Ethical issues of clinical trials in children

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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? The main push in the last decade has been to increase the number of medicines tested in the paediatric population. This culminated in the European Union 'Paediatric Regulation' in 2007 that meant that all new medicines, appropriate for use in children, must be researched in this population. The current challenge facing paediatricians involved in research is balancing harm, legislative requirements against the need for evidence based medicine. This review aims to debate some of the continuing ethical dilemmas, including practical considerations, faced by those involved with clinical trials in children.

Keywords clinical trials; ethics; paediatrics; research

Why do we need research in children?

Medical research involving children is essential for advancing child health and well being. In the past it was deemed acceptable to use adult research and extrapolate the results for use in children, but for a number of reasons this cannot be the case. Firstly, children are not small adults as the disease processes seen are different e.g. bronchiolitis in infants. Secondly, their physiological make up and their pharmacodynamic responses to drugs vary with age (and differ from adults). Therefore medicines need testing in all age groups from premature infants to adolescents, as child specific adverse drug reactions are seen. Finally therapies used for adult, such as tablets, are not well tolerated particularly in younger children because they are difficult to administer or unpalatable.

A large number of medications in all clinical settings in paediatrics are either unlicensed or used in an off label manner. One of the aims of the Paediatric Regulation is to stimulate research in these medicines. Companies will 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. This legislation however has failed to produce good results, with only one medication (buccal midazolam) being approved so far.

We do however need to take care in recommending research on all of the medicines used in children, as for many there is good clinical evidence of their safety and efficacy. A good example of this is the recent change to the labelling of amoxicillin in children to update the licenced recommendations for dose. Concern has previously been raised that the American legislation resulted in more paediatric clinical trials of medicines widely used in adults e.g. studies of antihypertensives. Therefore ethically, further clinical studies need to focus on medications relevant to children's clinical needs where there is limited evidence of efficacy.

Risk versus benefit

One of the hardest ethical challenges of paediatric research is the balancing of benefit from a study against the harm and risks. Risk assessment is a crucial step in evaluating a protocol and conducting a clinical trial. Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. The risks of any clinical trial 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.

The EU ethical guidance that supports the Paediatric Regulation defines three levels of risk, as seen in Table 1, and practical examples have been included for each group. Minimal risk is defined as the probability of harm or discomfort not greater than that ordinarily encountered in daily life or during routine tests.

The way we describe risk has a huge impact on families understanding and acceptance of research proposals. An interview study looked at parents and children views' on facing research risks; children aged 7–14 years and their parents with 81 child–parent pairs were interviewed. For a theoretical study that had no benefit but a one in a million chance of death, only 40% of children and 19% of parents were willing to participate. Interestingly when the risk was described as "the same risks as riding

Examples of risk categories

Risk category	Procedures
Minimal risk	History and examination
	Blood pressure
	Ultrasound
	Single venepuncture
Minor risk over minimal risk	Multiple venepuncture
	Nasogastric tube
	CT scan
	Lumbar puncture venous line
Greater than minor increase over minimal risk	Endoscopy
	Sedation
	Anaesthesia
	Surgery

Table 1

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in a car" (a single car trip across town during a rush hour poses approximately a 1 in 100,000 chance of death in a child), 89% of children and 93% of parents agreed. Further research is needed so that we can establish both child and parental understanding of the risks involved in clinical research.

Benefit can be defined as progress in treatment, diagnosis or prevention for the child or the group of children affected. This may be an increased efficacy, safety of a drug or an alternative to existing treatment. This may include a change to the administration, dosing frequency or duration of a drug but may involve reduction in medication errors or production of a more age appropriate formulation.

The current EU guidance allows the following levels of risk in balance with benefit in trials in children:

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

It is our ethics committees that are challenged with reviewing and assessing the risk and benefit of these research protocols. Shal et al. conducted a telephone interview of 188 heads of Institution Review Boards (IRB) in the USA and asked them to categorise the risk level and direct benefits of paediatric research procedures. They found the results to be variable, 27% of IRB chairpersons categorised allergy skin testing as too risky for IRB approval without a prospect of direct benefit to the participating children, while 66% deemed such testing safe enough for IRB approval without a prospect of direct benefit. One of the ongoing ethical challenges in our vulnerable population is therefore this ongoing balance of risk versus benefit.

Risk monitoring

As the level of risk may evolve over time during any research project or with expanding knowledge, risk should be continually monitored and pre specified within the protocol. The EU guidance recommends the use of a Data and Safety Monitoring Board (DSMB) and should include paediatric specialists. In a study of short duration or a single dose pharmacokinetic study a DSMB may not be necessary, this however should always be justified. A literature review over 7 years (1996–2002) of randomised control trials in children showed that only 13% of trials had a DSMB.

Informed consent

Consent is defined as the voluntary agreement, to participate in research based on adequate knowledge and understanding of relevant information. As the child (minor) is unable to provide legally binding consent, and his/her assent does not have sufficient authority to authorise research, the parent(s)/legal representative are required to provide consent on the behalf of the child for participation. It is important to understand that consent is an ongoing process and should be maintained throughout the study period which could be done regularly through consultations, and should be well documented.

Separate information sheets should be produced for adults and children including separate consent and assent forms. These should be written in appropriate wording and language and reviewed by families and children. Early review of study information and protocols should take place by children and their parents to enhance acceptability of the study, such as the number of visits, timing of appointments and invasiveness of proposed procedures. The CRN Young Person's Advisory Groups, with six around the UK, are an excellent resource in helping with this process.

The question on who takes consent is an ongoing ethical debate. There is concern that there may be conflict of interest when the same person acts as both a child's treating physician and as the investigator recruiting the child to a study. This was investigated in a qualitative study of almost 60 families who had been approached about one of four different trials, where some of the trials had used a dual-role clinician–investigator 'model' during recruitment while others maintained role separation by using clinicians who were uninvolved in the child's care to conduct the trial approach. They showed that parents tended to emphasise the benefit of whichever 'model' they had encountered. This perhaps indicates that parents do not have strong preferences either way, however, patient minors seemed to prefer interacting with practitioners whom they knew.

It is important that consent is given free from coercion. Payment in research around the world in adults is common but controversial. Payment can enable participation in research without disadvantage and boost recruitment, but it must not lead participants to ignore or significantly undervalue risk. This can have an added complexity when the inducement is offer to the parent and not the child taking the risk. It has been found that when inducements have been offered this can influence parental reasons for consent, with a positive correlation between the importance of free medication as a reason for consent and lower income families. The EU Paediatric Regulation states that there must be no financial inducement to enrol a child in a trial, with exception of compensation for time and expenses. The ethical balance is therefore a fine line, which should allow appropriate compensation but not lead families to ignore, misunderstand or significantly undervalue serious risks.

Assent

We both have an ethical and legal obligation, to obtain a child's permission for their participation in research. The US Code of Federal Regulations defines assent as a child's affirmative agreement to participate in research. Mere failure to object should not, in the absence of affirmative agreement, be construed as assent. Allowing children to be part of the decision process respects their evolving maturity. Time should be taken for this process and should be done along side obtaining consent from the parents. Research has shown that children from the age of 9 years can understand the risks and benefits of research. Across different countries, assent is widely but not globally recognised. The American Academy of Pediatrics endorses 7 years as a minimum age for assent, whilst different European states vary between 7 and 16 years.

Evaluation of whether a child can assent should not be based on chronological age alone but should depend on other factors