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ABSTRACT

Children should not be harmed by their participation in clinical trials, therefore should no clinical trials be performed? This is a view that needs to be balanced as clinical trials provide the evidence we need to allow children safe and effective prescribing of medicines. Therefore, is it unethical not to involve this population in research? This review looks at new ethical guidance released to support the recently introduced European legislation for the licensing of medicines.

European legislation, EU Directive 2001/20/EC, was introduced in January 2007. It should give rise to an increase in the number of clinical trials performed in children in Europe, as has been seen with similar legislative efforts within the USA. The EU legislation provides both a legislative framework, to necessitate trials of medicines relevant to the childhood population, and a financial incentive for pharmaceutical companies to perform them. This takes the form of a 6-month marketing authorisation extension for new drug applications for licensing, which now have to include a Paediatric Investigation Plan (PIP). There is also consideration given to medicines already on the market. The paediatric-use marketing authorisation (PUMA) will allow companies to benefit from 10 years of data protection as a reward for the development of a new indication in children or formulations appropriate for children of all ages.

Following the introduction of the legislation, guidance has now been published relating to ethical aspects of clinical trials from birth up to adulthood. This guidance was developed by the ad hoc group, chaired by the European Commission, responsible for implementing guidelines relating to good clinical practice. It is intended for everyone involved in any stage of a clinical trial including researchers, regulators, and ethics committees through to clinicians and families. This review article aims to give a practical summary of this guidance document, focusing on some of the themes highlighted including consent and assent, trial design and methodology, evaluation of risk and the challenges faced in special populations.

WHY DO WE NEED CLINICAL TRIALS IN CHILDREN?

It is well documented that children are not small adults, both in their changing physiological make-up and in their clinical needs. Therefore, although we have a responsibility to protect children we also have an obligation to ensure that they receive the best treatment. Currently, many medicines administered during childhood have not undergone formal studies during the licensing process. Approved drugs however are often used in an unlicensed and off-label manner: 90% of babies in a neonatal unit and 36% of children in a general paediatric ward. In certain cases, even though the medicines are used in an off-label manner there is good scientific evidence justifying their clinical use. This has been described for the use of proton pump inhibitors for the treatment of gastro-oesophageal reflux disease. Ethically, we need to focus our research on those medicines where there is a lack of efficacy and toxicity data in paediatric patients.

CONSENT AND ASSENT

Consent is a dynamic and continuous process obtained prior to enrolling a child in a trial, and as an ongoing dialogue between the child, parents and investigators throughout their participation. This point is highlighted in the EU guidance which discusses the need for periodic checks during the trial, suggesting a brief discussion during each repeat visit which could be documented in the medical notes or equivalent.

A key message from the guidance is the importance that consent is given free from coercion. Article 4(d) of the EU directive states that there must be no financial inducement to enrol a child in a trial, either for the parents or the child. The exception to this is the offer of compensation for the family’s time and expenses. In countries where inducements can be offered it has been shown this may have some influence on parental reasons for consent, with a correlation between the importance of free medication as a reason for consent and lower family income being shown. The complex relationship between a parent and their physician also needs to be considered, especially in patients with chronic disease, acute serious illnesses and in the situation of less educated parents. A parent’s wish to please their doctor may influence their reasons to consent. It is good practice for consent to be taken by the investigator and wherever possible not the treating physician. This however may not be practically possible, especially in the emergency situation. The investigator must however never take part in the decision-making, only ensuring the information has been understood and sufficient time has been allowed to come to a decision.

The directive requires a minor’s assent is “considered”, but it is not a legal requirement. The guidance recommends whenever appropriate that the child should participate in the informed consent process, and if a child’s assent is not sought, documentation of a justification of this
takes place. Separate information sheets for adults and children, and separate consent and assent forms need to be provided, as understanding and language will change with age. It has been shown that children from 9 years old may be able to understand the benefits and risks of research.\textsuperscript{11} A recent study of healthy children aged 6–8 years taking part in a follow-up study for a vaccine\textsuperscript{22} showed that two-thirds understood that they were to have a blood test but two-thirds did not know why. Three-quarters of parents in this study felt that they alone should make the decision and only half of children felt they were old enough. Consent like assent needs to be a continuing process and a child’s objections need to be considered. We need to respect a child’s will, in conjunction with their parents who know them best, and respect a child’s right to freely withdraw from a trial at any time.

**TRIAL DESIGN AND METHODOLOGY**

A typical pharmacokinetic (PK) study in adults will involve around 15 blood samples taken following the administration of the drug of interest. It is important that adult protocols are not used for children. Paediatric trials need to be designed by those with experience both in clinical trials and children’s medicines. There needs to be consultation from parents, and patients from the age groups to be included in the trial, where appropriate. A trial that involved a large number of samples examining the pharmacokinetics and efficacy of cyclosporine A in paediatric renal transplant\textsuperscript{13} was criticised, by an editorial in the same journal,\textsuperscript{14} as being unethical. It involved 13 blood samples of 5 ml during one dose interval in 18 patients. The invasiveness of this protocol was felt to be unnecessary and it was felt that the trial could have achieved its objectives with fewer samples.

Design methods can be optimised to allow for the smallest number of patients to be recruited to give a statistically and clinically significant result. The technique of population pharmacokinetics\textsuperscript{20} allows for fewer blood samples to be taken from a larger number of patients and Bayesian sequential design\textsuperscript{28} allows for the sample size to be recalculated after each observation. This potentially decreases the number of patients that need to be recruited. These methods are the same as those employed in adults. Interestingly, one of the authors from the cyclosporine paper mentioned above has published a more recent study examining a similar question using population pharmacokinetics and Bayesian modelling.\textsuperscript{29} The use of equivalence trials and non-inferiority trials is considered in the guidance. They usually involve recruiting a higher number of participants and their use should be limited to where superiority trials are not scientifically justified. Off-label treatments should be considered for use as a comparator drug in a trial if they are considered to be standard of care.

Study design needs to try to limit the invasiveness of the methods used. Alternative sampling methods such as urine\textsuperscript{18} or breath testing\textsuperscript{19} should be considered, although it has been difficult to find reproducible non-invasive methods to the standards that clinical trials require. When blood is needed for analysis, the timing of samples should coordinate as far as possible with therapeutic sampling. Micro-volumes and micro-assays\textsuperscript{30} should be used when available. Local anaesthetics need to be used for blood taking and indwelling catheters utilised whenever possible. If appropriate, sedation should be used for procedures and pain should be monitored by age-appropriate scales\textsuperscript{31} with prompt treatment. Pain, distress and fear should be minimised by using facilities appropriate to the child’s age, with personnel trained to look after children.

Placebo-controlled trials were regarded as the gold standard. This thinking has changed over the last few years and this is highlighted in the EU guidance. It states that placebo should not be used when this means that an effective treatment will be withheld. This has been the case in some asthma trials,\textsuperscript{22} for example, a study examining the efficacy and safety of nebulised budesonide which compared three different doses to placebo in children aged 4–8 years.\textsuperscript{23} Just under two-thirds of their recruited population were already being treated with a regular inhaled steroid, so children in their placebo group had a good chance of having a proven treatment stopped. The results showed a larger proportion in the placebo group dropped out due to asthma exacerbations and a higher number of courses of oral/parental steroids were prescribed. A comparator group of current treatment for these children would have been more clinically relevant and ethically acceptable. Placebos can be considered, for example, when there is no commonly accepted therapy for the condition or when the commonly used therapy is of questionable efficacy or has a high frequency of adverse drug reactions. Their use now needs careful consideration and good scientific justification.

**RISK/BENEFIT ASSESSMENT**

Risks and benefits need to be viewed in balance and a child’s interests should always prevail over society and science. The risks should be considered in conjunction with the severity of the condition or diseases to be studied, the age of the child and the risks and benefits of alternative treatments. For example, in oncology trials, the adverse drug reactions tolerated for a new treatment in a relapsing cancer would be higher than those for an antibiotic to treat otitis media. Potential harms can be physical, psychological or social, and they may be immediate or delayed. They can take many forms, from the risk of the medicinal product tested, or the control, through to the invasiveness and intrusiveness of the research. The guidance also discourages enrolment in multiple clinical trials which can take place when a condition is rare in childhood, such as hypertension.

Risk is summarised into three categories. These are shown in table 1, with examples of procedures that fall into each category. Minimal risk is defined as a probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examination of tests. This definition can be debated: a single car trip across town during a rush hour poses approximately 1 in 100 000 chance of death in a child. Therefore, if a PK research study poses a risk of death of 1 in 100 000, is it no more dangerous than an ordinary activity of normal life? In a telephone interview study around two-thirds of institutional review board chairs in the USA\textsuperscript{24} categorised this
proposed PK study as posing a risk of greater than minor increase over minimal risk.

Parents and children were asked their views on facing research risks for others in an interview study.23 Children were aged 7–14 years with 81 child–parent pairs interviewed. Overall, the children and parents were equally willing to enrol in non-beneficial research as charitable activities that posed the same risk. For a study that posed a one in a million chance of death, 40% of children and 19% of parents were willing to participate. Interestingly when the risk was described as “the same risks as riding in a car”, 89% of children and 93% of parents agreed. As the risk of riding in a car is higher, we can see the way that risks are described have an impact on their assessment. More research is needed on evaluating descriptions to enable children and parents to understand the true risks of clinical research.

Benefit can be defined as a progress in treatment, diagnosis or prevention for the child or the group of children affected. This could be seen as an increase in efficacy, a better safety profile or an alternative to an existing treatment. This alternative treatment may offer a better route of administration, decreased frequency of dosing, reduced treatment duration, a more relevant age-appropriate formulation or an improvement in relation to potential medication errors. The guidance gives the following levels of risk as being considered to be in balance with the benefit:

- Minimal risk with benefit for an individual or group.
- Minor increase over minimal risk, with benefit to the individual or group, and with the benefit to risk balance as being at least as favourable as that of the available alternatives.
- Greater than minor over increased risk with benefit for the individual that is especially favourable in relation to the alternative available approaches for the individual's condition.

SAFETY MONITORING

The level of risk can evolve over time, during recruitment into a trial and with evolving knowledge. It is essential that monitoring takes place. A review of paediatric randomised controlled trials20 from 1996 to 2002 has shown that very few (13%) paediatric trials had a data and safety monitoring board (DSMB). It is recommended in the guidance that an independent DSMB with appropriate expertise of conduct of clinical trials in children is used. When not appropriate, for example, in certain small PK studies, this should be justified. Age-appropriate formulations are recommended to reduce the risk of adverse reactions (eg, younger children choking on tablets) and the risk of dosing errors due to inaccuracy.

INTERNATIONAL DIFFERENCES

It is very important in a multinational study that research ethical review is carried out in each of the participating countries. Different international jurisdictions will have different regulations which will need to be considered and patient information needs to be presented in a culturally appropriate manner. For example, in the USA and Canada, studies can be approved that do not offer a prospect of direct benefit to healthy children when they pose either only minimal risk or minor increase over minimal risk.23 24

SPECIAL POPULATIONS

Healthy child research

In principle, children should not be enrolled as healthy volunteers within the EU. The exceptions in the EU that are highlighted in the recommendations are palatability testing such as swill and spit taste testing of a new medicine. Studies have shown that children’s tastes are different from adults25 and are very difficult to reproduce in an artificial environment. In certain situations, studies will need to take place in children who are healthy at the time of the trial. Prevention or vaccine trials contain healthy children but target a population likely to benefit from the result of those trials overall. Research has shown that within the UK and Canada views were very similar in health professionals when asked about research in healthy children. Over half felt that healthy children should not take part in research for general paediatric conditions even if this may be relevant to them in the future.30 The role of the healthy child in research still remains to be clearly defined.

Neonates

Neonates, be they preterm or term, represent the most vulnerable of our paediatric populations. Informed consent can be challenging especially in the emergency situation.31 They have limited blood volumes and are often anaemic due to frequent sampling related to pathological conditions.32 Limits for trial-related blood loss are recommended in the guidance. This equates to 2.4 ml blood per kg body weight for the 3% limit over a 4-week period, that is, <2 ml in an 800 g preterm neonate.

Adolescents

Research in this group can be challenging, as adolescents belong to the paediatric age group but may have the capacity to make adult decisions in many other areas of their lives. The need for consent, as already discussed, is paramount. There needs to be protection of confidentiality, and the disclosure of information to parents and other health professionals, needs to be transparent to the adolescent concerned at the start of any trial they assent to. An adolescent may cease to be a minor and become legally competent during a prolonged trial. This must be recognised and informed consent must be sought as soon as possible when this occurs.

CONCLUSION

The EU directive means that more clinical trials will be taking place within the paediatric population. The legislation represents a huge step forward for children’s medicines, in the testing of both new and established drugs. Research needs to focus on those drugs and conditions for which information is most lacking. We need to make sure that the conduct of these trials is both safe and ethical. This involves including those with knowledge of medicines, trial methodology and children themselves at the onset of a trial’s design. There are many ethical issues unique to children, as highlighted in this review. The EU guidance gives a good overview of these issues and is a good reference for anyone involved in drug research.

Competing interests: None.

REFERENCES


Acanthosis nigricans

A 9-year-old Malay girl was referred for simple obesity. She was developmentally normal and academically average in school. Her mother had type 2 diabetes mellitus. Examination revealed acanthosis nigricans of the neck (fig 1), axillae and cubital fossae. Her blood pressure was 128/70 mmHg. The 97th centile) and a body mass index of 35.

Acanthosis nigricans in children is usually associated with obesity. This association has been described in many different ethnic groups. The skin lesions are a manifestation of insulin resistance which activates epidermal growth. These children have an increased risk of developing type 2 diabetes mellitus. Management of this child involves lifestyle modification as well as dietary advice. Statins are contraindicated at present as the child is still pre-pubertal. Drug treatment is recommended for children 10 years of age or older, whose LDL levels persist at >4.1 mmol/l despite dietary restriction.

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Images in pediatrics

Figure 1 Hyperpigmented, hyperkeratotic plaques on the neck.

Patient consent: Parental/guardian consent obtained.

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