

## Safety in paediatric clinical trials – a 7-year review

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### Abstract

**Aim:** The safety of clinical trials in children has not been previously studied. We aimed to identify how safety is monitored and the extent of adverse drug reactions (ADRs).

**Methods:** A literature review of the Medline Database for therapeutic clinical trials involving oral and intravenous medicines in children from 1996 to 2002. Papers were read to determine the safety monitoring and the presence of adverse events (AEs) or ADRs.

**Results:** Seven hundred thirty-nine trials were identified. Thirteen (2%) had safety monitoring committees (SMCs). Five hundred twenty-three (71%) trials reported AEs and 151 (20%) of these trials reported a serious AE. ADRs were present in 270 (36.5%) trials, with 80 (11%) of trials having a moderate or severe ADR. Six clinical trials were terminated early because of significant drug toxicity. All of these had SMCs. There were deaths in 83 (11%) trials. In the majority of trials, mortality was thought to be unrelated to the investigational drug; however, in two trials mortality was higher in the treatment group.

**Conclusions:** About 11% of trials have a moderate or severe ADR. All paediatric clinical trials should have a SMC.

### INTRODUCTION

The need for clinical trials of medicines in children is now well established. Many studies have shown that significant numbers of medicines used for paediatric patients of different ages, both in hospital and in primary care, are either unlicensed or off label (1–3). Studies have shown that the use of off label and unlicensed medicines may be associated with a greater risk of drug toxicity (4).

In order to improve the situation, legislation has been introduced in the United States (5). This provides a financial incentive to the pharmaceutical industry to perform paediatric trials. Similar legislation has recently been approved by the European Parliament for adoption by member states in 2007 (6). There is general agreement by paediatric health professionals, regulatory authorities and the pharmaceutical industry as well as politicians and parents that clinical trials of medicines in paediatric patients are essential in order to improve drug therapy.

One of the reasons for performing clinical trials is to improve the safety of medicines. It is recognized that conditions such as the grey baby syndrome induced by excessive doses of chloramphenicol in the neonatal period would have been prevented by appropriate clinical trials (7). Similarly it has been argued that a carefully conducted clinical trial would have prevented the propofol infusion syndrome resulting in the deaths of numerous children (8). Unfortunately, recent experience in the United States has shown that clinical trials can sometimes be associated with significant morbidity and mortality (9). We have previously identified the nature and extent of clinical trials of medicinal products in children over a 7-year period (10). We wished to evaluate the extent of drug toxicity in association with these clinical trials.

### METHODS

The methodology for establishing the published clinical trials has been described previously (10). Briefly it involved a literature search on Medline to identify therapeutic clinical trials involving oral and intravenous medicines in children from 1996 to 2002. The search was limited to those studies in which an English language version was available. The areas of oncology and HIV were excluded as there had been previous reviews in these areas and the morbidity and mortality of the underlying conditions is significantly high (11,12).

All the papers were carefully read to determine whether there was a safety monitoring committee (SMC) and if any adverse events (AEs) were detected. An AE was defined as any untoward occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relation to the treatment (13). AEs were then further classified by using The European Agency for the Evaluation of Medicinal Products (EMA) and ICH Guideline on Clinical Safety Data Management, Definitions and Standards for reporting AEs in clinical trials (14). The definitions used were:

A 'serious AE' is any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistence or significant disability/incapacity, or is a congenital anomaly or birth defect (14).

'Other significant AEs' are 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 (14).

It was not always possible, by the reporting in the papers, to determine whether the AE was due to an investigational drug. Therefore, it was noted whether the incidence of AEs

**Table 1** Adverse events in trials

Grade	No of trials	% of total no of trials
Serious	151	20
Significant	203	28
Other	169	23
Nil	58	8
Unable to assess	158	21
Total	739	100

were greater in either drug group (that is the experimental drug or conventional drug group) or in comparison to placebo. If this was the case then the AE was regarded as an adverse drug reaction (ADR).

Additionally, all papers with AEs classified as serious were reviewed by two paediatric clinical pharmacologists separately. Agreement was then reached as to if the AE was considered an ADR. ADRs were then classified by severity as severe, moderate or mild (4):

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

The most severe AE/ADR in each trial was noted. This was then used to classify each trial, that is a trial with serious and significant AEs was recorded as a trial with serious AEs.

## RESULTS

Seven hundred thirty-nine trials were identified over the 7-year period. This includes three trials which were not initially identified (10). Seven hundred eighteen (98%) were randomized clinical trials, with the remainder being pharmacokinetic studies. Over half (396, 54%) compared a drug with a placebo. Over one third of trials (256, 35%) involved a new medicine. A smaller number (193, 26%) involved a direct comparison between two established drugs. Disease areas most frequently studied included neurology and developmental disorders (148, 20%), general paediatrics (118, 16%), infectious diseases excluding HIV (109, 15%) and neonatal diseases (99, 13%). Five hundred forty-nine (74%) trials mentioned within their methods how safety monitoring was performed during the study. Only 13 (2%) trials had SMCs. Five hundred twenty-three (71%) trials reported AEs and 151 (20%) of these trials reported a serious AE (Table 1).

Following evaluation of the papers, it was felt that ADRs were present in 270 (36.5%) trials. In the majority of cases, the ADRs were mild, but 80 (11%) of the trials were judged to have contained a moderate or severe ADR (Table 2). The severe ADRs reported ranged from acute problems (apnoea, hypotension, gastrointestinal haemorrhage and sepsis) to long-term effects (left ventricular hypertrophy, renal calculi, ototoxicity and visual field defects). The ADRs are shown in

**Table 2** Adverse drug reactions in trials

Severity	No of trials	% of total no of trials
Mild	190	25.5
Moderate	43	6.0
Severe	37	5.0
No ADR	212	28.5
Unable to assess	257	35.0
Total	739	100.0

Tables S1, S1 and S1 (Tables S1, S2 and S3 in Supplementary Material on line).

Six clinical trials were terminated early because of significant ADRs (15–20). In two trials (15,16), both in neonatology, mortality was found to be higher in the treatment group. These trials are presented as the first two entries in Table S1 (Table S1 in Supplementary Material on line) and both had SMCs that called a halt to recruitment. There were two trials where one of the investigational drugs was removed from the protocol because of safety concerns in that particular arm of the randomization (21,22). These drugs were phenobarbitone and pindolol. One trial (20) was terminated early due to evidence that was published in the literature during the trial raising concerns about the investigational drug vigabatrin causing visual field defects. One trial was halted not because of drug safety issues but because of trial design.

Thirty-seven papers reported other clinical trials with severe drug toxicity (Tables S2 and S3 in Supplementary Material on line). Eleven of these papers involved neonates and these are summarized together in Table S2. Three of these papers however related to one clinical trial comparing dexamethasone to placebo in the prevention of chronic lung disease in neonates (23–25). The numbers varied with each paper but there was significant overlap in the trial design and reported ADRs. The three papers are therefore summarized as one clinical trial. The 26 clinical trials with severe drug toxicity in paediatric patients are shown in Table S3.

There were deaths in 83 (11%) trials. In the majority of trials, mortality was thought to be unrelated to the investigational drug. Mortality was greatest in trials involving neonates, where 55 (56%) of the 99 trials reported a death. There was a trend to higher mortality (8 patients vs. 2,  $p = <0.1$  but  $>0.05$ ) in one trial comparing midazolam to diazepam for status epilepticus (26). The other major specialities in which deaths were reported were infectious diseases (12 [11%] of 108 trials), neurology (7 [11%] of 62 trials) and respiratory (3 [5.5%] of 55 trials and renal (2 [25%] of 8 trials).

## DISCUSSION

Clinical trials in children are essential for the development of medicines and provide evidence for the best treatment strategies for specific conditions. It is therefore not an option to not test medicines within the paediatric age group. This would lead to their introduction unsupervised in an off label or unlicensed manner which can lead to increased drug

toxicity (4). What we therefore need to ensure is that these trials are conducted in a safe manner.

Our results have shown that 11% of trials have a moderate or severe ADR taking place within them. It is important to note that this is not 11% of children taking part within clinical trials experiencing an ADR. Parents being approached for consent for a clinical trial involving their child need to be aware of the risk of an ADR occurring. The background ADR rate in hospitalized children is 9.5% with severe ADRs accounting for 12.29% of them (27). For outpatient children, the total incidence fell to 1.46%.

We excluded trials in the clinical areas of HIV and oncology as we felt these would have a high mortality rate from the inherent diseases. It has previously been shown that paediatric patients being treated on a haematology-oncology unit have an incidence rate of ADRs of 56% (28). Therefore, it is likely that the ADR rate within trials may be higher, although this has not specifically been studied. A weakness of our current study is the use of only one database to identify trials.

The risk and benefit of the disease, and the treatment, within a trial are all important influences on a parent when making a decision to consent to a clinical trial (29). Discussion about the potential for ADRs should be part of the consent process along with the rationale for carrying out the trial. Within our sample neonatology was the speciality with both the highest number of trials with severe ADRs and the highest number of trials containing children who died. The latter was most often linked to the natural mortality seen in the speciality.

Two studies were noted to have a higher mortality within the investigational drug treatment group (15,16). If these drugs had been introduced into clinical practice without a randomized controlled trial taking place, then this rise in mortality may not have been noticed for a longer time. Both trials had SMCs which halted the trials as soon as a difference was noted. Therefore, overall when significant drug toxicity is demonstrated within a clinical trial, this is an advantage as it prevents future drug toxicity for the population as a whole.

Of surprise was the small number of trials that documented that they had SMCs. As clinical trials are invaluable, an independent monitor who has the ability to swiftly question any ADRs or inequalities in morbidity and mortality is essential. The number of people required for a SMC is small, but they need to have appropriate expertise and to be completely independent of the trial in question (30). There is a trend within the United Kingdom for more paediatric clinical trials to have a SMC. It is also important that whilst a trial is taking place that the investigators monitor other evidence that is being published from other trials within their area. The importance of this was shown in the trial that was halted early because of vigabatrin visual field toxicity shown in another trial (20).

In conclusion, clinical trials within the paediatric population are essential. There is however a risk of ADRs occurring within these clinical trials. SMCs provide independent monitoring and allow for early detection of ADRs. We feel

therefore there is a strong argument for all paediatric clinical trials to have a SMC. During the consent process it is important that all parents are made aware of the potential for an ADR and the mechanisms that will be used to safeguard their child.

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### Supplementary material

The following supplementary material is available for this article:

**Table S1** Clinical trials that were terminated prematurely or underwent significant modification due to drug toxicity

**Table S2** Neonatal clinical trials with severe drug toxicity

**Table S3** Paediatric clinical trials with severe drug toxicity

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