EMIG Ethical Medicines Industry Group

An EMIG Member Perspective on the Nuffield Council on Bioethics Call for Evidence – Children and Clinical Research: Ethical Issues

How should children be recruited to clinical research?

Questions 1-6

In responding to the questions below, you may find it helpful in some cases to distinguish between three broad groups of children:

- *those incapable of any meaningful involvement in a decision (e.g. babies)*
- *those capable of expressing a view, whether verbally or through their behaviour (in varying degrees, from young children to teenagers)*
- *those who would be regarded as competent to consent for themselves if the intervention were for treatment, rather than research (those who are 16 or over, or under–16s meeting 'Gillick' requirements in connection with the particular intervention(s))*

What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?

Poor awareness and lack of understanding appears to be a significant obstacle to the recruitment of children to research. Parents, whose worries have to be overcome at an emotionally fraught time, are, too often, badly presented with complex information about rationales for random allocation, the use of placebo etc by doctors that don't understand it well themselves. Careful planning to enhance communication and provide clarity about the trial process could significantly alleviate parental concerns and serve to avoid misunderstandings and misconceptions. The type of material used has to be thought about also. For instance, communication material designed for a 12 year old might not work well for a 16 year old. One thing is common to all ages though, young people do not like to be told constantly about the potential consequences of their condition. They like to hear positive messages of hope. It is these that make them enthusiastic to try new treatments.

Operationally, one of the main obstacles for recruiting young children is the thought of blood sampling. Incredibly, in growth hormone studies in the early 90s, many potential study subjects were put off by the annual requirement for blood samples. To overcome this problem, the need for each sample should be clearly explained and justified so that the child knows the good they are doing.

The key to successful research in children fundamentally therefore, lies in the careful design of studies. Is blood sampling, for instance, essential in all cases?

Additionally, provided standard clinical practice is incorporated, placebo control is no longer a problem. Most new approaches are add-ons to established practice. However, it should be noted that placebo responses in paediatric trials very frequently exceed that of improvement in normal practice. This correlates with the experience in adult trials across the spectrum of disease and argues for the totality of clinical of evidence (i.e. efficacy, safety and *effectiveness*) to play a greater role in defining the risk/benefit of interventions.

The challenge of recruitment could also be reduced by taking every appropriate opportunity to involve children in the process of identifying their needs and wishes in relation to research. The MCRN has had children's panels and some paediatric investigators have also included children to help with research planning, now as a matter of routine. They have particularly helped in preparing presentation materials providing information to child recruits. Children should also be members of development programme/individual study advisory panels, wherever practical and appropriate.

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.)

The ethical principle that underpins all paediatric clinical practice and research is that the physician must act in the best interests of the individual child. The same principle also guides all health professionals and researchers. Conflicts of interpretation need to be addressed, understood and resolved on an individual basis because variables such as the child's age are very influential. For instance, children that have the capacity to understand research should only be recruited when both the parents and children agree, thus limiting a retention issue later in the study. If such children wish to withdraw, then it should be their decision. If the child wishes to proceed and the parents wish to withdraw, then it should be the parents' decision.

How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?

An inevitable tension exists between the need to protect an individual child from potential harm and the need to advance medical research for the good of all children. Currently, consent for paediatric clinical trials is obtained by proxy from parents or guardians. Many protocols also now recommend the use of assent forms for minors. The

advantage of assent forms is that they help to ensure that the nature of the clinical trial has been well explained to the child. It appears that while parents are usually happy to share decision-making with their children in less serious situations, they want to retain control over decisions for entering trials in life threatening conditions. Therefore, in these situations, parents can override children's expressed wishes.

Opinions do vary on the objectivity of assent, but overall, when asking parents for written consent, it is recommended that children with the capacity to understand should be involved and at least provide verbal assent. Of course, all proposals must abide by the over-riding principle that the child's welfare is paramount. While there is no question of over-riding a parent's refusal to allow their child to participate, there are times when clinicians have over-ruled a consenting parent

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?

We believe that a shared approach, where all have access to accurate, clear and relevant information, is essential. This should facilitate open discussion around all aspects of the trial and its impact on all concerned. Such a collaborative approach may also serve to obviate conflict between parental and children's wishes.

So, the current approach is the right one. Problems with the approach can be overcome, or more likely won't arise, if the law is clear on the matter.

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?

This variability is unavoidable. However, the use of assent forms can help ensure that, even if the individual child cannot have the final say in terms of consent, he/she understands what is involved in the trial. A discussion between the medical staff and the child when completing the assent form also facilitates the opportunity for children to have their say, and for doctors to respond accordingly.

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?

Incentives to enhance recruitment into paediatric trials that don't involve the treatment are fraught with ethical problems. However, fun things specifically for children to do while undergoing trials, for example educational games/apps/tools/ activity books etc , could offer real value without raising ethical concerns. It appears that altruism itself is a motivating factor for many children when entering clinical trials. It is doubtful that anyone could complain if those brave enough to take the risk in clinical trials should reap the reward of free access to the therapy on its approval.

What research proposals should be regarded as ethically acceptable?

Questions 7-10

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

In this context, the best interests of the child relate to the need to safeguard that individual child. Thus, the risks and benefits for the participant need to be considered and balanced against the individual's needs. It is easiest to make these decisions where there is clinical equipoise – substantial uncertainty – over which treatment is best.

A key issue is to be able to balance "best interests" with "autonomy". The latter presupposes an ability to understand information, and the current and future impact of deciding to participate in research. Clearly this increases with age. However, even adults have variable understanding and make bad decisions. Children have far more understanding than is usually credited by adults. They should be involved in the process once they have the capacity to understand which can be as early as 4-5 years of age.

Research ethics committees should be willing to approve research with higher levels of risk, if children and their parents are willing to accept these risks. That is, they would be operating after due consideration, in the best interests of the child.

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)?

This issue is problematic in all areas of research, but most especially where children are involved. Once again, retaining a sense of the 'best interests' for the *individual* child is of critical importance. Only when this has been ascertained, can the interests of the wider society be considered. It would not therefore, be ethical to attempt to justify the application of more pressure on children and parents to participate in clinical trials simply to satisfy the greater good.

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.

No.

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?

Yes. But the problem of what is appropriate information rears its head. For children with terminal diseases, where there is high unmet medical need and scientific evidence that a currently unlicensed treatment might have benefit, carefully conducted "individual patient research", with a waiving of rights of indemnity could be considered. This would be aligned with the principles of the recently launched Halpin Protocol (http://www.telegraph.co.uk/health/healthnews/10314789/Motor-neurone-disease-campaigner-Les-Halpin-dies.html)

How should research in children be encouraged?

Questions 11-13

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?

Research in pre-school-age children presents a significant challenge. Currently, much paediatric practice is based on the extrapolation of data from studies in older subjects. The evidence base diminishes exponentially with decreasing age. Therefore it could be argued that clinical practice in pre-school children should always have a research component. While placebo controlled trials may not always be possible, observational

studies certainly are and all too frequently these opportunities are ignored. It is incumbent on paediatricians to improve the evidence base of their practice and for regulation to evolve accordingly and appropriately to enable the science.

The information that children have access to on clinical trials - what is involved, what might be the consequences – is currently inadequate. This has been highlighted in a number of studies, some which suggest a different approach to delivering such information, for example in a graphic novel format.

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

Academics and clinicians generally decide on what areas of research they tackle. The public, through the media and charities, influence the funding. This works pretty well. Good ideas don't generally come from pots of money, but good ideas do attract money. This being said, there is a view that a greater degree of proportionality is needed when deciding or mandating what areas of research need a specific paediatric focus vs. what areas are already served reasonably well and/or clinical application could be extrapolated from experience in adults. This is all about benefit/risk to the child. Some parents would wish to understand fully the true degree of medical need for new research before agreeing to submit their child to it. Greater use of registries as research tools is another potential mechanism to garner useful data and would likely receive good support from industry.

The groups of patients that really understand the need to research in children are those that have life-long diseases, often inherited. Parents are frequently very well informed – although they may, as a result, also have very strong opinions. Witness the debate between haemophiliacs on the wisdom of bearing children at all.

Life-long diseases are more likely to have well-run patient societies that are key advocates for research. But, because such conditions are often rare, these are the poor children most likely to fall prey to the commercial realities of drug development and reimbursement. As a result, some might argue that commercial organisations are not appropriate to address such diseases and that state sponsorship through organisations such as MRC and NCRI is better.

While charities and advocacy are important to furthering research, sometimes the attention they bring is unbalanced when one disease is compared to another. For instance, the Sickle Cell Disease (SCD) Society can feel quite aggrieved by the attention given to breast cancer compared to its own campaign. Is it fair that more effort is directed towards breast cancer patients that have usually had 50 good years when SCD

affected children are having their first stroke at three years old? Clearly, decisions about the distribution of research resources cannot be left to the 'charity market' alone.

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

In this context we define "coordination" as a collective cooperation with a responsibility to improve the quality and quantity of children's clinical research. This must start with all stakeholders taking time to understand each other's motivations, needs and challenges. This is poorly done in children's clinical research that is no different to other aspects of life sciences research where vital interactions between the public and private sectors are required. Insufficient attention has been paid to this issue that is often characterised by long-established false perceptions of one of another. Its removal will result in better research outcomes for all.

What should happen when the research is over?

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

The idea that trial participants are treated as partners in research is a good one. Researchers should be involved with the subjects for as long as the subjects need them. For most people their contact with the researcher is the same as their contact with the clinician. While the child is ill, it's most likely that contact will remain either directly or indirectly.

Children and parents should have ample opportunity for giving feedback on their experience, and a strategy for ensuring that such feedback is acted upon should be in place, and shared with participants. All participants should be informed of the outcome of the study, both positive and negative. Information on why such studies are initiated, and a reiteration of the purpose and importance of trials, both for the individual and for society, should also be undertaken.

Bibliography

1. Cohen E, Uleryk E, Jasuja M, Parkin PC. A absence of pediatric randomized controlled trials in general medical journals. *J Clin Epidemiol* 2007; 60:118–123.
2. Chessells JM. Treatment of childhood acute lymphoblastic leukemia: present issues and future prospects. *Blood Rev* 1992; 6:193–203.

3. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. *Lancet* 2004; 364:803–811.
4. Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. *Lancet Oncol* 2008; 9:392–399.
5. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to children's participation in randomized controlled trials. *J Pediatr* 2003; 142:554–9.
6. Jacobsen RM. Pediatrics and Evidence-Based Medicine Revisited. *J Pediatr* 2007; 150:325-7.
7. Chester P, Kennedy ED, Lowes L, Greene A, Matthews DR. Getting the message across – working with young people to change perceptions of health research. Chapter 12 from The Active Involvement of Children and Young People in Health and Social Care Research. Pub Routledge. 2012

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