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Children and clinical research: ethical issues. Submission to the Nuffield Bioethics Council - some comments from Professor Andrew Tomkins of the Institute for Global Health, Institute of Child Health, University College London (a.tomkins@ucl.ac.uk) – 23/10/13 - most of my comments refer to research among children that I have been involved with in developing countries. Many of the responses are different for infants and young children (from birth to 5 years) compared with older children (older than five years).

Question 1 - what do you consider to be the main obstacles to recruiting children to research? How might these be overcome?

Among infants and young children, there are several obstacles. 1) parents are frightened that the procedures will hurt or harm the infant 2) parents do not understand the significance of the research 3) parents feel that the infant is very vulnerable and they feel responsible for allowing their infant to enter a study.

Among older children, the obstacles include 1) lack of willingness to speak on a child's behalf because they feel they are imposing on the child's autonomy 2) fear that the child may be harmed by the study.

In both age groups, these obstacles could be overcome by improved awareness of the benefits of research. This involves improved public understanding of the benefits of child research as well as improved ways of engaging better with parents and children in studies so that understanding is improved.

Question 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?

This question is difficult to answer because there are many ways of responding to "disagreement". Does this mean that a child who cries when he has a blood spot taken for a biochemical measurement is a child who disagrees? Does this mean that a child who is in a trial of a nutritional supplement among school age children and decides that he does not like the taste of the tablet is actually disagreeing?

Among infants and young children this could mean evident discomfort by the child who might be frightened by a blood test or anthropometric measurement or cognitive tests or EEG while the parent understands that these are not harmful procedures.

Among older children, this could mean a refusal by the child to continue taking a medicine or a micronutrient supplement while the parent feels that this could be in the best interest of the research and is not harmful.

As regards, who should make the decision-among infants and young children, most situations would involve the parent making the decision. Among older children, dialogue between child parent and researcher should involve a joined up decision by parent and older child. Researchers have responsibility for ensuring that parents understand all the implications of research for infants and young children, taking responsibility for assisting in the study despite some apparent discomfort. Because of their lack of understanding of the research, infants and young children do not really have a key position in making a decision about whether to enter or persist in a study. Among older children, researchers have a great responsibility for ensuring

that both children and parents are equally informed about all aspects and potential discomfort of the research, including the knowledge that the research may not actually benefit themselves necessarily. In certain cultures, schoolteachers of boarding schools may take responsibility for giving permission for research on children on behalf of parents , but this should only be accepted if there is clear evidence that the children themselves have an opportunity of leaving the study or not entering it in the first place.

Question 3. How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?

These are useful distinguishing terms. The word Consent infers a full understanding of all the rationale for doing the research and a full understanding of the benefits or lack of benefits of entering a study. The word Assent infers an agreement to enter a study, trusting in the integrity of researcher and parent/carer alike, without necessarily understanding the full benefits or lack of benefits of entering a study. The ages at which a child is able to give consent as opposed to assent will vary considerably according to culture, education, and complexity of the research methodology. It is important to distinguish between the two however, because consent can only occur if the child fully understands and agrees whereas assent can occur if the parent/carer fully understands and the child assents by agreeing to trust the researcher and the parent.

Question 4. A shared or collaborative decision-making model is often advocated for decisions about child is 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?

This shared collaborative decision-making model is not relevant for infants all young children because they cannot fully understand the implications of the study. It is very important for older children. In certain cultures, the involvement of community leaders and schoolteachers might also be considered in the shared model. A key question of integrity is important, particularly in those cultures where children's rights are not emphasised and there may be unduly and inappropriate pressure on a child from parent or community leader to become a participant in a study. It is important in shared models of decision-making to ensure that the child's rights are respected at all times, even when these are counter-cultural.

Question 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 researchers take account of such different parenting approaches?

All countries except the United States of America and Somalia have signed up to the Convention on the Rights of the Child. While this is a legally binding agreement that governments have signed up to, judging from my experience in some countries there are examples of serious lacks in its implementation. All researchers should ensure that the CRC is as fully implemented as possible in the countries in which they work. Furthermore, researchers should be aware of situations where the CRC is not implanted. This has profound implications on whether a child is able to give consent or assent to entry into a study. In all situations - clarification of the ability of an older child to make up his own mind, rather than be coerced by parent or guardian or community leader should be performed.

Question 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. What forms of compensation/awards/expression of gratitude for research involvement do you think acceptable and why?

A key "reward" for a child entering the study is the knowledge that the child will be looked after by a caring and competent health professional. Another "reward" is repayment of travel costs and provision of food. More obvious gifts of badges and T-shirts showing films/DVDs are also used. A risk analysis should be performed for all "rewards" that are given in any study, assessing the risk to the child and to the study itself. All the above examples do not represent high risk. Provision of money, toys, and clothes are all likely to influence decision-making about consent or assent and are best avoided.

Question 7 how helpful is the notion of the best interests of the child participant? How would you define "best interests"?

The best interest of a child entering a steady involves ensuring that the health (physical and mental and psychological) nutrition and development of the child is not compromised by the study.

Question 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)?

Question 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

The above two questions cover similar ground. It is acceptable for children to enter a study where there is a possibility of no benefit to the child. Examples are randomised controlled trials of micronutrient supplementation, investigation of deworming, longitudinal studies birth involving cohorts, which had a series blood, anthropometric and cognitive investigations. In these and many other studies, it is acceptable for children to receive placebo provided that parental and Guardian understanding is comprehensive for infants and young children and understanding is present among older children. Ensuring the rights and interests of individual children is essential and, particularly in those studies involving some degree of discomfort, such as anthropometric measurement, blood sampling or cognitive tests, it is essential to ensure that no harm comes to the child as a result of an investigation. It is important to distinguish harm from discomfort.

Question 10 are there any circumstances where it would be right for a research ethics committee to approve research involving risks they would usually regarded as too high, if parents and young people had clearly expressed their willingness to accept these?

This would be an unusual situation where ethics committees allow more invasive investigation, then parents or children would be prepared to undergo.. Parents are more likely to "over-volunteer" their children in order to please medical staff or get access to regular surveillance. Children need to be protected against over enthusiasm of parents to enter their children into studies, particularly where there are

very limited medical resources available locally. At all times, ethical committees should ensure the best interest of the child.

Question 11 do you think the current regulations strikes the right balance between promoting clinical research in children, protecting child participants, and involving children in decisions about their own participation? What would you like to change?

Regulations and practice vary considerably between countries, and even within countries, particularly in developing countries. There are currently considerable problems in ethical committees in a number of developing countries. In some universities and ministries of health, for instance, there are several layers of ethical committees. Some, usually unpaid, committees have members with very little understanding of the nature of research and they sometimes objects to studies being formed on irrational bases. Others have committees which have paid members, requiring investigators to submit large fees. Ethical committees (both paid and unpaid) vary considerably in standards and efficiency. The investigator may well have a choice of which ethical committee to he might submit a protocol, knowing that the chance of a protocol be approved is likely to be higher in a particular ethical committee. This is a very disturbing and worrying trend. It would be valuable to have a critical review of ethical committees in developing countries and to develop some guidelines which would be accepted through international organisations such as the International paediatric Association or others.

Question 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 a matter of principle, decisions about priorities (which hopefully would be supported by donor preferences) should be based on the likely improvement in mortality, morbidity and child development that would occur as a result of the implementation of interventions being investigated. Decisions on priorities of research in developing countries require very close interaction with colleagues in universities, research units and ministries of health, together with other cognate ministries such as education and community development. A key task of investigators is to make relevant and strong cases to donors and grant giving bodies for an increase in support of key areas for research.

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

Key activities such as communication and collaboration are probably more important than cooperation. A most important issue is to prevent "reinventing the wheel" in research by ensuring that all research is coordinated by a national body in country and that all research results are made available to a central coordinating body. As soon as possible after analysis of results, bearing in mind the need for peer-reviewed publication. All of the above players need to ensure that children's research is given a high priority and protocols and results are shared optimally. Open access publications are essential

Question 14 what responsibilities do, researchers have towards child participants and parents for the study is over?

Providing study participants and/or their parents or guardians with an overall summary of the findings is important. Ensuring that all data is maintained in an accessible, but anonymous format is crucial. Confidentiality is vital, particularly where there are links between child health and maternal health, such as HIV.

Any other comments?

1) *Nearly all my experience has been in developing countries with a focus on child health and nutrition interactions. A key issue in planning such research is the need to ensure that any outcome from research has a practical implication for clinical or public health management. All ethical committees should ask "How will the results of this research improve the clinical care or health of communities of children?"*
2) *While there are examples of high quality ethical committees in some developing countries, there are some that are dysfunctional and do not work efficiently or safely. It would be invaluable to have a critical review of ethical procedures and committees responsible for research among children in developing countries. A particularly valuable outcome could be the development of Good Practice guidelines. While there have been some recommendations produced (e.g. the Nuffield Report on Bioethics of Research in Developing Countries) for these, my experience is that these recommendations have not been put into practice widely and there is urgent need to assist the improvement of ethical review and care of children in research in developing countries.*
3) *There is frequently suspicion and concern about research; there are various reasons. It would be valuable to have a well thought through campaign to improve the public understanding of the importance of research in children in the UK.*