

Nuffield Council on BioEthics

Children and clinical research: ethical issues

Call for evidence

A group of paediatricians, research nurses and other research staff from the Academic Department of Paediatrics met to discuss the Nuffield proposals on the 11th October 2013. The attendees were:

Professor David Dunger – Professor in Paediatrics and acting Head of Department
Dr Carlo Acerini – Senior University Lecturer in Paediatrics (diabetes and endocrinology)
Dr Kathy Beardsall – University Lecturer Neonatology
Dr Burak Salgin – Clinical Research Fellow
Dr Martin Tauschmann - Clinical Research Associate
Janet Allen – Research Nurse
Catherine Fullah – Research Nurse

We also consulted colleagues in the NHS who are engaged in Clinical Research across the NIHR Cambridge Universities NHS Trust.

General Comments

Medical research involving children poses particular ethical issues and these have been summarised in the recent MRC ethics guide: *Medical Research Involving Children (2004)* and mirrored in similar documents produced by The Royal College of Paediatrics and Child Health, the British Medical Association, EC Directive 2001/20/EC and the European Medicines Agency.

Although it may be challenging, we need research involving children. Disease and disorders in children may differ fundamentally from those encountered in adults and have to be understood in terms of the growing and developing child. We cannot assume that children are “small adults” and the pharmacological properties of drugs and their effectiveness may relate to physiological changes during childhood and are not always directly related to body size. Increasingly, early childhood origins of adult disease are being recognised and successful prevention of many adult diseases may need to start in childhood.

While our instinct may be to protect children, their participation in research is essential to refine the treatments they receive and reduce harm from dangerous or ineffective drugs or other interventions. Where conditions are only encountered or have a fatal outcome during childhood, it is imperative that we encourage active research into potential interventions, even if the disease or condition is rare.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recognised the long standing problems around the reluctance of pharmaceutical companies to carry out trials of their products in the paediatric population. They have preferred to allow the off-license use of drugs without proper consideration of the importance of formulation and potential pharmacokinetic (PK) and pharmacodynamic (PD) differences which could have potential impact on the efficacy in childhood populations. The introduction

of Paediatric Investigation Plans (PIPs), where pharmaceutical companies are obliged to demonstrate their plans for application in paediatric populations, at a very early stage of drug development, has been a step forwards. Increasingly the pharmaceutical industry is proposing complex, early phase PK, PD and efficacy studies in young people. Although this is encouraging it poses many practical issues relating to repeated blood sampling, potential risk and the overall intensity of many protocols, which may disrupt the child's family home or hospital environment. These studies are very important and working with the NIHR research networks (e.g. MCRN, CLRN and the DRN) we can contribute to these studies and make sure that they are carried out in a safe environment using appropriately trained paediatric consultants and nursing staff.

The principles of gaining ethical consent from parents and assent from children have been established and are embedded in Medicine and Healthcare products Regulatory Agency (MHRA), research ethics committee (REC) and local research & development (R & D) approvals. They recognise the importance of consent procedures, accurate methodology and appropriate study design, to limit risk to children, whilst ensuring research is informative, widely disseminated and thus of benefit for future generations. Adherence to the principles of valid consent and 'good clinical practice' (GCP) must be embedded in research governance, not only in the case of interventional studies, but at all levels of research in vulnerable childhood populations.

References

- (1) MRC Ethics Guide: Medical research involving children 2004
<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430>
- (2) Royal College of Paediatrics and Child Health: Ethics Advisory Committee 2002, Guidelines for the ethical conduct of Medical Research involving children. *Archives of Disease in Childhood*. 82, 177-182 2000.
- (3) Consent rights and choices in health care for children and young people. *British Medical Association*. 200,1 J Med Ethics 2003:29.
- (4) Ethical considerations for clinical trials on Medicinal Products conducted with the paediatric population. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.
- (5) European Medicines Agency: Note for guidance on clinical investigation on Medicinal Products in the Paediatric population (CPMP/ICH/2711/99). January 2001.

Specific questions

- **How should children be recruited to clinical research?**
 1. **What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?**
 - Currently research is not embedded in general Paediatric practice with the possible exception of Paediatric Oncology.
 - Patients and parents are often not aware of the research opportunities and are not familiar with research procedures and potential benefits to participants and future patients with the same condition.
 - Some paediatricians and other health professionals are still reluctant to engage and some have a protective, negative response to research activity involving children.

The ways in which we could overcome these could be by:

- Raising general awareness of research opportunities and the importance of research for the development of new therapies for children.
 - Communicating research procedures and benefits in a way that is easier for parents and children to understand.
 - Seeking new approaches to recruitment, for instance by using social networks and the internet.
 - Making more convenient for busy parents and children to participate in research studies.
2. **Who should make the final decision as to whether a child participates, or continues to participate, in clinical research when parent and child disagree? What responsibilities do health professionals or researchers have in such cases? (You may wish to distinguish between children at different stages of development and/or the different ways in which disagreement may arise or be expressed.)**
 3. **How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?**
 4. **A 'shared' or 'collaborative' decision-making model is often advocated for decisions about a child's research involvement, involving the child, relevant family members and professionals. Is this a helpful approach? How might any problems arising in this model be overcome?**
 5. **Parents' views on whether (and how) children should be involved in decisions vary enormously both within and beyond the UK. How should the law and professionals take account of such different parenting approaches?**

Questions 2-5 have been answered together because they are very closely related:

- Generally we felt that the current parent's full consent and children's assent procedures work well. They encourage researchers to provide appropriate information for the children as well as

more extensive information for the parents. This means that the children can be involved in the decision as to whether they are involved in the clinical study or trial.

- Issues around Gillick competence¹ are still poorly defined but in practice they are rarely an issue. Where there is a disagreement between a child under the age of sixteen and parents as to whether he or she should be involved in a clinical study, this can usually be resolved through discussion or the involvement of a neutral third party. There may be rare examples where the conflict cannot be resolved and in these cases, which we suspect only involve early phase clinical trials, an additional form of mediation may be required. This may be particularly pertinent to MHRA regulatory trials where Gillick competence is not acknowledged.

6. Rewards (such as vouchers) for children participating in research may be welcomed as an appropriate way of saying 'thank you', or criticised as a form of undue incentive (to either child or parent). What forms of compensation/reward/expression of gratitude for research involvement do you think acceptable, and why?

- With regard to non investigational medicinal product (IMP) studies, the ethics committees have become very adept at balancing the need for simple rewards and the imperative that they should not become inducements. Often in Paediatric studies certificates and other acknowledgements of involvement in studies can be very useful to young people in preparing their CVs for applications to university, etc.
- The rules covering IMP studies are understandably much more prohibitive but do seem unnecessary rigid. Whereas it is important that no child or parent participates in the study because of the obvious rewards, the current restrictions also prohibit reward for staying in the study over a long period of time. Where children and families commit to 3 or 4 years in a study, some rewards for continued involvement will improve compliance and ensure the study reaches a successful outcome.
- In line with EMA Paediatric Investigational Plans, it will be essential that drugs are tested not only for efficacy but also to determine their pharmacokinetics properties (PK). PK studies may involve short periods of time in hospital, multiple blood sampling and the perceived benefit for that child may be very limited. In these cases, as in adults, issues around reward need to be debated.

- **What research proposals should be regarded as ethically acceptable?**

7. How helpful is the notion of the best interests of the child participant? How would you define 'best interests'?

8. How can the rights and interests of individual children (potential participants in research) be balanced against the rights and interests of all children (potential beneficiaries of the knowledge gained by the research)?

¹ The right to make a decision on any particular matter concerning the child shifts from the parent to the child when the child reaches sufficient maturity to be capable of making up his or her own mind on the matter requiring decision.

9. Are there any situations in which you think it would be acceptable for a child to be invited to participate in clinical research when there will not be any personal benefit to them? If so, please give examples.
10. Are there any circumstances where it would be right for a research ethics committee to approve research involving risks they would usually regard as too high, if parents and young people had clearly expressed their willingness to accept these?

Questions 7-10 have been answered together.

The notion of the 'best interests to the child participant' is not particularly helpful. As with all research projects, the best interest of the patient is paramount and research must balance risk/benefit and should be carried out in a way which leads to robust conclusions which can be used in informing treatment in future generations.

A research question is in the interest of children if it is:

- Based on sound research questions
- Well designed and adequately powered
- Has an appropriate risk/benefit ratio
- The results are appropriately analysed and disseminated to inform future clinical practice.

In principal, 'the best interests of a child participant' are not different to those of an adult participant in clinical research.

These principles relate to the balance between the rights and interests of individual children participating in research and the interests of all childhood potential beneficiaries of the knowledge gained by research. It is perfectly acceptable for parents and children to engage in clinical research where they may be no personal benefits to them. This is true for all the randomised placebo control clinical trials, or for that matter, comparisons of active drugs where one may prove to be superior to another. If these trials cannot be carried out in children we will forever be condemned to off licence use of drugs that have been evaluated in adults.

It is understood that young children may not have an understanding of risk/benefit and consent will be obtained from parents. Nevertheless current common consent procedures, which also involve some degree of assent from the children, are probably adequate as long as full information is disclosed. Just as an adult may agree to participate in an early phase study of potentially life extending drug in a terminal condition; can we really prevent parents make the same decision for their terminally ill child? Perhaps in these rare circumstances involvement of a third party may be important.

- **How should research in children be encouraged?**

11. Do you think the current regulations strike the right balance between promoting clinical research in children, protecting child participants, and involving children in decisions about their own participation? What (if anything) would you like to change?

Generally the regulatory framework for research in children has improved with more rapid responses from REC and MHRA but local R&D risk assessments and approvals can still lead to major delays in study initiation. The MHRA has recently recognised that there should be a distinction between the degree of regulation required for commercially-driven IMP developments and academic studies, particularly in

children where established drugs are being evaluated to ensure their efficacy and safety. However the MHRA has yet to clearly demarcate how these different studies will be regulated.

12. With limited resources, how would you decide which childhood conditions should be the priorities for research? Who should be involved in making these decisions

As paediatricians we believe that the condition in childhood should always be given priority for research as it has implications over a lifetime. Increasingly the childhood origins of adult disease have been identified and early prevention may be critical. Furthermore there are childhood conditions which, although rare, may lead to considerable morbidity and mortality. Many paediatric diseases are so called 'rare conditions' and have been neglected for many years.

Decisions as to which 'rare conditions' or even 'common conditions' in childhood are prioritised for research have not previously been an issue as relatively little research has been carried out in these patient groups. If decisions do need to be made around priorities they should be taken by parent groups, professional organisations and charities representing these young people, and cannot be left to the pharmaceutical industry where they may see the profit margins as being very slim.

13. What responsibilities do funders, researchers and stakeholder groups have to encourage the coordination of children's clinical research?

These different groups are absolutely essential to the development of children's clinical research. It is essential that they work together to:

- Ensure that studies are sufficiently large and well powered to provide robust outcomes
 - Ensure that studies are not repeated and the minimum number of children are involved
 - By using NIHR research networks, parents and children nationwide are aware of such studies, giving them the opportunity to participate.
- **Encourage network development and identification of sites which provide full recruitment, delivery and cost-effectiveness.**
 - **What should happen when the research is over?**

14. What responsibilities do researchers have towards child participants and parents when the study is over?

- Expressing gratitude for their participation.
- Keeping them informed about the results of the study and new developments.
- For commercial studies exploring new therapies, where there is no currently available effective therapy, to ensure that the patients still have access to effective therapies until the approved licence is achieved.
- On-going responsibilities. Let participants know of any adverse outcomes of the therapies that they may have been exposed to.

Archiving patients' information in case we need to get in touch with them in the future about beneficial/adverse outcomes of any clinical studies.