

Children and clinical research: ethical issues

Call for evidence

(closing date: 31 October 2013)

This submission has been prepared on behalf of the Christian Medical Fellowship (CMF) by CMF members, Professor Andrew Tomkins of the Institute for Global Health, Institute of Child Health, University College London, Professor John Wyatt, Emeritus Professor of Ethics and Perinatology, University College London, Philippa Taylor, Head of Public Policy at CMF and Peter Saunders, Chief Executive at CMF.

CMF has over 4,000 doctor members and around 1,000 medical student members and is the UK's largest faith-based group of health professionals. A registered charity, it is linked to about 70 similar national bodies in other countries throughout the world.

CMF regularly makes submissions on ethical and professional matters to Government committees and official bodies. We have responded to a number of Nuffield consultations over the past years, including the consultation in 2010:

'Give and take? Human bodies in medicine and research.'

<http://www.cmf.org.uk/publicpolicy/submissions/?id=127>

CMF welcomes this Nuffield Council consultation on the use of children in clinical research and the opportunity it provides to contribute to the debate. Our doctrinal beliefs and ethical values are outlined on our website: <http://www.cmf.org.uk/>

CMF holds that:

1. The imperative to clinical research comes from our creation as human beings and the creation mandates. Because the universe is created by God, Christians believe that we have a two-fold responsibility of stewardship towards it: we are required to preserve it and we are encouraged to explore it. Both activities enable us to care more effectively for creation including humankind. The latter constitutes the Christian's mandate for research and if carried out with respect for Christian principles it is a positive and God-honouring activity.
2. Children are intrinsically vulnerable and open to manipulation and abuse by the strong, including powerful academic, commercial and government agencies. Therefore all research must be regulated to minimise risks to children, to minimise coercion and abuse and to protect their interests. This is particularly the case in randomised clinical trials where one arm is placebo treatment. Minimal risks are also essential in clinical research which extends scientific knowledge but in which there is no possibility of benefit to the individual child.
3. Children should be treated with respect and care. In general older children should not be forced to engage in research without their agreement or assent.

4. Parents have responsibilities to care for and to protect their children. Hence parents should be both informed and involved in all decisions about research in their children and should give consent for those children who require it.

These underlying principles should be foundational to research involving children.

CMF notes that:

1. Clinical research in children in the UK is highly regulated and in principle the rights and interests of children are well protected. There is a danger that excessive bureaucracy and regulation in the UK unnecessarily restrict and impede clinical research in children. This is not the case in many less developed countries and there is an urgent need there to improve the quality of research ethical committee review and regulatory oversight of research in children.

2. Many parents appreciate the possibility of their child participating in research that may benefit other children with similar conditions. This is particularly the case if there is no treatment for their child and the child dies or is permanently disabled. Parents draw great comfort from the fact that because of research other children may benefit in some way from the tragedy which befell their own child. Hence clinical research may have positive psychological benefit for parents.

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?**

Among infants and young children, there are several obstacles to recruitment:

1. Parents are fearful 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
3. Consent: children's responses are varied, often unpredictable, and alter as children develop. A procedure that does not bother one child may arouse distress in another.

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.

Improving awareness would include covering the overall goals of clinical research, the oversight that is provided by ethical committees and regulatory bodies, the nature of the informed consent process, the design of randomised clinical trials etc.

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.)**

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

Infants and young children may show evident discomfort or be frightened by a blood test or anthropometric measurement or cognitive tests or EEG while the parent understands that these are not actually harmful procedures.

Among older children, a child might refuse 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** or guardian making the decision. Because of their lack of understanding of the research, infants and young children do not really have a key role to play in making a decision about whether to enter or persist in a study.

More attention should be paid to training researchers in communication with young children.

Researchers clearly 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. It is more difficult to exercise 'substituted judgment' on behalf of others and the responsibility is thereby heightened.

Most paediatricians think that children above the age of 5-7 should not be forced to participate in research against their will unless they have a severe medical condition and a therapeutic research trial is under way (as for example in the treatment of leukaemia). This reflects respect for the integrity and interests of children. There is strong research evidence that with appropriate information and skilled assistance children as young as five years old are able to comprehend the nature of even quite complex research and give informed assent.

Among older children, dialogue between child, parent and researcher should involve a joined up decision by parent and older child. 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.

A reasoned refusal by a child to participate in research is likely to be taken as evidence of such understanding, and it would be unwise to rely on parental consent in such circumstances.

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.

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' implies 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.¹

The word 'assent' implies an agreement to enter a study, trusting in the integrity of researcher and parent/carer alike, without necessarily understanding the full benefits, lack of benefits or risks of entering a study.

The age 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. There are also some legal guidelines as the consultation document notes on p3.²

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.

Occasionally a child may be too afraid, confused, or ignored to refuse. So the term assent may be misused to cover children's refusal.

4. A 'shared' or 'collaborative' decision-making model is often advocated for decisions about a child's research involvement, involving the child,

¹ 'For treatment, the law in the UK presumes that young people over 16 have the capacity to consent to treatment for themselves, although those with parental responsibility (usually their parents) retain the right to consent on their behalf up to the age of 18. Children under 16 who are considered 'Gillick competent' – that is, those who are judged to have "sufficient understanding and intelligence to enable them to understand fully what is involved in a proposed intervention" – are also deemed to have the capacity to consent to that particular treatment' <http://www.nuffieldbioethics.org/children-and-research/children-and-research-call-evidence>

² 'The Clinical Trials Regulations specifically define a 'minor' as being under the age of 16. Young people aged 16 and 17 in the UK are therefore regarded as adults, entitled to give, or withhold, consent for themselves if invited to participate in a clinical trial... Where a child is under the age of 16, the UK regulations require the "informed consent" of a person with parental responsibility, and the child has no right of veto, although their explicit refusal should be considered by the researcher... The concept of assent, however, is used in quite diverse ways: from compliance by a child as young as three, to the active agreement of a teenager who would be considered competent to consent to their own treatment; and there is on going disagreement about how useful it may be.' <http://www.nuffieldbioethics.org/children-and-research/children-and-research-call-evidence>

**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 or all young children because they cannot fully understand the all implications of a 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 undue 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.*

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?

All countries except the United States of America and Somalia have signed up to the Convention on the Rights of the Child (CRC).

While this is a legally binding agreement, it has been the experience of some CMF members in some signatory countries that there are examples of serious deficiencies 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** implemented. This has profound implications for whether a child is able to give consent or assent to entry into a given study.

In all situations clarification of the ability of an older child to make up his/her own mind, rather than be coerced by parent or guardian or community leader, should be obtained.

Respect for the rights and interests of parents means that we must accept that attitudes to research will vary widely and hence we should not recruit children into clinical research against the wishes of the parents. As we note in Q1 above, the reactions of the parents may often reflect misunderstanding and lack of knowledge about research, therefore detailed explanation in a form which is culturally appropriate is helpful.

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?

In general incentives are dangerous in this area, whether financial incentives or compensation in kind. There is a great danger that vulnerable children and parents

may be exploited or subtly coerced. So while in principle we would have no objection to considering different forms, a key issue is whether vulnerable people are put under particular pressure (eg the poor being offered financial rewards) such that their involvement no longer allows for fully informed consent or full assent.

It can be very difficult to assess whether something constitutes an 'undue incentive' or not. Is there significant 'incentive'? If so, would it be 'undue' in general, to all or most people? Would it be 'undue' to that individual?

The underlying principle should be that we avoid the use of rewards which are in any way coercive or manipulative and which are in danger of overwhelming or compromising judgement and rationality. The essence of clinical research is that it should be freely entered into as an expression of altruism and solidarity with the rest of suffering humankind. Altruism (care and concern for others) is an important concept that should be encouraged.

A key 'reward' for a child entering a study is the knowledge that the child will be looked after by a caring and competent health professional. Another 'reward' (more accurately compensation) 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. The above examples do not represent high risk. It is essential that any compensation should be modest in scale and should not represent a covert incentive scheme.

Provision of money, toys, and clothes are all likely to influence decision-making about consent or assent and are best avoided.

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'?

The best interests of a child entering a study are best served by ensuring that the health (physical, mental and psychological), nutrition and development of the child is not compromised by the study.

We suggest that, legally and operationally, the definition provided by the UK Mental Capacity Act is helpful.

The section on 'Vulnerable Groups and individuals' from the Declaration of Helsinki³ is highly relevant here:

'Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm...Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.'

³ WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects <http://www.wma.net/en/30publications/10policies/b3/>

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)?**

Third person consent for treatment, from a parent or guardian, is easy to justify when the proposed action is likely to result in direct benefit to the patient. It is less easy to justify when the child may end up in the control group and not receive direct benefit. This can give rise to problems - many potentially useful drugs are not licensed for use in children because the relevant studies have not been carried out.

Nevertheless, clinical research that has no possibility of benefitting the individual child should only be entered into if the risk of significant harm is extremely low and the child where of sufficient age gives informed assent.

Pharmaceutical trials in resource-poor countries should only be undertaken if arrangements are made to ensure that the treatment is made available to children in the same country. There is a risk that research is undertaken in resource-poor countries which is only of benefit to children in richer countries.

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.**

Questions 8 and 9 cover similar ground.

It is acceptable for children to enter a study where there is a possibility of no benefit to the child. The Declaration of Helsinki (see above) recognises this. 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.

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?**

It would be an unusual situation where ethics committees allow more invasive investigation than 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.

We would be very concerned about any situation in which a child under the age of 16 were willing to accept greater risk than either parents or ethical committees.

At all times, ethical committees should ensure the best interest of the child.

In principle, we consider that only adults are sufficiently mature to agree willingly to risk their own health or well-being for altruistic reasons. Children are too vulnerable to all forms of coercion, especially emotional coercion.

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?**

We believe that the situation in the UK is satisfactory.

However, 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 object to studies being formed on non-rational 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 which he might submit a protocol, knowing that the chance of a protocol being approved is likely to be higher in one rather than the other. 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.

- 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?**

Questions about priorities are difficult and complex.

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.

From a Christian perspective we would support priorities which are focussed on the most poor and vulnerable sections of the community, and on those who are open to neglect and abuse by the strong.

We strongly resist research priorities based solely on commercial criteria or on crude and misleading outcome statistics like QALY and DALY.

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 a given 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.

What should happen when the research is over?

14. What responsibilities do researchers have towards child participants and parents when 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?

Please highlight any relevant areas you think we have omitted, or any other views you would like to express about the ethical issues arising in clinical research involving children.

CMF is able to draw upon relevant experience of our members 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?'

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. Particularly valuable outcome could be the development of **good practice guidelines.**

While there have been some recommendations produced (eg. the Nuffield Report on Bioethics of Research in Developing Countries), our 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.**

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