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Clinical Trials, Ethical Issues and Patient Recruitment: an Australian Perspective

Alissa Lim
Clinical Pharmacology, Royal Children's Hospital, Flemington Road, Parkville 3052, Australia

Noel Cranswick Corresponding Author
Clinical Pharmacology, Royal Children's Hospital, Flemington Road, Parkville 3052, Australia.
Email: noel.cranswick@rch.org.au

A minority of drugs are currently studied in children and consequently, medications are commonly prescribed for children in an unlicensed or off-label manner. As children have vulnerabilities that may not be predicted in adult studies, there has been an international movement aiming to address this inequity of access to appropriately tested medicines for children. The expectation is that there will be an increase in the number of clinical trials involving children. There are a number of ethical and practical issues around conducting paediatric clinical trials that are important to consider, including protocol design and recruitment. Of note, research involving children must have the potential to benefit the individual child. Specialised paediatric clinical trials centres can provide the expertise to ensure trials are carried out efficiently and ethically.

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Introduction

The history of drug regulation reveals that major advances in legislation within the United States (US) have followed pharmacological disasters in children. After 13 children died in 1901 following exposure to diphtheria toxoid contaminated with tetanus bacilli[1], the Food and Drug Administration (FDA) introduced legislation to ensure the purity and quality of medicines[2,3]. In 1937, 107 persons, many of whom were children, died from renal failure after ingesting sulfanilamide diluted in diethylene glycol[4], and subsequently, legislation was enacted to ensure safety testing of medicines[5]. Finally in 1961, thalidomide was recognised as a potent teratogen as many hundreds of children were born with phocomelia[6]. After this, the Kefauver-Harris amendments required that medicines be tested for efficacy as well as safety.

Despite the fact that children have been pivotal to our current safe and efficacious use of medicines, they have not enjoyed the same benefit as the adult population. The inequity of access to appropriately evaluated medications for children has been well recognised since 1967 when Shirkey coined the term "therapeutic orphan"[7]. Only a minority of drugs are currently studied in the paediatric age group[8, 9]. Consequently, medicines are frequently prescribed for children in an unlicensed or off-label manner[10-13]. In Australia, over 70% of prescription medicines have no information about paediatric use or a disclaimer and 36% of paediatric inpatients receive at least one medication prescribed in an unlicensed or off-label manner[14, 15]. The lack of clinical trials in children has resulted from a number of factors including the ethical issues of involving children in trials, recruitment problems, the practical challenges of conducting trials in children, as well as the additional costs of undertaking these studies and the associated lack of financial incentive for pharmaceutical companies for this smaller market[16].

The problem of off-label and unlicensed drug use in children extends beyond the obvious disadvantages of access to appropriate medicines and the potential safety risks to the children exposed to these medications. The use of a drug for an unlicensed indication may expose the prescriber to litigation[17, 18]. Additionally, there are the potential difficult discussions with families around the issue that a medication is not licensed for use in children due to lack of data and there may be higher costs imposed on families if medicines are used in an unlicensed way.

The FDA in the US has initiated a series of plans and legislative changes in an attempt to address this problem. The 1997 FDA Modernization Act (FDAMA) provided an incentive for paediatric studies by giving a six month exclusivity extension for drugs if paediatric studies were performed[19]. In 1998, the Pediatric Rule required all new drugs to be tested in the paediatric population except in exceptional situations[20]. However, in 2002, this was successfully challenged when a US District Court ruled that the FDA did not have the authority to require such testing. The Best Pharmaceuticals for Children Act (BPCA) of 2001 continued FDAMA as well as establishing a specific office to deal with paediatric issues[21].

The European Medicines Evaluation Agency (EMEA) is responsible for co-ordinating drug licensing in the European Union. In January 2002, a Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population was released. It outlines issues for a safe, efficient and ethical approach to study of medicines in children with the aim of increasing the number of applications with paediatric data[22].

In Australia, the legal requirement for the use of medications is set out in the Therapeutic Goods Act 1989 and the Therapeutic Goods Administration (TGA) is responsible for administering the Act. There is no specific legislation to mandate paediatric labelling. The TGA offer some incentives, which may encourage submission of paediatric data. These include fee reductions for products not commercially viable or whose supply is in the public interest; the Orphan Drug program, which waives all fees and offers priority review; modified literature-based submissions to facilitate submission of modified packages based on existing published data[23]. However, the majority of medicines that require paediatric labelling in Australia have not been affected by these incentives.

In 1997, the Australian Drug Evaluation Committee (ADEC) commissioned a working party to address the problem of labelling in children. Although a wide range of reforms were suggested, few have been implemented. The Australian Health Ministers' Advisory Council is in the process of setting up another working party to address the issue of registration of medicines in children. The Australian Association for Paediatric Teaching Centres have also recommended a number of changes to help facilitate improved labelling for children[24]. A recent inquiry by the New South Wales Parliament into the use of medicines by children also made a number of recommendations including market and registration incentives for clinical trials in children; support for research into paediatric pharmacology; establishment of monitoring and reporting mechanisms in hospitals for adverse effects of medicines in children; and the development of guidelines to ensure that information from post-marketing surveillance is appropriately recorded in the product information[25]. However, there has not been a co-ordinated national approach in relation to the use of unlicensed and off-label medicines in Australia. The National Health and Medical Research Council (NHMRC) in their statement on ethical conduct in research provide direction with respect to research involving children[26]. These guidelines include the statement that research should not be conducted if it is contrary to the child's best interest.

Clinical Trials: Ethical and Technical Considerations

With this international movement towards studying medicines in children, it is likely that the number of clinical trials will increase. However, there remain a number of ethical and practical issues around conducting paediatric clinical trials that continue to act as a barrier. Of note, research involving children must have the potential to benefit children; it must be well designed and necessary[27].

The ethics process encompasses both the technical review and the specific ethical issues of a study. In contrast to adult studies, paediatric studies need to be of clearer potential benefit to the individuals participating. The balance between the potential for exploitation of the individual versus the need to provide adequate data for use in children so that they are not disadvantaged can be a complex issue. This has been used as a barrier to clinical trials in children in the past. However, it is unethical to continue to use medicines for children that have not been adequately tested in the appropriate population and age range.

Study designs that are unable to adequately address the aims are not ethical, as they expose participants to potential harm without the balance of adequate group data. The studies in which a review of the

literature has been inadequate, pose the most significant danger to participants. The best known example in recent times is the hexamethonium asthma incident, which occurred at Johns Hopkins in 2001. In this case, a 24 year old healthy volunteer died from bronchiolitis obliterans following exposure to inhaled hexamethonium, used to induce bronchoconstriction[28]. Adequate literature review would have revealed this as a potentially fatal side effect of the drug and alerted the researchers and ethics committee to alter the protocol to a safer alternative. Children have vulnerabilities that may not be predicted in adult studies. Adequate review for a paediatric pharmaceutical trial must include a paediatrician and a physician with an expertise in drug action on children. Ideally, a paediatric clinical pharmacologist should be involved. A minimal requirement would include review of the protocol by an experienced paediatric pharmacist.

Trial design for paediatric studies may need to vary as compared to adult studies to ensure appropriateness for children in particular age groups and to address the issue of individual benefit for that child. Different designs have been used to address the need for potential individual benefit. These designs include study designs with crossover and *n*=1 trials. Crossover trials have the advantage that the outcome of a treatment is compared to the outcome of another treatment in the same patient[29]. *n*=1 trials are randomised, placebo double blind crossover studies of a medicine in an individual. This design is of particular benefit in determining the effectiveness of a therapy for an individual. Also, newer novel designs are becoming available. An example is where all participants receive the drug, and then responders are randomised with a double-blind placebo crossover design. This method has been successfully used in paediatric studies. A particular difficulty encountered in paediatric clinical trials is the lack of valid comparators, as many "reference medicines" have not themselves been studied.

Paediatric Research Units

In 1994, the Pediatric Pharmacology Research (PPRU) Network was established in the US. This network is a group of specialised centres that conduct paediatric drug trials. Their goals include providing a foundation for drug studies in children and improving paediatric clinical data on new and already marketed drugs[30]. Based on this model, in 1998, the Australian Paediatric Pharmacology Research Unit (APPRU) was established in Melbourne at the Royal Children's Hospital.

The APPRU is a dedicated paediatric unit that facilitates high quality clinical trials in children. The unit was formed jointly with the Royal Children's Hospital, Melbourne and the Murdoch Childrens Research Institute. The team includes an experienced paediatric clinical pharmacologist and a group of skilled trial co-ordinators. There is also an accredited training position in paediatric clinical pharmacology. The APPRU conduct clinical trials across a broad range of therapeutic areas and have close links with speciality areas within this tertiary referral hospital. Studies have ranged from phase I to phase IV trials, including both short studies and long-term, intensive ones. Single centre and international multicentre studies are conducted and have varied in size from 1–2 participants to 100 participants. The APPRU has the ability to conduct pharmacokinetic, bioequivalence and pharmacodynamic studies. Table 1 summarises the role of the APPRU.

Patient Recruitment

Recruitment of children for paediatric clinical trials has been identified as one of the most difficult problems to overcome in paediatric trials[31]. Depending on the trial, significant issues include the ratio of potential benefit to potential

Table 1. Key features and role of the Australian Paediatric Clinical Trials Unit (APPRU)

Features
Dedicated clinical trials unit
Led by paediatric clinical pharmacologist
Multi-disciplinary team
Links with hospital and community groups
Standards in accordance with the ICH GCP, Declaration of Helsinki and the NHMRC Statement on Ethical Conduct in Human Research Involving Humans
Role
Facilitate high quality clinical trials in children
Appropriate protocol development for paediatric studies
Ethics committee submissions
Expertise in subject recruitment
Study co-ordination
Study evaluation
Expert in regulatory matters
Advocate for quality use of medicines in children
Education in paediatric clinical pharmacology

inconvenience or harm, effective communication and motivation of colleagues[32]. Appropriately, both parents and clinicians may be more cautious and protective in their approach to information about and participation in trials. Thus the challenges of recruitment differ considerably from those encountered in adult populations. Many paediatric studies may require participants who are not linked to a hospital and thus alternative recruitment strategies may need to be employed. In our local experience, depending on the study and the specific inclusion criteria, enrolment of those screened varies from 1 in 4 at best to 1 in 14.

Clearly, the trial design has an impact on recruitment. Factors such as inclusion and exclusion criteria and simplicity for the child and family are important to consider[32]. Ideally, inclusion and exclusion criteria should reflect as accurately as possible the intended target population. Narrow inclusion criteria will impact negatively on the ability to recruit and thus successfully complete the trial, as well as, limit the study's ability to generalise to a larger population.

Careful consideration of the issues that are important to the acceptability of a study to a family will also impact on the ability to recruit. From a technical viewpoint, minimising the number of invasive procedures, for example, will help improve recruitment. Inadequate provision of resources to conduct the trial will also adversely impact on the acceptability of a study. Dedicated paediatric clinical trial units can provide the expertise to assure the ethics committee and regulatory authorities as well as families that the trial will be carried out efficiently and ethically[33]. A dedicated unit can also provide a higher level of availability and flexibly for families, which may increase the number of families able to participate.

The benefits of a research nurse in improving recruitment have been previously demonstrated[34]. It has been our experience that a recruitment officer has further improved recruitment as well as improving study retention rates. The ability to focus on recruitment has enabled rapid dissemination of information to appropriately selected groups and then detailed screening of children and their families. In turn this has led to appropriate selection and thus high retention of participants in studies. In addition, the recruitment officer has established important links with hospital groups and relevant community groups including doctors, nurses, schools and the media. Feasibility studies conducted by the recruitment officer have provided accurate estimates of recruitment targets and have identified potential difficulties that may impact on the success of the trial, which can be addressed and minimised at an early stage.

Consent

Consent and assent are important considerations in clinical trials for children. In the past, paediatric trials have often been dismissed as treating children as guinea pigs. However, if fully informed on the unsatisfactory use of medicines in an unlicensed and off-label way, many families support the clinical trial process[35].

Appropriate steps are obviously required for consent in a trial by a child's parent or legal guardian. Consent is only valid if it is fully informed and freely given. One of the difficulties encountered can be, once appropriate information is given, how it is received and understood. This is particularly the case in situations where parents are likely to be distressed and there is less time for reflection[36].

The additional issue of child consent is also important. This acknowledges the right of the child as an individual to participate in the decision. The National Health and Medical Research Council guidelines clearly state that a child's refusal to participate in a research project must be respected. The age at which a child is able to fully understand the issues needs to be judged on an individual basis and will vary from child to child and be dependent on issues such as developmental stage. Currently in Australia, written informed consent for children should be comprehensible to the average 10 year old child. The American concept of assent is not used in Australia although, for practical purposes, the differences between the two are mostly semantic.

The issue of influence and inducements is an important one. This includes the situation where a study may provide access to a new, otherwise unavailable, therapy that may be perceived as more effective by the family or the clinician[30]. A balanced viewpoint regarding both potential benefits and risks need to be clearly defined in this situation. Remuneration is acceptable only to compensate for expenses that families are likely to encounter while participating in a trial, such as car parking fees. It is unethical to offer further inducements that may sway the decision a family makes.

Another issue that frequently arises is the use of a drug after the study. Ethically if a child has benefited from the use of medication that is not yet available then it may be unethical to withdraw this medicine at the completion of the study. Strategies to ensure the safe and ongoing use of the medicine need to be discussed and managed beforehand.

Conclusion

In conclusion, historically few drugs have been adequately tested in children. This has led to an inequity between children and adults with respect to the provision of safe and effective medicines. International moves toward improving this situation will hopefully result in a larger number of clinical trials being conducted in the paediatric population. Addressing any ethical issues or potential study problems early and carefully designing protocols will maximise the success of trials in children. Furthermore, the development of specialised paediatric clinical trials centres will encourage both pharmaceutical industry and families to participate in this process. A measure of a society is said to be the way it treats its children; how will ours be judged?

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