NUFFIELD COUNCIL ON BIOETHICS

Children and clinical research: consultation on the ethical issues

Introduction

The UK-based Nuffield Council on Bioethics has set up a Working Party to develop a report on *Children and research: ethical issues*, to be published in early 2015. One remit of the Working Party is to consult as widely as possible with groups of people who may be affected by the report in future, including children and young people, parents, researchers, health professionals and a wider public. The Working Party is now seeking additional input to the report from stakeholders in low and middle income countries.

Clinical research involving children is essential if we are to improve our understanding of childhood diseases and conditions, and provide care for children based on the best possible evidence. Parents are often surprised, for example, to find out that many medicines given to children have not been tested in children, and so there is limited evidence about how children may react to them. Clinical research involving children takes many forms including: clinical trials of new medicines or vaccines, research comparing existing standard treatments, research into psychological therapies, participation in longitudinal cohort studies or biobanks, and observational or interview-based research.

However, clinical research in children also raises ethical and practical difficulties. While adults may choose to undergo any inconvenience, discomfort and potential risks that may be involved in clinical research, it may be harder for parents to make such decisions on behalf of their children. Importantly, there is little consensus on what part children themselves should play either in decisions about their own research involvement, or in wider questions of how research is promoted and regulated. This consultation seeks your views on these ethically challenging issues.

Note: throughout this consultation we have used the term ‘children’ as shorthand for children and young people up to the age of 18. We are interested in your comments regarding children and young people across the age-range, especially given the difficulties of matching chronological age with particular abilities or intellectual/emotional maturity.

Section A: How should children be recruited to clinical research?

[Go straight to questions]

Guidelines on the ethical conduct of research generally take the view that children under the age of 18 years should not be allowed to decide for themselves whether to take part in clinical research, given their status as 'minors'. Consent must instead be sought from a parent, or from another adult with parental responsibility for the child. There are, however, exceptions to this approach. In the UK, but not the rest of Europe, for example, children over 16 years can give their own consent to participation in clinical trials but not necessarily for other forms of research. In Kenya, children under 18 years who are married, pregnant, a mother or a household head are considered 'mature' minors and are able to give consent for their own or their child's participation in research. Some argue that a child's age is not a very useful guide to a child's capacity to give or withhold consent, given how much children vary in ability and maturity.

Although in most cases children are not permitted to give their own legally-valid consent to research participation, the importance of *involving* them in the decision, through obtaining their 'assent' before proceeding with research, is widely recognised. The concept of assent, however, is used in quite different ways: from compliance by a child as young as three, to the active agreement of a teenager who might well be considered competent to consent to their own treatment. Attitudes also differ as to whether a child's *dissent* should be treated as a veto, meaning that they cannot be enrolled in research, or less strongly as just one factor to take into account in decision-making. An alternative approach to that of seeking separate parental consent and children's assent is that of 'collaborative' or 'shared' decision-making, where decision about research involvement is reached with the family as a whole.

Ethical dilemmas arise for researchers and clinicians when they consider whether or not to invite a child to participate in a particular research study. An invitation to participate, when given by a trusted professional, may be seen as support for the project, and may influence a parent's/child's decision. The extent to which parents expect their children to participate in important decisions will also vary considerably, and researchers may be unsure whether it is their role, for example, to challenge parents who do not wish to involve their child in the decision-making process. Difficulties may arise for researchers and clinicians where there is disagreement between adult family members or between parents and their child about research participation. Views also vary whether it is acceptable to offer children any form of reward as compensation or as a 'thank you' for taking part in research.

1. What do you think are the main obstacles to recruiting children to research? How might these be overcome?

2. Who should make decisions about a child taking part in research? What part should the child play in the decision?

3. Concerns are sometimes expressed that families agree to take part in research for other reasons - eg because they think they will then get access to better healthcare, or because rewards have been offered. What responsibilities do researchers have in this regard?

Section B: What research proposals should be regarded as ethically acceptable?

[Go straight to questions]

International conventions such as the Declaration of Helsinki[1] and CIOMS guidelines,[2] as well as national laws and guidelines, set down broad principles that should govern all research involving human participants. These guidelines aim to ensure that the well-being of individual participants should always take precedence over all other interests.

Additional protections are set out for research involving children: for example that consent has been given by an authorised representative, and that the research cannot be carried out in adults instead.

Despite these protections, there still remain significant ethical challenges for those undertaking research in children, because it is usually seen as the job of families and professionals to take decisions that are in the 'best interests' of the particular child. The primary aim of research, on the other hand, is to obtain knowledge to improve healthcare in the future, not to benefit the child taking part (although research may often go alongside treatment that *is* designed to benefit the child). Without such research, though, professionals cannot be confident that they are offering the best possible treatment to the children under their care.

4. How can the interests of those children taking part in research be balanced against the interests of the future, unknown children who might benefit from the research?

5. Is it helpful to use the term 'best interests' in connection with children's participation in research? Can you suggest any alternatives?

How should research in children be encouraged?

[Go straight to questions]

Children, from newborn babies to teenagers, have long been seen as a ‘vulnerable’ group, in need of special protection to ensure that they are not exploited in research. In addition, practical difficulties (for example the need to develop age-appropriate protocols) and commercial concerns (such as the limited financial returns from what is perceived to be a comparatively small market) have also played a part in limiting the amount of research taking place with children.

In recent years, widespread regulatory changes have aimed to encourage new research (specifically clinical trials) in children, and to increase the amount of information available about the effect of medicines in children. ‘Carrot and stick’ approaches have been introduced in both Europe[3] and the US:[4] these include financial incentives to pharmaceutical companies for providing more information for prescribers about the effect of medicines in children, and the requirement, where relevant, that data *must* be provided from studies in children before a new medicine can be licensed.

Concerns have, however, been raised as to whether these incentives encourage companies to carry out research that is high priority for children, rather than research into primarily adult conditions that may affect only a limited number of children. A lack of coordination between research funders who are exploring similar childhood conditions can also lead to unnecessary duplication of research effort, with the resulting unnecessary burden on research participants (sometimes the same participants). Awareness is also increasing about the potential for involving young people themselves to influence what research should be prioritised, and how it should be carried out.

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

7. Do you have any views on whether 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?

Any other comments?

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[1] World Medical Association (2013) *Declaration of Helsinki*, available at http://www.wma.net/en/30publications/10policies/b3/.

[2] CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: http://www.cioms.ch/publications/layout_guide2002.pdf.

[3] Council Regulation (EC) 1901/2006 on medicinal products for paediatric use, as amended by Council Regulation (EC) 1902/2006.

[4] Since 1997 the US Government has provided financial incentives to the pharmaceutical industry to conduct paediatric clinical trials through legislation that offers an additional six-month market exclusivity to patents for all paediatric formulations of products that have been trialled in children. More recently, the Paediatric Research Equity Act (2003) gave the Food and Drug Administration (FDA) the authority to *require* paediatric studies of a new medicine if the FDA determines either that the medicine is likely to be used in a substantial number of children, or that it would provide a meaningful benefit for children over existing treatments.