINTO, J., HUANG, S.-M., LEE, P., MATHIS, L., MURPHY, D., MURPHY, S., ROBERTS, R., SACHS, H. C., SUAREZ, S., TANDON, V. & UPPOOR, R. S. (2008) Improving Pediatric Dosing Through Pediatric Initiatives: What We Have Learned. *Pediatrics*, 121, 530-539.

210. ROSE, K. (2009) Challenges in pediatric drug development: A pharmaceutical industry perspective. *Pediatric Drugs*, 11, 57-59.

211. ROYAL COLLEGE OF PAEDIATRICS AND CHILD HEALTH (2000) Guidelines for the ethical conduct of medical research involving children. *Archives of Disease in Childhood*, 82, 177-182.

212. SACKETT, D. L., ROSENBERG, W. M., GRAY, J. A., HAYNES, R. B., RICHARDSON, W. S. (1996) Evidence based medicine: what it is and what it isn't. *British Medical Journal*, 312, 71-2.

213. SAINT-RAYMOND, A. & SEIGNEURET, N. (2009) The European paediatric initiative: 1 Year of experience. *Pediatric Drugs*, 11, 9-10.

214. SAMMONS, H. (2009) Ethical issues of clinical trials in children: a European perspective. *Archives of Diseases in Childhood*, 94, 474-477.

215. SAMMONS, H. M., ATKINSON, M., CHOONARA, I., STEPHENSON, T.(2007) What motivates British parents to consent for research? A questionnaire study. *BMC Pediatrics*, 7, 12.

216. SAMMONS, H. M., CHOONARA, I. (2005) Clinical trials of medication in children, 1996-2002. *European Journal of Clinical Pharmacology*, 61, 165-7.

217. SAMMONS, H. M., GRAY, C., HUDSON, H., CHERRILL, J., CHOONARA, I. (2008) Safety in paediatric clinical trials--a 7-year review. *Acta Paediatrica*, 97, 474-7.

218. SAMMONS, H. M., NAYLOR, C., CHOONARA, I., PANDOLFINI, C., BONATI, M. (2005) Should paediatricians support the European Paediatric Clinical Trials Register? *Archives of Disease in Childhood*, 90, 559-60.

219. SAMPSON, M., BARROWMAN, N. J., MOHER, D., KLASSEN, T. P., PHAM, B., PLATT, R., ST JOHN, P. D., VIOLA, R., RAINA, P., (2003) Should meta-analysts search Embase in addition to Medline? *Journal of Clinical Epidemiology*, 56, 943-55.

220. SCHIRM, E., TOBI, H., DE VRIES, T. W., CHOONARA, I. & DE JONG-VAN DEN BERG, L. T. (2003) Lack of appropriate formulations of medicines for children in the community. *Acta Paediatrica*, 92, 1486-9.

221. SCHMIDT, B., GILLIE, P., CACO, C., ROBERTS, J. & ROBERTS, R. (1999) Do sick newborn infants benefit from participation in a randomized clinical trial? *Journal of Pediatrics*, 134, 151-155.

222. SCHREINER, M. S. & GREELEY, W. J. (2002) Pediatric Clinical Trials: Shall We Take a Lead? *Anesthesia and Analgesia*, 94, 1-3.

223. SCOTT RA, L. S., SANDER JW. (2001) The treatment of epilepsy in developing countries: where do we go from here? *Bulletin of the World Health Organization* , 79, 344-51.

224. SCHULZ, K. F., CHALMERS, I., HAYES, R. J. & ALTMAN, D. G. (1995a) Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association*, 273, 408-12.

225. SCHULZ, K. F., GRIMES, D.A., ALTMAN, D.G., HAYES, J. (1996) Blinding and exclusions after allocation in randomised controlled trials: survey of published parallel group trials in obstetrics and gynaecology. *British Medical Journal*, 312:742-744

226. SCHULZ, K. (1995b) Subverting Randomization in Controlled Trials. *Journal of the American Medical Association*, 274: 1456-1458.

227. SEIBERT-GRAFE, M., BUTZER, R. & ZEPP, F. (2009) German paediatric research network (PAED-Net). *Pediatric Drugs*, 11, 11-13.

228. SHAH, S., WHITTLE, A., WILFOND, B., GENSLER, G. & WENDLER, D. (2004) How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research? *Journal of the American Medical Association*, 291, 476-482.

229. SHANN, F. & STEINHOFF, M. C. (1999) Vaccines for children in rich and poor countries. *Lancet*, 354, SII7-SII11.

230. SHIRKEY, H. (1999) Therapeutic orphans. *Pediatrics*, 104, 583-4.

231. SHIRKEY, H (1968) Therapeutic orphans. *Journal of Pediatrics*, 72(1): 119-20.

232. SHUSTER, E. (1997) . Fifty years later: the significance of the Nuremberg Code. *New England Journal of Medicine*, 337:1436-40.

233. SIFERS, S. K., PUDDY, R. W., WARREN, J. S., ROBERTS, M. C. (2002) Reporting of demographics, methodology, and ethical procedures in journals in pediatric and child psychology. *Journal of Pediatric Psychology*, 27, 19-25.

234. SLUTSKY, A. S. & LAVERY, J. V. (2004) Data safety and monitoring boards. *New England Journal of Medicine*, 350, 1143-7.

235. SMITH, P. B., BENJAMIN, D. K., JR., MURPHY, M. D., JOHANN-LIANG, R., IYASU, S., GOULD, B., CALIFF, R. M., LI, J. S. & RODRIGUEZ, W. (2008) Safety monitoring of drugs receiving pediatric marketing exclusivity. *Pediatrics*, 122, e628-33

236. SMYTH, R. L. (2007) Making a difference: the clinical research programme for children. *Archives of Disease in Childhood*, 92, 835-837.

237. SMYTH, R. L. (2001) Research with children. *British Medical Journal*, 322, 1377-1378.

238. SMYTH, R. L. & WEINDLING, A. M. (1999) Research in children: ethical and scientific aspects. *Lancet*, 354, SII21-SII24.

239. STANDING, J. F., KHAKI, Z. F. & WONG, I. C. (2005) Poor formulation information in published pediatric drug trials. *Pediatrics*, 116, e559-62.

240. STANDING, J. F. & TULEU, C. (2005) Paediatric formulations--Getting to the heart of the problem. *International Journal of Pharmaceutics*, 300, 56-66.

241. STEINBROOK, R (2002) Testing medications in children. *New England Journal of Medicine*, 347, 1462-70.

242. SUAREZ-ALMAZOR, M. E., BELSECK, E., HOMIK, J., DORGAN, M. & RAMOS-REMUS, C. (2000) Identifying Clinical Trials in the Medical Literature with Electronic Databases: MEDLINE Alone Is Not Enough. *Controlled Clinical Trials*, 21, 476-487.

243. SULLIVAN, P. B., LEWINDON, P. J., CHENG, C., LENEHAN, P. F., KUO, B. S., HASKINS, J. R., GOODLAD, R. A., WRIGHT, N. A., DE LA IGLESIA, F. A. (2007) Intestinal mucosa remodeling by recombinant human epidermal growth factor(1-48) in neonates with severe necrotizing enterocolitis.[erratum appears in J Pediatr Surg. 2007 Aug;42(8):1470 Note: dela Iglesia, Felix A [corrected to de la Iglesia, Felix A]]. *Journal of Pediatric Surgery*, 42, 462-9.

244. SWINGLER, G. H., VOLMINK, J. & IOANNIDIS, J. P. A. (2003) Number of published systematic reviews and global burden of disease: database analysis. *British Medical Journal*, 327, 1083-1084.

245. T' JONG, G. W., STRICKER, B. H., CHOONARA, I., VAN DEN ANKER, J. N.(2002) Lack of effect of the European guidance on clinical investigation of medicines in children. *Acta Paediatrica*, 91, 1233-8.

246. T' JONG, G.W., ELAND, I.A., STURKENBOOM, M.C., VAN DEN ANKER, J.N., STRICKER, B.H. (2002) Unlicensed and off label prescription of drugs to children: population based cohort study. *British Medical Journal*, 324: 1313-4.

247. T' JONG, G. W., VULTO, A. G., DE HOOG, M., SCHIMMEL, K. J. M., TIBBOEL, D. & VAN DEN ANKER, J. N. (2001) A Survey of the Use of Off-Label and Unlicensed Drugs in a Dutch Children's Hospital. *Pediatrics*, 108, 1089-1093.

248. TAIT, A. R., VOEPEL-LEWIS, T. & MALVIYA, S. (2003) Participation of Children in Clinical Research: Factors that Influence a Parent's Decision to Consent. *Anesthesiology*, 99, 819-825.

249. TEBBI, C. K., LONDON, W. B., FRIEDMAN, D., VILLALUNA, D., DE ALARCON, P. A., CONSTINE, L. S., MENDENHALL, N. P., SPOSTO, R., CHAUVENET, A., SCHWARTZ, C. L. (2007) Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *Journal of Clinical Oncology*, 25, 493-500.

250. THAKUR, A., WANG, E. C., CHIU, T. T., CHEN, W., KO, C. Y., CHANG, J. T., ATKINSON, J. B., FONKALSRUD, E. W. & GROSFELD, J. L. (2001) Methodology standards associated with quality reporting in clinical studies in pediatric surgery journals. *Journal of Pediatric Surgery*, 36, 1160-4.

251. THIERS, F. A., SINSKEY, A. J. & BERNDT, E. R. (2008) Trends in the globalization of clinical trials. *Nature Reviews Drug Discovery*, 7, 13-14.

252. TROTTER, A., MAIER, L., KRON, M., POHLANDT, F. (2007) Effect of oestradiol and progesterone replacement on bronchopulmonary dysplasia in extremely preterm infants.[erratum appears in Arch Dis Child Fetal Neonatal Ed. 2007 May;92(3):F234]. *Archives of Disease in Childhood Fetal & Neonatal Edition*, 92, F94-8.

253. TROUILLER, P. & OLLIARO, P. L. (1999) Drug development output from 1975 to 1996: What proportion for tropical diseases? *International Journal of Infectious Diseases*, 3, 61-63.

254. TURNER, S., LONGWORTH, A., NUNN, A. J., CHOONARA, I. (1998) Unlicensed and off label drug use in paediatric wards: prospective study. *British Medical Journal*, 316, 343-5.

255. TURNER, S., NUNN, A. J., FIELDING, K., CHOONARA, I. (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica*, 88, 965-8.

256. TUTAREL, O. (2005) How international are leading general paediatric journals? *Archives of Disease in Childhood*, 90, 816-7.

257. UNITED NATIONS DEVELOPMENT PROGRAMME (UNDP) (2002). Human development report 2002. Available from: http://hdr.undp.org/en/reports/global/hdr2002/. Accessed 17-9-2008.

258. UNITED NATIONS DEVELOPMENT PROGRAMME (UNDP) (2007) Human Development Report 2007/2008, New York, Palgrave Macmillan.

259. UNGAR, D., JOFFE, S., KODISH, E. (2006) Children are not small adults: documentation of assent for research involving children. *Journal of Pediatrics*, 149, S31-3.

260. UNICEF (2009). The State of the World's Children 2009: Maternal and Newborn Health. Available at http://www.unicef.org/publications/index_47127.html. Accessed 12-2-2010.

261. UNICEF (2009) Global child mortality continues to drop. Press release. Available at: http://www.unicef.org/media/media_51087.html. New York. Accessed 13-5-2010.

262. US NATIONAL LIBRARY OF SCIENCES. (2008) MEDLINE factsheet. Available at http://www.nlm.nih.gov/pubs/factsheets/medline.html. Accessed 15-1-2010.

263. VANDENBROUCKE, J. P. (2004) Benefits and harms of drug treatments. *British Medical Journal*, 329, 2-3.

264. VAN MEURS, K. P., HINTZ, S. R., EHRENKRANZ, R. A., LEMONS, J. A., BALL, M. B., POOLE, W. K., PERRITT, R., DAS, A., HIGGINS, R. D., STEVENSON, D. K. (2007) Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. *Journal of Perinatology*, 27, 347-52.

265. VAN STUIJVENBERG, M., SUUR, M. H., DE VOS, S., TJIANG, G. C., STEYERBERG, E. W., DERKSEN-LUBSEN, G., MOLL, H. A.(1998) Informed consent, parental awareness, and reasons for participating in a randomised controlled study. *Archives of Disease in Childhood*, 79, 120-5.

266. VIST, G. E., HAGEN, K. B., DEVEREAUX, P. J., BRYANT, D., KRISTOFFERSEN, D. T. & OXMAN, A. D. (2005) Systematic review to determine whether participation in a trial influences outcome. *British Medical Journal*, 330, 1175-82.

267. WALLER, D. G. (2007) Off-label and unlicensed prescribing for children: have we made any progress? *British Journal of Clinical Pharmacology*, 64, 1-2.

268. WATTS, G. (2007) WHO launches campaign to make drugs safer for children. *British Medical Journal*, 335, 1227-.

269. WEBER, E. H., TIMMERMANS, I. T. F. & OFFRINGA, M. (2009) The Dutch medicines for children research network: A new resource for clinical trials. *Pediatric Drugs*, 11, 161-163.

270. WEIL, E., NELSON, R. M., ROSS, L. F. (2002) Are research ethics standards satisfied in pediatric journal publications? *Pediatrics*, 110, 364-70.

271. WEISS, C.F., GLAZKO, A.J, WESTON, J.K. (1960) Chloramphenicol in the newborn infant. *New England Journal of Medicine*, 262, 787-794.

272. WILCZYNSKI, N. L., MCKIBBON, K. A., HAYNES, R. B. (2007) Response to Glanville et al.: How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association*, 95, 117-8.

273. WILSON, J. T. (1999) An update on the therapeutic orphan. *Pediatrics*, 104, 585-90.

274. WONG, S. S., WILCZYNSKI, N. L., HAYNES, R. B. (2006) Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. *Journal of the Medical Library Association*, 94, 451-5.

275. WOODS, D., TREWHEELLAR, K. (1998) Medline and Embase complement each other in literature searches. *British Medical Journal*, 316, 1166.

276. WORLD BANK (2007) World Development Indicators 2007, Washington DC, The World Bank.

277. WORLD HEALTH ORGANIZATION (WHO) (2008). The global burden of disease: 2004 update. WHO, Geneva. Available at: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html. Accessed 20-3-2010.

278. WORLD HEALTH ORGANIZATION (WHO) (2005). Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards. World Health Organization, Geneva. Available at http://apps.who.int/tdr/svc/publications/tdr-research-publications/operational-guidelines. Accessed 7-8-2008.

279. WORLD HEALTH ORGANIZATION (WHO) (2007) International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2007. Available at http://apps.who.int/classifications/apps/icd/icd10online/. Accessed 23-9-2008.

280. WORLD HEALTH ORGANIZATION (WHO) (2008) Collaborating Centre for Drug Statistics Methodology ATC/DDD Index. Available at http://www.whocc.no/atc_ddd_index/. Accessed 14-8-2008.

281. WORLD MEDICAL ASSOCIATION. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed 19-9-2009.

282. YUSUF, S. (2002) Clinical research and trials in developing countries. *Statistics in Medicine,* 21(19):2859-2867.

283. ZHANG, D., YIN, P., FREEMANTLE, N., JORDAN, R., ZHONG, N. & CHENG, K. K. (2008) An assessment of the quality of randomised controlled trials conducted in China. *Trials*, 9, 22.

APPENDICES

1. COUNTRY SETTINGS OF SINGLE COUNTRY RCTS

Country	No of RCTs	Country	No of RCTs
USA	115	Guatemala	2
India	32	South Africa	2
Turkey	27	Pakistan	2
Iran	25	Sudan	2
Germany	21	Tanzania	2
Canada	20	Benin	2
United Kingdom	19	Switzerland	1
Italy	17	Greece	1
Brazil	16	Singapore	1
Australia	14	Qatar	1
Netherlands	13	Czech Republic	1
France	11	Hungary	1
Japan	10	Poland	1
Israel	9	Chile	1
Thailand	8	Lithuania	1
South Korea	8	Argentina	1
Egypt	8	Cuba	1
Nigeria	8	Kazakhstan	1
China	8	Colombia	1
Taiwan	6	Jordan	1
Denmark	6	Gabon	1
Belgium	5	Indonesia	1
Mexico	5	Cambodia	1
Vietnam	4	Madagascar	1
Sweden	4	Senegal	1
Hong Kong	4	Gambia	1
Saudi Arabia	4	Guinea	1
Uganda	4	Guinea-Bissau	1
Austria	4	Mali	1
Spain	3	Congo	1
Croatia	3	TOTAL	508
Lebanon	3		
Ghana	3		
Nepal	3		
Bangladesh	3		
Burkina Faso	3		
Afghanistan	3		
Mozambique	3		
Finland	2		
New Zealand	2		
Russia	2		
Tunisia	2		
Philippines	2		

2. ALL RCTS THAT REPORTED A SERIOUS ADVERSE EVENT (SAE)

Ref	Drug	Control/ Comparator	Disease	Age	N	Country	SAEs	Comments
18	Vancomycin	Teicoplanin	Cardiac surgery -post op MRSA prophylaxis	0-28 months	11 vs 11	Japan	1 death Post-op Cr increase 2xVan	
44	IFN-Beta	Azathioprine	Multiple Sclerosis	13-48 years	47 vs 47 ?paed	Iran	1xsevere depression	GI Ses Flu-like Sx
78	Deferiprone PO Desferrioxamine IV	Deferiprone PO	Thalassemia major	5-24.5 Years	12 vs 12	Turkey	1 death arrhythmia-CHF 1 agranulocytosis Neutropaenia - 3xDFO, 2xDFP Aseptic meningitis Acute cerebellar syndrome	Nausea Arthralgia grade 2
109	IV methylpred	Nebulised budesonide OR untreated control	Meconium Aspiration Syndrome	Neonates	34 v 32 v 33	India	Death x2 – pneumothorax, DIC (both control group) Hypotension req. inotropes: 4 v 3 v ? (control)	
128	SP-Artesunate	CQ vs SP vs SP-AS	Malaria	6-59 Months	79 vs 77 vs 81	Benin	Convulsions Severe anaemia ARIs Pyomyositis	
161	Levetiracetam	Placebo	Idiopathic generalised epilepsy	4 to 65 years	80 v 84	Eu,NA,Mex, Aus/NZ	Agression, depression, suicide attempt	?paed SAE Hypotension
206	Mannitol	Placebo	Cerebral Malaria	6-60 months	80 vs 76	Uganda	22 deaths + 1 lost to f/up 10 vs 13 (not sig)	No other AEs
227	Fexofenadine 15mg OR 30mg	Placebo	Allergic rhinitis	6 mo – 2 years	85 v 108 v 199	US	RSV x 1 – placebo group	GI sx

228	Levalbuterol	Racemic albuterol	Asthma	12 and above	496 v 250	US	SAEs 18v13 –no details	
288	Triethyl citrate + ethyl linoleate lotion	Vehicle	Acne	16-45 ?paed	20 vs 20	UK	1 depression (unrelated)	?paed
298	Venlafaxine ER	Placebo	Paed Social Anxiety Disorder	8-18 years	148 vs 137	US	Suicidal ideation 3 Ven vs 0 plc	Multiple TEAEs Behavioural AEs
317	Liposomal AmB + Caspofungin	Lipo AmB (hi-dose)	Invasive Aspergillosis – haem. Malignancies	16-75	15 vs 15	France	3 deaths (unrelated) Renal disorder (related)	
410	Recombinant Factor VIIa Bolus	Continuous Vs control	Haemophilia undergoing surgery	10-67 years	12 vs 12 vs 12	US	Haemorrhage/ haematoma (Rx failure) Deep thrombophlebitis	Multiple other AEs
429	Methylphenidate (crossover placebo, 5, 10, 15 mg – 6 dosing orders)	Placebo	Bipolar disorder & ADHD	5-17 yrs	20	US	Hospitalisation for mood sx – before any Rx	Discont x2 – elevated liver enzymes, urticaria & vomiting
438	Azithromycin PO 4.5g OR 6.0g OR 7.5g	3 doses	Acne	16-37 years	36 v 34 v 34	Croatia	Ankle fracture	Elevated AST GI Sx
469	Botulinum-A Toxin Alone (intravesical)	Botox+ anticholinergics	Neuropathic bladder	2-11 years	12 v 11	Saudi Arabia	Acute pyelonephritis (f/up)	
489	Sibutramine	Placebo (crossover)	Secondary Obesity	7-20 yrs	45	Sweden	2 depression – plc 3 tumour recurrence Type 2 DM - plc	
518	Dexamethasone	Placebo	Bacterial meningitis	15-91 yrs	217 vs 238	Vietnam	49 deaths (22 vs 27 not sig) GI bleeding (p=0.2)	Herpes (p=0.69) ?paed
521	IV Valproate	IV Diazepam	Status epilepticus	5-144 months	20 vs 20	India	7 deaths (4 vs 3) Resp depress 0 vs 12 Hypotension 0 vs 10	Breakthrough seiz 8 vs 8

557	Ketoconazole Topical	Placebo vehicle	Seborrhoeic dermatitis	12 and older	1162	US	1% SAEs – 13. Diverticulitis, CVA, CHF, CAD – all rated unrelated	?paed Local sx
562	Ciclesonide inh 80 mic 160 mic	Fluticasone inh	Persistent asthma	12-75 years	278 vs 270 vs 259	Multi EU Countries	SAEs: 3 vs 4 vs 3 Not mentioned	
574	Quinine rectal	Quinine IV	Cerebral Malaria	6 mo – 5 years	56 vs 54	Uganda	Neuro sequelae 1 vs 3 Death 4 vs 5	No PR bleeds No SEs known with quinine Vomiting 3 vs 10
575	Nifurtimox-eflornithine	Eflornithine	Sleeping sickness Trypanosoma brucei gambiense	15-70 years	51 vs 52	Congo	Death 1 – treatment failure* 247 drug reactions* 14 major drug reactions* Seizures 4 vs 1 Arrhythmia 1 vs 1 Neutropaenia/anaemia 1 vs 6	
576	Valtropin (rhGH)	Humatrope (rhGH)	Growth Hormone Deficiency	3-11 years	98 vs 49	Morocco Turkey S.Africa Russia Slovakia Serbia	9 SAEs 7 vs 2 1 gen. urticarial rash 1 high Alk.phos+vit D def 1 ALL***	
593	Bupropion X 2 doses	Placebo	Smoking cessation	14-17 yrs	103 vs 105 vs 104	US	Jimson weed poisoning Suicide attempt Pregnancy	
607	Amoxicillin PO	Benzylpenicillin IV	Comm. Acq. Pneumonia	1.4-5.4 yrs	100 vs 103	UK	3 Empyema IV vs 0 PO	

617	Early Fixed-dose Insulin Rx	Std glycaemia monitoring	VLBL neonates Hyperglycaemia	Preterm neonates	8 vs 8	UK	3 deaths	
626	Botulinum toxin A	Different dosing regimen	Cerebral palsy	2-8 yrs	42	Australia	Epilepsy Shunt malfunction Fractures	All unrelated
657	Benazepril	Placebo	IgA nephropathy	9-35 yrs	32 vs 34	EU	1 death – car accident Pregnancy – interrupted	
675	Ibuprofen PO	Indomethacin PO	Patent Ductus Arteriosus	Preterms	18 vs 18	Iran	Death 1 sepsis vs 1 NEC NEC 0 vs 3 p=.03	
689	Levofloxacin	Amoxiclav/ceftriaxone (0.5 - <5) Clarith/ceft+clarith or erythro) >5	Community-acquired pneumonia	6 month – 16 years	529 vs 180	Argentina Brazil Chile Costa Rica Mexico Panama US	33 vs 8 (6% vs 4%) Respiratory 13 vs 4 1 Hepatomegaly (possible) <u>Probable/very likely:</u> Hepatitis Rash Aggravated pneumo. 2 deaths*** 1 bronchoscopy procedure 1 severe bronchospasm	
693	Infliximab	Placebo	Juvenile RA	4-17 yrs	60	NA,SA,Eu	2 deaths Serious infections + inf. reactions + SAEs higher in Ix 3mg/kg group	6mg/kg group better
710	IV Valproate	IV Phenytoin	Status epilepticus	2-17 (22 pts)	22	India	8 deaths ?paed Diazepam – hypotension, resp. depression	Valproate-elevated liver enzymes
716	Ciclesonide	Fluticasone	Asthma	12-74	233 vs 239	Eu, S.Africa	SAEs not described – unrelated	

720	Caffeine citrate	Placebo	Apnoea of prematurity	Preterm neonates	1006 vs 1000	US	Death + Neurodevelopmental disability	Caffeine sig. better than plc – death & neurodevelopmental disability
723	Dexa. IV vs Dexa+Glycerol PO vs Glycerol PO	Vs Placebo IV + PO 4 arms Double dummy for all	Bacterial meningitis	2-184 months	166 vs 156 vs 166 vs 163	Latin America Dominica Ecuador Argentina Venezuela Brazil	Death 23v20v17v**26** p=.3 Neuro seq 10v8v7v**19** p=.02* Hearing loss 10v9v12v12 PR blood **6**v**5**v1v2 p=.03*	
754	Fluoxetine	Placebo	Adolescent depression	12-17 yrs	439	US	Suicidal ideation!	TADS study – multiple papers Suicidal ideation prominent
766	Olanzapine	Placebo	Bipolar Mania	13-17 yrs	107 vs 54 (plc)	US	Exacerbation of bipolar Neutropaenia? Suicidal ideation – TEAE	?blood dyscrasia – not discussed
771	Idebenone X 3 doses	Placebo	Friedreich's Ataxia	9-17 yrs	48	US	Chest pain GI symptoms Neutropaenia- related	
784	Ceftriaxone + amikacin	Imipenem	Febrile neutropaenia	18 and below	66 vs 63	Egypt	4 Deaths (2 vs 2)	Reversible cholestasis –C+A, p=0.02 GI symptoms – Imipenem, p=0.05

798	Carvedilol Low & high dose	Placebo	Heart failure	Below 18	161	US	11 deaths (5 vs 3 vs 3 -not sig) Worsening heart failure	Favouring carvedilol but not sig. Underpowered?!
799	Continuous SC Insulin Inj. (Aspart/Lispro Insulin – quick acting)	Multiple Daily Inj. (Glargine OD + human Insulin)	Type 1 DM	9-18 years	18 vs 18	Italy	Severe hypo (similar in both groups)	No description of AEs
815	Salmeterol/fluticatisone	3 doses	Persistent asthma	12 -76 yrs	325	Canada	Multiple SAEs None related	Candidiasis Hoarseness Throat irritation
823	Growth Hormone	No Treatment	Turner Syndrome	9 mo – 4 years	45 vs 44	US	4 vs 4 Gastro Bac. Pneumonia Bleeding post-tonsillectomy Hypoxaemia post adenoidectomy	All Unrelated
828	Atomoxetine	Placebo	ADHD + Major depression	12-18 years	72 vs 70	US	1 worsening depression – placebo group	Discont – Atx grp. Mod.nausea Aggression – 2 in placebo No mania Mild Aes more in Atx grp
873	Ibuprofen high-dose	Placebo	Cystic Fibrosis	6-18 yrs	142	Canada	GI bleed x 1 – significant	SMC recommended H2-antagonists post event
894	Amifostine	No treatment	Chemo for Osteosarcoma (toxicity protection)	7-15 years	15 vs 13	Mexico	Death x 1 – relapse Renal tox – 20%v30% Audio tox-100%v80% Cardiotox- 0v2	Grade 3 vomiting 93%v7% p=0.000

903	Miglustat	No Rx	Niemann-Pick C disease	4-11 yrs, 12 above	12, 29	US,UK	Severe confusion Salivary hypersecretion Severe dehydration RSV infection depression None related	
921	Budesonide + Formoterol	Budesonide & Formoterol alone, placebo	Asthma	12 -78 yrs	480	US	Lobar pneumonia Facial fracture Intestinal obstruction None related	Mild arrhythmias Upper airway Sx No cardiac SAEs
929	Budesonide inh suspension 4 doses	Budesonide dry-powder inh	Asthma	12-65 yrs	57 paed	US	8 SAEs Asthma x 2, others unrelated	Mild AEs – upper resp. tract mainly
931	Ertapenem	Ticarcillin/clavulanate	Intra-abdo/pelvic Infections	2-17 yrs	84 vs 28	US,Mex, Brazil	14 SAEs 11 vs 3 Abdo abscess (Er)	Diarrhoea – C.difficile negative (Er) Rated as severe ADR Rash (T/c) Rated ADRs 10 (Er) vs 6 (T/c)
943	Recombinant factor VIII	Regular vs episodic infusions	Severe haemophilia A	6-30 months	32 vs 33	US	Life-threatening bleeding 3 (episodic) vs 0 High titer inhibitor 0 vs 2	

946	Doxo,Bleo,Vinb,Dacarbazine + RT	No Rx RT only	Hodgkin's Lymphoma	16-75yrs recruited ? paed	16 below 20 ?paed	Eu	51 deaths Multiple toxicity	Onco
957	Amphotericin B	1mg/kg OR 0.75mg/kg alt day OR 1mg/kg OR 0.75mg/kg daily	Indian visceral leishmaniasis	2-65 yrs	245 v 244 v 500 v 496	India	14 deaths 13 discont d/t toxicity - vomiting&diarrhoea - hepatotoxicity - nephrotoxicity - severe thrombocytopaenia - recurrent hypothermia	Increased fever and rigours
965	Levocetirizine	Placebo	Atopic children	12-24 months	255 v 255	10 Euro countries, Aus, S.Africa	SAEs 12.2v14.5% ALL x1 – judged unlikely **Febrile convulsion 4v0-judged unlikely Bronchopneumonia 4v1 Cough 4v2 Pneumonia 2v0 (see table of SAEs)	Discont 2v1.2% - unrelated to med
976	Denufosol tetrasodium 20mg OR 40mg OR 60mg	Placebo	Cystic fibrosis	8-45yrs (62<18 years)	23 v 22 v 23 v 21	US	Hodgkins lymphoma Pulm oedema – both considered unrelated 5 disconts – 0v2v1v2 Haemoptysis, pulm fx test decrease, lung infiltration, cough	Cough Lung fx test decrease-resolving later OxyHb sat decrease- Not clinically sig
977	Inactivated Polio vax	Both OR Oral polio vax	Prophylaxis of polio	6-11 week infants	166 v 168 v 166	Guatemala	1 death – PDA 26 SAEs – hosp. d/t diarrhoea, resp diseases All rated unrelated	Fever Mild sx Local reactions

1001	Invasive chemo with high-dose cytarabine & methotrexate (ONCO)	Std post-remission rx	ALL	12 months or younger infants	95 v 96	22 countries	25 deaths and multiple toxic events: Infections Mucocitis Renal Liver Neuro	Non-sig diff in EFS
1007	Albuterol neb 1.25mg OR 0.62mg	Placebo	Moderately severe asthma	6-12 yrs	115 v 117 v 117	US	6 SAES- undescribed, rated unrelated	Beta-adrenergic sx
1013	Dexamethasone	Placebo	Mod-severe bronchiolitis	2-12 months	305 v 295	US	Pneumonia 1v2-empyema	Vomiting 5.5v4.7%
1017	Salmeterol/Fluticasone	Fluticasone	Moderate asthma	12-80 yrs	182 v 180	9 countries	3 SAEs- undescribed, rated unrelated 1 discont- headache	Upper resp. sx Oral candidiasis
1022	Ciclesonide intranasal	Placebo	Perennial allergic rhinitis	12-73 yrs	441 v 222	US	SAEs 16v6 all rated unrelated	Epistaxis Pharyngolaryngeal pain Sinusitis higher in ciclesonide
1037	Topiramate 400mg/kg maintenance dose (titrated)	Topiramate 50mg/kg Maintenance dose (titrated)	Epilepsy	6-15 yrs	77 v 74	US, Canada, Europe, S.America	Testicular torsion, appendicitis (rated unrelated) 7 disconts in higher dose-neurobehavioural AEs	Dose related: Wt loss, paraesthesia, mood problems, non-specific cognitive dysfunction
1123	Ciclesonide	Budesonide	Asthma	6-11 yrs	416v 205	8 countries 6 Euro, Aus, S.Africa	SAEs 4v4 –all rated unrelated Disconts 2.9v1.0% - asthma exacerbations	URT sx Oral candidiasis dysphonia

1125	Recomb. Growth hormone	No treatment	Juvenile idiopathic arthritis on steroid rx	18mo-9yrs (girls), 11yrs (boys)	15v15	France	Deaths x2- post-op for spinal cord compression Discont x4 incl. deaths – BMTx2	Fasting hyperinsulinaemia 47v7%,p=0.03 Elevated HbA1C 7v1,p=0.03 Asymp DM 1v0 – resolved ?steroid-related
1165	Olanzapine	Quetiapine AND risperidone	Early psychosis	16-40 yrs	133 v 134 v 133	USA	SAEs 4v7v7 Olanzapine-2 suicide attempts + 1 alleged homicide Quetiapine-2 suicides + 1 suicidal ideation Risperidone – 1 suicide attempt	Extrapyramidal sx ???Paed
1169	Seq high-dose chemo (ONCO)	Single. high-dose chemo	Relapse/ refractory germ cell tumours	16-59 yrs	108v 103	Germany	***Terminated – excess toxicity in arm B Mortality 4v16%,p<.01 Multiple rx-related toxicities	TERMINATED ?paed
1228	Paromomycin	Amphotericin B	Visceral leishmaniasis	5-55 yrs	502 v 165 Paed 188v64	India	4 deaths – before rx, alcoholic (rated poss. related), septicaemia (unrelated), gastro (prob. related to amphotericin). 2 more SAEs: Elevated LFTs Bacterial pneumonia ???ages	Inj-site pain, ototoxicity, elevated LFTs in paro. Pyrexia,rigors, Vomiting, nephrotoxicity in amphotericin
1238	Intensified maintenance chemo. (ONCO)	No treatment	Post-remission Acute Promyelocytic Leukaemia	15-70yrs	89 v 86	Japan	***Relapses 28v10% Deaths 15v3% ?ages	***Treatment more toxic

1253	IV Terbutaline	Placebo (NSaline)	Status asthmaticus	2-17 yrs	25 v 21	US	Cardiac arrhythmia x1 Hypotension 8v9	Hyperglycaemiax1 Chest pain x1
1262	Anidulafungin	Fluconazole	Invasive candidiasis	16-91 yrs	127 v 118	US	SAEs 2v2 Anidula-AF,seizures Fluconazole-DVT, el. LFTs Disconts 15v27	
1286	ChemoRT with carboplatin (ONCO)	ChemoRT with cisplatin	Locoregionally advanced Ca nasopharyngeal	16-70 yrs	106 v 101	Thailand	Deaths 18.1v15.8% Toxic death 0v1 (sepsis) ?paed	
1327	Recomb. Growth hormone 0.07mg/kg OR 0.039mg/kg	Placebo	CF	9-20 yrs	20 v 22 v 21	Germany	SAEs equal 4v5v4 -resp infection req antibiotics (see table 3)	Pulm exacerbations 7v6v4
1330	Prednisolone PO daily	IV methypred monthly	Infantile haemangioma	1-4 months	10 v 10	Canada	Growth retardation@1 yr in PO group, wt&ht lower (p=0.003&0.001) Resp distress 1v1 HPTx1 in PO grp,req rx	
1351	Tobramycin neb	Placebo	CF and P.aeruginosa	6-45 yrs	161v 86	Hungary, Poland, Russia	SAEs 20v27 Worsening of CF + pulm infections (table IV) Deaths 1(cardiomyopathy) v 2(resp failure)	Tobra: Bronchospasmx1 Voice alterationx1
1352	Tobramycin neb.	Placebo	CF and P.aeruginosa	6-30 yrs	29v30	France, Italy, Ukraine, Moldova	SAE 1v3 –undescribed 1 death – placebo	Discontx3 – CF exacerbation

1369	IV Paricalcitol	Placebo	Secondary hyperparathyroidism on haemodialysis	5-19 yrs	15 v 14	US	10 subjects with SAEs All rated unrelated	
1389	Daunorubicin 1-hr infusion (ONCO)	24-hr infusion	Chemo for newly diagnosed ALL	1-18 years	43 v 58	Germany	Death in remission?2nd malig?	"no specific analysis of toxicity"
1396	Ibuprofen PO	Indomethacin IV	PDA	<35 weeks gest	9v12	Egypt	Pulm haemorrhage 0v2	
1401	Inhaled nitric oxide	Placebo	Preterms with severe resp failure	<34 weeks gest	14 v 15	US	Gd3/4 IVH 0v2 Death 5v4 BPD 3v5	****STOPPED BY DSMB
1405	IFN based chemo (ONCO)	Primary haematopoietic stem cell transplantation (HSCT)	Chronic Myeloid leukaemia	11-59 yrs	219 v 135	Germany	Multiple deaths	?drug toxicity not reported '…or adverse drug effects). No differences were found between the 2 groups)'
1409	Amodiaquine+SP OR Amo+artesunate	Artemether-lumefantrine	Uncomplicated falciparum malaria	1-10 yrs	111 v 113 v 105	Uganda	45 SAEs 9 seizures possibly related El. LFTs – all rated unrelated	Anorexia+ weakness in Amo+SP
1447	Fluticasone 100mic bd OR Montelukast 5-10mg nocte	OR Fluticasone + salmeterol nocte	Mild persistent asthma	6 yrs and older	169 v 166 v 165	USA	SAEs 6v4v4 Def. Related : 1 burning in mouth and tightening of throat Poss related: 2 asthma Unrelated: 11 Unclear: 1 depression	Monte: less URTI and viral resp. Fluti: more N+V, fever

1470	Reformulation of Recomb. Factor IX	Original form	Mod.severe to severe Haemophilia B	12-61 yrs	34 (cross over)	US	3 SAEs: cellulitis, pyogenic arthritis – both rated unrelated, Haematuria-rated unrelated	Headache, nausea, dizziness, unpleasant taste-at least possibly related
1493	Different chemo regimes (ONCO)	As noted	B-cell non-Hodgkin lymphoma	2.5-20.5 yrs	657 to 4 arms	France, Belgium, Netherlands, US, Can, Aus, UK	Multiple deaths Lower toxicity with half dose of cyclophosphamide	
1494	8-course CHOP regimen (ONCO)	6-course intensified CHOP regimen	Agressive non-Hodgkin lymphoma	16-65 yrs	239 v 238	Netherlands Belgium	Treatment-related mortality 4v6 Cardiotoxic deaths 5v2 Second malign. deaths 2v3 + 7 other second malig	
1496	Reduced intensity chemo (ONCO)	Standard intensity FAB chemo	High-risk CNS non-Hodgkin B lymphoma and B acute lymphoblastic leukaemia	6 mo – 21 yrs	52+ 44 v 51+ 43	France USA UK	11 non-disease progression deaths Haemorrhage 3 Pneumonia 2 Thrombosis 1 Infection 2 Prior to rx 1 Post intensification of stem cell transplant 2	
1497	Heat shock protein peptide (DiaPep277) Sc inj	Mannitol as placebo	Type I DM	7-14 years	15 v 15	Israel	Acute gastro req. adm 2v0 – considered unrelated Optic neuritis – 2yrs post study	
1498	Heat shock protein peptide (DiaPep277)	Mannitol placebo	Type 1 DM	16-58 yrs	17 v 18	Israel	SAEs 2v2 all rated unrelated	Local sx
1520	Beclomethasone PO (related to ONCO)	Placebo	Prednisone-sparing in GI graft-vs-host disease	6-70 yrs	62 v 67	US	Deaths 29%v42% p=0.04 SAEs, ADRs, disconts. all higher in placebo	

1541	IV paracetamol	Proparacetamol	Acute fever d/t infection	1 mo – 12 years	33 v 32	France	1 overdose/admin error- 2yo given 2g instead of 420mg, no toxicity	TEAE 5v13 Vomiting 1v2 Rigor 0v1 Pain 1v0 Inc lfts 0v1 Rash 1v0
1543	Trimethoprim/ Sulfamethoxazole	Placebo	Acute otitis media	12-143 months	50v51	Netherlands	Mastoiditis 1v1 req. mastoidectomy & IV abs Rash – discont. Rx + req cetirizine	Vomiting+ Diarrhoea 9v2%
1544	Botulinum toxin a inj	No rx	Hemiplegic cerebral palsy	3-16 yrs	21v22	Australia	SAEs 1(seizure)v5 (2 seizures in 1 child+3 hosp. adm) Anxiety 1 Depression 1	Vomiting and cough Excessive weakness Headache Flulike sx
1633	Fosmidomycin-Clindamycin	Sulfadoxine-pyrimethamine	Falciparum malaria	3-14 yrs	54 v 51	Gabon	1 SAE – convulsion in FC group	All AEs 64v100 p=0.05 Vomiting 1v13,p=0.002
1648	Azithromycin eye drops for 2/7 OR 3/7	Azith single oral dose	Trachoma	1-10 yrs	224 v 225 v 221	Guinea-Conakry, Pakistan	1 death – head injury – unrelated	Ocular AEs 10.8v8.9v13.1
1661	Liposomal Amphotericin B high-loading dose 10mg/kg (ONCO)	Std dosing 3mg/kg	Invasive mold in immuno compromised patients	2-78yrs	107 v 94	10 countries	Deaths, survival 88%v93% p>.05 Nephrotoxicity 31v14%,p<.01 hypoK 30v16%,p=.015	Multiple disconts -elevated creat -abnormal LFTs -hypoK
1662	Rupatadine 10mg OR 20mg	Placebo	Chronic idiopathic urticaria	12-65 yrs	113 v 112 v 109	Spain, Poland, Romania, Argentina, Germany	Deterioration of arterial hpt and metrorrhagia, rated unrelated	Headache and somnolence both similar to placebo

1733	Sibutramine	Placebo	Obesity	12-17 yrs	12 v 12	Netherlands	1 clinical depression	Abdo complaints sig higher in sibutramine
1772	Glimepiride	Metformin	Type 2 DM	8-17 yrs	143 v 142	USA	SAE 1(DKA)v1(convulsion) Severe hypo 1v1	Hyperglycaemia Upper abdo pain Abdo pain Diarrhoea Nausea Headache
1793	Lamotrigine OR Topiramate (SANAD trial)	Valproate	Gen and unclassifiable epilepsy	5 years and above	239 v 239 v 238	UK	Multiple stated SAEs eg MI, status epilepticus etc. No further details	
1794	Carbamazepine OR Gabapentin OR Lamotrigine (SANAD trial)	Oxcarbazepine OR Topiramate	Partial epilepsy	5 yrs above	378 v 377 v 378 v 210 v 378	UK	Multiple stated SAEs No specific details	
1798	Infliximab Every 8 weeks	Infliximab every 12 weeks	Crohns disease	6-17 yrs	52 v 51	N. America, W. Europe and Israel	SAE 8v7 Serious infection 3v4 Pneumonia 2v1 Intes stenosis 1v0 Inf. Reactions 9v9 Discount 2v4 El. AST 0v3	
1838	Antibiotic Clarithromycin + rifabutin	Surgical excision	Nontuberculous mycobacterial cervicofacial lymphadenitis	0-15 years	50 v 50	Netherlands	Permanent facial nerve dysfunction x1 – surgery grp 'severe' AEs – jaundice Gen. rash	74%v20% AEs Multiple AEs-no disconts.
1865	Drotrecogin alfa	Placebo	Severe sepsis	38weeks to 17 years	237 v 240	18 countries	CNS bleeding 11v5, p=.13 Mortality 41v41 Drug SAEs >placebo!	SAEs in <4yos ***paed vs adult PROWESS v RESOLVE

1897	ABX-CBL hybridoma-gen. murine IgM monoclocal antibody (ONCO-type)	Antithymocyte globulin	Steroid-resistant acute graft-vs-host disease	2-65 yrs	48 v 47	US	Deaths + multiple SAEs similar between groups Pneumonia 15v30, p=.002	
1908	Artemether-lumefantrine	Dihydroartemisin-piperaquine	Drug resistant falciparum and vivax malaria	1-60 years	387 v 387	Indonesia	Sudden death -32yo,NAD in blood, no further details	Rash 3yo-rx with antihistamines
1909	Recombinant human epidermal growth factor 1-48	Placebo	Severe NEC	Below 12 weeks	4 v 4	Hong Kong	Deaths 1v1 – unrelated Intraab abscess 2v1	**CANCELLED d/t admin reasons, Targeted 20
1921	IV Oestradiol + Progesterone	Placebo	Broncho pulmonary dysplasia	Extremely preterm infants <29 wks gest	43 v 42	Germany	Multiple SAEs related to disease (table 2) Cholestasis 3v6 Cirrhosis 0v1 Thrombosis 4v4	Hypertriglyceridaemia 16v7 p=.05
1935	Growth Hormone	No Rx	Prader-Willi syndrome	4-37 months	25	US	Scoliosis progression – GH treated 3yo	
1956	Etoposide-Ifosfamide + HD MTX (ONCO)	Doxorubicin + HD MTX	Osteosarcoma	3.1-19.5 yrs	120 v 119	France	Severe neutropaenia 74v59% p=.02 Non-haemato toxicity 63v79% p=.005 (hepatotoxicity) Neurotoxicity x2 Nephrotoxicity x6 Second malig. 2v4 Deaths d/t disease	
1966	Dapsone gel	Vehicle	Acne	12 and older	1506 v 1504	US	9 hospitalisations – all rated unrelated	2 discont in Dapsone group – skin sx

1988	GM-CSF (ONCO)	No Rx	Priming for Induction regime for ALL	15-50 yrs	124 v 135	France	Multiple chemo related toxicities and deaths	
1996	Clindamycin+Benzoyl peroxide LA	Erythromycin+Zn Acetate LA	Acne	12-39 yrs	73 v 75	Poland	EtOH intoxication Discont. 2 skin reactions	
2001	Idursulfase	Placebo	Mucopolysaccharidosis II (Hunter Syndrome)	6-20 yrs	12	US	Life-threatening resp. distress in 20yo – x3 episodes – anaphylaxis?	Infusion reactions in high-dose
2031	IV methylpred	Placebo	Kawasaki Disease	6 mo above	101 v 98	US, Canada	SAE 2v2 Shock& resp. failure/sensorineural hearing loss/coronary art thrombus/anaphylaxis to IVIG Hypotension 5v1,p=.21	*hypotension ?severity
2066	Artemether-lumefantrine	Amodiaquine + Sulfa-pyrimethamine	Uncomplicated falciparum malaria	6 mo above	261 v 260	Burkina Faso	2-anaemia hb<50 g/l	pruritus
2076	Mometasone inh 400mic OR 800 mic	Placebo	Severe persistent asthma	13-83 yrs	42 v 43 v 38	US	2v4v2 Pneumonia, adr insuff, intest perf, diverticulitis, ca pros, atrial fib, cad – all rated unrelated 1 death – pneumonia	?paed Pred withdrawal sx
2078	Dexrazoxane	No Dexrazoxane	Prevention of cardio-pulmonary toxicity during chemo of paed Hodgkins	21 yrs and younger	239 v 239	US	Excess risk of second malig. Neoplasm 3.43%v0.85% p=.06	
2119	Montelukast	Placebo	Intermittent Asthma	2-14 yrs	107 v 113	Australia	SAEs 24 v 21 – all rated unrelated	

2130	Venlafaxine	Placebo	Generalised Anxiety Disorder	6-17 yrs	157 v 163	US	Suicidal ideation-10yo in ven group* Withdrawal syndrome with agitation and confusion – 10yo ven group*	Anorexia 13%v3% Somnolence adol. 11%v0%
2138	Ofloxacin	Ceftriaxone	Multidrug-Resistant Typhoid fever	Up to 12 yrs	93	India	Hepatitis Intestinal perf. Pleural effusion Intestinal perforationx1	Disease-related
2175	Dihydroartemisin supp + Sulfadoxine-pyrimethamine PO	IM artemeter + Sulfadoxine-pyrimethamine PO	Moderately severe malaria	6 mo – 10 yrs	37 v 35	Nigeria	Cerebral malariax1	Perianal redness Mild sx
2178	Posaconazole	Fluconazole/Itraconazole OR Fluconazole OR Itraconazole	Prophylaxis of fungal infection in neutropaenic patients	13-82 yrs	304 v 298 v 240 v 58	Worldwide	Death 49v67 (p=.048) SAEs 19v6 p=.02 QT prolongation 12v9 Atrial fib, decreased EF, torsades - posaconazole	?paed *MORE SAEs in Posa*
2179	Posaconazole	Fluconazole	Prophylaxis of fungal infection in graft-v-host disease	13-72 yrs	301 v 299	Worldwide	40 v 29 SAEs Deaths 156 v 167 1 death rated poss related – ITP Increased liver enz+GGT 11v4* Hepatocellular dmg 4v0*	?paed *Hepatotoxicity*
2180	High Dose Methotrexate Intrathecal (ONCO)	Low dose Methotrexate intrathecal	Chemotherapy for acute lymphoblastic leukaemia	1.5-15 yrs	316+ 77 v 290 81	France	Neurotoxicity 3+15 v 0+17 Seizures Neuropathy Encephalopathy	
2181	Omalizumab	Placebo	Allergic asthma with risk of helminth infection	12-30 yrs	68 v 69	Brazil	SAE 1 v 2 – all rated unrelated (2xabortion,severe asthma)	

2189	G-CSF (ONCO)	No G-CSF	Infection prophylaxis after induction Rx	0-18	156 v 161	Germany, Austria	Infectious mortality 4 v 9 Sepsis 9 v 2 Febrile neutropaenia (all non-sig)	No sig diff in Diarrhoea Nausea Vomiting Hepatic and CVS
2192	Fenofibrate	Placebo	Burn injury	4-16 yrs	21	US	Death x1-sepsis (Fen grp)	
2211	Metoprolol 0.2mg/kg OR 1.0mg/kg OR 2.0mg/kg	Placebo	Hypertension	6-16 yrs	45 v 23 v 49 v 23	US	SAE x2-pneumonia -menometrorrhagia	Mild sx
2217	Sitaxsentan 50mg	Sitaxsentan 100mg	Pulm arterial hpt	12-75 yrs	Safety: 4v9 Efficacy: 20v15	US, Canada, Australia	1 death-disease deterioration No SAE related to sitaxsentan	
2222	Isoniazid	Placebo	Prophylaxis of TB in HIV	8 weeks above	132 v 131	South Africa	Deaths 8%v16% p=0.015 -multiple infectious causes+unknown Gd 3/4 toxicity 5v8 – increased LFTs -11 haem events	No disconts
2233	Chemo regimen (ONCO)	Chemo regimen	Osteosarcoma	4-41 yrs	250 v 254	Multi country	12 treatment related deaths	
2237	Insulin detemir	NPH insulin	Type 1 DM	6-17 yrs	232v 115	16 countries in Europe & Israel	DKA 1.7%v1.7%	URTI, headache, pharyngitis, gastro, flu-like Inj site reactions
2245	Vincristine pulses + dexamethasone (ONCO)	Untreated controls	ALL continuation rx	Younger than 18	1325 v 1293	10 countries	Mortalities 10v5 and second malignancies 5v9	

2315	Erythromycin	Placebo	Feeding intolerance in preterm neonates	Preterms	30 v 30	Egypt	Sepsis, Cholestatic jaundice, NEC, Mortality all similar with placebo	
2328	Magnesium sulphate	Placebo	Neuroprotection after traumatic brain injury	14 above	250 v 249	US	Mortality high conc 2x mortality vs placebo Other major medical complications comparable Slight excess of pulm. Oedema and resp failure in lower Mg group	?paed
2332	Allupurinol	Placebo	Cerebral injury following birth asphyxia	Neonates	30 v 30	Turkey	6 deaths 20 severe impairment or microcephaly Severe adverse outcome 39%v54%, p<0.05	
9992	Azithromycin	Placebo	Prevention of BPD	ELBW <1000g preterm neonates	19v16	US	Death 4v5	No SEs attrib to drug
88851	Anti-D immunoglobulin	Placebo	Thrombo cytopaenic dengue	27 children	25v22	Philippines	2 deaths – 1 child – rated dengue related	
99912	Chemo regimens (ONCO)	Other chemo regimens	Early-stage Hodgkins	15-70 yrs	542 and 996 pts	8 Euro countries	Second malignancy 55 pts Cardiotoxicity	?paed
99924	Fluconazole 6mg AND 3mg	Placebo	Prophylaxis of fungal infection in VLBW inf	Preterm neonates	225 v 111	Italy	Deaths 8%v8.7%v9.4% p=1 Sepsis NEC Retinopathy	Elevated LFTs –no Rx
99929	Fluconazole	Placebo	Prophylaxis of fungal infection in VLBW	Preterm neonates	60 v 60	India	Deaths 17v17 Fungal inf 1v3	No other AEs mentioned

99934								
99935	Ciclesonide inh	Budesonide inh	Persistent asthma	12-75 yrs	198 v 201	Germany	3 SAEs –all rated unrelated	Oral candidiasisx1 4x0 Aes Dyspnoea, voice alteration, cough, headache
99938	Propanolol	No treatment	Severely burned patients	Below 18 yrs	102 v 143	US	Death 5%v6% Multi organ failure 6%v9% Sepsis 7%v10% All non-sig	?ADRs not looked for
888147	Gatifloxacin	Cefixime	Uncomplicated Enteric fever	2-65 yrs	203 v 187	Nepal	Death 1 -?disease related Rash 1 req rx Excessive vomiting x2 in gati group	N&vomiting – 23 2 req rx
888217	Steroid for 3 days + Tacrolimus, mycophenolate, basiliximab induction	Steroid maintenance	Immuno Suppression for live-donor renal transplant	5-60 years	50v50	Egypt	Avascular bone necrosis x 1	Experimental< Control DM,p=.037 Bone/joint pain, p=.04 Acne, p=.001 Infections p=.02 Admissions p=.02
888256	Strain-spec serogrp B meningo vax (2 cohorts)	Norwegian parent vax strain	Prophylaxis of meningococcal disease	8-12 yrs	A-241 v 61 B-250 v 63	New Zealand	9 SAEs – all judged unrelated	Local rx Headache

888335	Indacaterol 400mic OR 800 mic	Placebo	Asthma	12-65 yrs	59 v 59 v 26	Belgium Canada Czech Slovakia	5 SAEs- bronchospasm 1v1v0 -thought related to study drug Hyperventilation Acute asthma Ectopic	AEs all similar % ?paed
888430	Indian Hep B vax	European Hep B vax	Prophylaxis of hep B	Infants	180 v 180	India	SAEs- pneumonia x2 UTI, bronchiolitis, gastro – rated unrelated	Fever
888476	Budesonide/formoterol	Salmeterol/fluticasone	Uncontrolled asthma	12 above	1154 v 1155	17 countries	1 death-severe typhoid fever SAEs 3%v3% Discont 11v20 Beta-adr effects 8v1	
888507	Human rotavirus vaccine	Placebo	Rotavirus gastroenteritis	6-14 weeks	2646 v 1348	6 Euro countries	SAEs 11%v13% 1 intussusception 8 days post vaccine 2 cases 2nd rota season	Safety data not described?
888582	Combined vax DTPa-HBV-IPV/Hib	Separate admin	Prophylaxis	Infants 11-17 weeks	75 v 75	Singapore	7 SAEs- bronchitisx2,UTI, gastrox2,brochiolitis,head inj All rated unrelated	Pain,redness, swelling Irritability
888649	Frozen live att flu vax	Refrigerated cold-adapted flu vax	Prophylaxis of influenza	5-49 yrs	190+ 281 v 186+ 285	US	2 SAEs – gastro in 24yo and lymphadenitis in 7yo – both unrelated	Disconts x3 Reactive airway disease Runny nose and cough Tooth abscess Others: Asthma, adhd, reactive airway disease Kidney stones Hpt Sleep apnoea Gallstones,migrain es

888671	Sulfadoxine-pyrimethamine	Placebo	Intermittent preventative treatment in infancy	Infants from 3 months	600 v 600	Ghana	Deaths 29v30 (all unrelated)	9022 AEs – GI and Resp Scabies 1 child with severe rash-poss related
888702	RTS,S/AS02D malaria vax	Hep B vaccine	Malaria	Infants	107 v 107	Mozambique	SAEs 31v30 4 deaths – septic shock,gastro. & dehydration	Pain,swelling,fever , loss of appetite,drowsines s – vaccine related sx
888704	Hep A vax	Immune globulin	Prophylaxis post exposure	2-40 yrs	2272 v 2252	Kazakhstan	28 SAEs 25 Hep A, appendicitis, rubella, bronchitis – all rated unrelated	
888729	Chemo (ONCO)	Allogeneic OR Autologous stem-cell transplantation	Very high risk Acute LL	Infant-17 yrs	38 v 24 v 38	Spain	2 transplantation related deaths	?chemo related toxicity not mentioned
888737	Combined DTP-IPV booster	Separate vax	Prophylaxis	4-8 yrs	779 v 126	Germany	2 SAEs – extensive local reaction to vax + hospitalised 2/7 Forearm fracture	Local and systemic mild vax reactions
888839	Hep A vax + hexavalent combi vax	Hep A vax + separate vax	Prophylaxis	Infants	311 v308	Belgium & Germany	74 SAEs 36v38 Gastro, pneumonia, bronchiolitis, URTI All rated unrelated 2 SAEs reported: Resp apnoea/missed SIDS – probably not related Serum sickness related to amoxiclav acid –probably not related	Local & systemic mild reactions Fever
888855	Peribulbar block OR Topical lidocaine + GA	GA alone	Paed strabismus surgery	2-13 yrs	15 v 15 v 15	India	Ventricular bigeminy 2 pts Asystole 1 pts All 3 in control group Oculocardiac reflex req atropine 1v1v3	

888913	Fully liq vax –dpt-ipv-hib	Reconstituted hib with dtp-ipv	Prophylaxis	Infants	339 infants	Canada	1 SAE – afebrile seizure 3 occasions-on phenobarb rx	Mild systemic& local inj site rx
888928	Dexa OR glycerol OR dexa+glycerol	Placebo	Bacterial meningitis	2mo – 12 yrs	12 v 13 v 20 v 13	India	3 deaths 0v1v1v1 GI bleed 1v0v1v1 Neuro+hearing sequelae – disease related	
888949	New combined DTPw-HBV vax	Separate vax or combined vax	Prophylaxis	Infants	Primary 239 Booster 215	Czech Slovakia	10 pts had SAEs 1 rated related – gastritis in new combi. Grp All other SAEs rated unrelated	Fever Drowsiness irritability
888950	Inhaled Zanamivir	Placebo	Prophylaxis of influenza	12 yrs and above	1678 v 1685	Canada Czech France Germany Latvia US	SAEs 17v16 1 death-MI rated unrelated Rated drug related(?) Acute asthmatic bronchitis v 2 in placebo-arrhythmia and dyspnoea/cough	Chest tightness 2v2 Mod&severe in rx grp
8881099	Virosome-adjuvanted Hep. A vaccine (Epaxal) 0.25ml v 0.5 ml	Havrix Junior (hep A vax)	Prophylaxis	1-16 years	123 v 123 v 62	Belgium	SAE 7v3v3 All rated unrelated	Fever Local inj reaction
8881104	Hib vax (Hiberix) –DTP	Hib vax –DTP OR Hib vax – DTP (Tritanrix)	Prophylaxis	6-12 week	120 v 120 v 120	Thailand	8 SAEs- undescribed – all rated unrelated	Local inj Rx Grade 3 fever = all groups
8881141	Morphine iv	Codeine im	Intraop analgesia for cleft palate repair	Infants mean = 7 mo	22 v 22	UK	‘vomited blood’ x1 – codeine	Morphine -vomiting -retching -facial itching
8881235	Virosomal hep. A vax concomitantly admin. with DTPH-IPV-OPV-MMR	Hep. A vax alone OR Alum adjuvanted Hep. A vax-DTPH-IPV-OPV-MMR	Prophylaxis	12-15 month old	109 v 105 v 108	Israel	29 SAE-all rated unrelated	Fever Local inj rx

8881295	IV immune globulin IHN-A21	Placebo	Prevention of Late Onset Sepsis in VLBW neonates	Prem. Neonates	994 v 989	US Canada	NEC Gastro. Perf Retinopathy Pneumothorax Sepsis Hydrocephalus Bradycardia All = Placebo + rated possibly related 2v4 SAEs	
8881334	Growth hormone	Untreated (treated after 12 months)	Small for gest. Age	2-5 years	39 v 37	Spain	Fever+convulsions+hosp. 1v1 Rated unrelated	All AEs rated unrelated
8881335	Growth hormone	Untreated controls	Juvenile idiopathic arthritis	Pre pubertal Mean= 10+/-2	13v18	Germany	Deathx1 – undescribed	No safety section Mean obs time=8.4 years!***
8881428	Atomoxetine	Methylphenidate	ADHD	6-16 years	164 v 166	China, Korea, Mexico	Simple partial seizure x 1	TEAEs: atx>mph Anorexia,nausea,somnolence, Dizziness,vomiting: atx>mph p<0.05
8881448	4 groups Choroquine (CQ) 50mg v Amodiaquine (AQ) 15mg v AQ 30 mg v CQ 25 mg		Uncomplicated malaria	2-177 months	184 v 181 v 182 v 182	Guinea-Bissau	2x convulsions – hospitalised	Vomiting itching
8881466	Fluticasone	Budesonide inh.	Growth velocity in asthma	6-9 years	114 v 119	11 countries	SAE 1v4 – undescribed	Candidiasis 2v1

8881482	Live Att. rotavirus vaccine	3 different virus concentrations VS placebo	Prophylaxis	6-12 weeks	101 v 101 v 102 v 101	Mexico	2 deaths – SIDS, Road accident 31 SAEs 1 intussusception – rated unrelated All SAEs rated unrelated	All sx = 3 group = PLACEBO
8881543	P.aeruginosa flagella vaccine	Placebo	Prophylaxis in Cystic Fibrosis patients	2 – 18 years	239 v 244	Germany France Italy Austria	Death x 1 – rated unrelated SAE =5 1 definite related – pers. Severe pain 4 no/improbable - atelectasis -epilepsy - Acute L. leukaemia - meningitis	Local inj. Sx Fever Nausea Headache
8881694	MMRV vax co-admin with DPTH	MMRV alone OR DPTH alone	Prophylaxis	12-23 months	150 v 150 v 150	Germany	11 SAEs- all rated unrelated Febrile convulsionx1- unrelated	Fever No diff Rash No diff Parotid gland swelling – not mumps Local inj. sx
8881735	Attenuated Flu vax	Placebo	Prophylaxis	12-<36 months	1653 v 1111	8 Asian countries	2 deaths – unknown cause (placebo), drowning Bronchospasm 7 v 3 Bronchitis 3v2 Rhinitis 3v0	Discont – 1 persistent fever Fever > in vax Local inj. Sx
8881788	HPV vaccine	Hep A vax	Prophylaxis	15-25 years	9319 v 9325	14 countries	5 deaths – all unrelated SAEs related to infectious events and abnormal preg. Outcomes (no sig. diff)	Local inj. Sx

8881837	Low-dose hydrocortisone	Placebo	Prevention of chronic lung disease in preterms	Preterms 24-30 weeks	25 v 25	Italy	Death 4v10 p<0.05 GI perf. 2v1, HPT, hyperglycaemia, Hyperkalaemia, Sepsis, fungal inf. All Non-sig.	*****STOPPED BY SAFETY COMT – RISK OF GI PERF*****
8881847	Artemether-lumefantrine	Dihydroartemisin-piperaquine	Malaria	6 months-10 years	256 v 253	Uganda	SAE = 6 3 x febrile convulsion 1 AOM, 1 asthma, 1 pyomyositis All rated unrelated	Malaria sx
8881944	Fridge-stable MMR+Varicella vax	Frozen formulation vax	Prophylaxis	12-23 months	1006 v 513	US Sweden	7 v 2 RSV infection,pneumonia, dehydration, pharyngitis, gastro, accidental exposure Gastro, pneumonia, neuroblastoma	Insomnia/dermatitis> in fridge Viral URTI < in fridge Fever Local inj sx
8881965	Topical Vitamin E	Placebo	Prophylaxis for chemo-induced oral mucositis (N-of-1 trial)	6.4-15.1 years	16 kids 45 cycles 22v23	Canada	2xBacteraemia –both placebo	***N-OF-1***
8882011	Beclomethasone aerosol	Fluticasone inh	Asthma	5-12 years	139 v 141	Belgium, Netherlands, UK	Severe stomatitis - unrelated Arm fracture – unrelated	Dysphonia coughing
8882072	Pneumovax booster at 15 mo	At 18 mo	Prophylaxis	12-15 months	168 v 167	Canada	SAEs = 4, not mentioned	Local inj sx
8882108	Cyclophosphamide + antithymocyte globulin	Cyclo alone	Conditioning regimen for bone marrow transplant ***chemo***	<10-60 years	70 v 60	US, Swiss, France	Graft-v-host disease (Rx failure?) Infections-55/68v40/60 p=.07 Deaths-no sig diff	***CHEMO***

8882114	Quadrivalent HPV vax	Placebo	Prophylaxis	16-24 years	2723 v 2732	16 countries	SAEs 48v45 – no sig diff Bronchospasm Rx-related	Local inj sx *SAEs in supp table
8882120	Hib-MenC-TT vax (novel)	3 other formulations + 1 control group	Prophylaxis	Infants 8-16 weeks	102 v 104 v 101 v 104 v 109	Germany	No deaths 13 SAEs- all unrelated	Local inj sx
8882123	Sildenafil	No treatment	Pulm Hpt after congenital heart surgery	1-16 years	20 vs 22	Iran	Postop complications Haemothorax,pneumonia,pleural eff.,gastric haemorrhage,aborted cardiac arrest+pulm. Hpt crisis	Erections Nasal stuffiness GI upset
8882193	Erythromycin	Placebo	Parenteral nutrition-assoc cholestasis	Preterms	91 vs 91	Hong Kong	Death 2v4 (2v4%) NEC 0v1 Sepsis 9v11	
8882342	Inactivated Polio Vaccine (together with DTPHib)	No treatment	Prophylaxis	Full term infants	82 vs 84	Cuba	Transient hypotonia Persistent crying x5	Substantial attrition due to hypotonia
8882343	Budesonide/formoterol	Salmeterol/fluticasone fixed dose Budesonide/formo. Fixed maintenance dose	Asthma	12 above	1107 vs 1123 vs 1105	16 countries	2 deaths – resp.failure,cardiac failure – unrelated 4 SAEs – pneumonia,gastritis,asthma asthma	URT sx ?paed
8882412	Malaria vaccine RTS S/ASO2A	Malaria vaccine RTS S/ASO2D	Malaria	3-5 years	100 vs 100	Mozambique	11SAEs –all unrelated 1 death due to AIDS	
8882418	Propofol-remifentanil	Sevoflurane-fentanyl	Anaesthesia	4-6 month	17 vs 22	Denmark	2nd op due to bleeding	
8882448	Tick-borne encephalitis vaccine	3 schedules	Prophylaxis of TBE	1-11 years	82 vs 73 vs 139	Germany Hungary	25 SAEs – all unrelated	Arthralgia Nausea Fever

8882502	Ketamine (iv ketamine through surg, iv ketamine end of surgery)	placebo	Preventive analgesia during tonsillectomy	5-15 years	30 vs 30 vs 30	Turkey	Resp distress re:postop bleeding 1v3	Erythema in ketamine p=.045 Emesis p=.06
8882546	Hep B vax 2-dose	Hep B vax 3-dose	Prophylaxis	11-15 years	258 v 126	Australia Belgium Ukraine	4v1 Septic arth./fracture/Crohns/RTA/dental surg All unrelated	General + inj site
8882568	Rotavirus vaccine	Placebo	Prophylaxis (gastro)	6-12 weeks old	651 vs 661	US Finland	1 death Rx group – SIDS SAEs 21vs27 *fever 2v0 *pneumo 3v1	No intussusception
8882641	HPV vaccine	Placebo	Prophylaxis	9-15 years	1184 vs 597	10 countries	5v0-all rated unrelated ARF,type 1 DM,infection,anaemia, Appendicitis	Discont. 2v0 Inj. Site sx
8882686	Tetracaine 4% gel	Placebo	Venepuncture pain	Infants Incl preterms	71 vs 71	Canada	1 death – placebo NEC	Erythema 7v4
8882699	DTPPolioHib liquid	DTPPolio at different sites (IM)	Prophylaxis	Infants 2 months above	100 vs 100	Taiwan	13v8 All unrelated No withdrawals	
8882748	Adapalene gel 0.1%	Placebo vehicle	Acne	12-30 years	73 vs 63	Europe	Wisdom teeth extraction	Local reactions 2 discont Skin infection Erythema+desquamation

8882755	Live attenuated flu vax	Inactivated flu vax	Prophylaxis	6-59 months	4179 vs 4173	US	136v128 Death 1v1: Foreign body aspiration House fire Live-vax: Bronchiolitis x2 Asthma Wheezing Gastro Inactivated vax: Pneumonia Wheezing Febrile convulsion+pneumo Viral gastro	No difference in hospitalisation rate
8882867	DTPH + polio + pneumo. + Hib vaccine	Same vax but separately	Prophylaxis	6-12 weeks	667 vs 333	US	23 vs 16 SAEs Fever+hospitalisation	All unrelated
8883021	Growth hormone	No treatment	Short stature	3-12.3 years	27 vs 25	US	Scoliosis x2 Clavicle fracture ? group	Arthralgia 3v2 Gyneco 1v0 Cutaneous nevi 2v0 OM 1v1 Scoliosis 1v0
8883033	Deferasirox	Deferoxamine	Transfusional iron overload with sickle cell disease	3-54 years	132 vs 63	US	46.2%v42.9% Sickle cell anaemia with crisis 33.3%vs31.7%	Elevated ALT 5v0
8883073	Malaria vaccine	Hep B vaccine	Malaria prophylaxis	1-4 years	30 vs 30	Mozambique	2v2 Malaria+febrile convulsion Bronchopneumonia Glomerulonephritis All full recovery	Elevated ALT due to hepatitis A

8883098	DPT vaccine Adolescent-adult formulation	DPT vaccine Paed. formulation	Prophylaxis DPT	4-<7 years	299 vs 294	Canada	1 SAE – circumsicion for phimosis	Local + fever

*Where available, group nos. follow group description order