

**NUFFIELD
COUNCIL^{ON}
BIOETHICS**

**Children and clinical research:
ethical issues**

Call for evidence

August 2013

(closing date: 31 October 2013)

Introduction

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 and alarmed, for example, to find out that many medicines given to children have not been tested in children, and hence the evidence available as to how children may react to them is necessarily limited.¹ Clinical research involving children takes diverse 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: for children and parents; for research professionals and researchers; and for regulators and research funders. While adults may choose to undergo any inconvenience, discomfort and potential risks that may be involved in clinical research, it is much 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. Please follow the links below to comment on any, or all, of the highlighted areas of concern, explaining, where possible, *why* you hold a particular view. Your responses will help inform the deliberations of the Nuffield Council's Working Party on *Children and research: ethical issues*, whose aim is to publish a report with recommendations in early 2015.

<u>How should children be recruited to clinical research?</u>	<u>What research proposals should be regarded as ethically acceptable?</u>
<u>How should research in children be encouraged?</u>	<u>What should happen when the research is over?</u>
<u>Any other comments?</u>	
<u>How to submit your response</u>	

Note: throughout this consultation we have used the term 'children' as shorthand for children and young people up to the age of 18. Although the UK Clinical Trials Regulations define young people aged 16 and above as adults, 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.

How should children be recruited to clinical research?

Background ([skip to questions 1-6](#))

Who decides if a child should take part in clinical research? This depends both on whether the research is categorised as a ‘clinical trial’ of a new medicine, and on the age of the child. Moreover, although the law is clear as to when children are entitled to make their own *treatment* decisions, it is much less clear about *research* decisions.

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.² However, there is no equivalent case law as yet on whether these rules should also apply to clinical research. Views differ on this point, and in particular as to whether it would be appropriate to use the ‘Gillick’ approach for under 16s in research decisions as well as in decisions about treatment.³ The only area of clinical research where the legal position on children’s consent is set out clearly is that of clinical trials of new medicines (“investigational medicinal products”), which are governed by their own regulations.⁴

For clinical trials of new medicines, 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. (Most other European countries, by contrast, define ‘minors’ as those under the age of 18 in their legislation governing clinical trials.⁵) 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.

UK children under the age of 16 are not, therefore, legally entitled to make their own decisions about whether or not to participate in clinical trials of new medicines, and their legal position with respect to other forms of research is uncertain. This does not, of course, mean they will be excluded from all involvement in a decision about research involvement: the importance of obtaining the ‘assent’ or acquiescence of the child before proceeding with research is widely recognised.⁶ The concept of assent, however, is used in quite diverse ways: from compliance by a child as young as three,⁷ to the active agreement of a teenager who would be considered competent to consent to their own treatment;⁸ and there is ongoing disagreement about how useful it may be.⁹ An alternative approach to that of seeking separate parental consent and children’s assent is that of ‘collaborative’ or ‘shared’ decision-making, in which researchers and health professionals explicitly aim to negotiate a decision about research involvement with the family as a whole.¹⁰

Responsibilities of researchers and clinicians: Ethical dilemmas arise for researchers and clinicians when they consider whether or not to invite a child to participate in a particular research study. The very suggestion, by a trusted professional, that a child

might consider participation, may be seen as an active endorsement of the project, and hence 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 think it appropriate to involve a child in the decision-making process. Difficulties may, in particular, arise for researchers and clinicians where there is disagreement about a child's participation, whether between adults with differing views, or between parents and their child. 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.

Certain kinds of research are the source of additional ethical challenges for researchers: for example research aiming to improve emergency care, or research relating to the treatment of injuries such as head injuries where non-accidental causes may sometimes be suspected.

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))*

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

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?

What research proposals should be regarded as ethically acceptable?

Background ([skip to questions 7-10](#))

International conventions such as the Declaration of Helsinki,¹¹ CIOMS guidelines¹² and the Council of Europe Oviedo Convention,¹³ set down broad principles that should govern all research involving human participants, with the aim of ensuring that the well-being of individual participants should always take precedence over all other interests. Key requirements set out in the Declaration of Helsinki include that:

- participation should be fully voluntary;
- any risks have been adequately assessed and can be satisfactorily managed;
- the importance of the research must outweigh the inherent risks and burdens of the research; and
- the research proposal must be submitted to a research ethics committee for scrutiny and approval before the research may begin.

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.

While there is general consensus on the importance of protecting children involved in clinical research, the various international conventions differ in some of their detailed requirements, and further differences emerge in the way these are then interpreted in national laws. In particular, approaches differ with regard to the central question of how to balance the risks and burdens faced by research participants against the potential benefits to future patients. This question is further complicated by the fact that in many cases a research study is closely connected with a child's treatment: for example in a clinical trial of a new medicine, or in a comparison of two or more standard forms of treatment. Sometimes the research procedure may be the treatment itself (such as the new medicine), while at others it will be separately identifiable (such as additional scans or blood tests to collect research data).

Approaches to balancing risk and benefit include:

- allowing only research that involves “minimal” risk or “minor increase over minimal risk” if there is no prospect of direct benefit to the child participant;¹⁴
- allowing risks that are “justified by the anticipated benefits to the subjects” if the research does offer the prospect of direct benefit to the child participant;¹⁵
- allowing research where the risks are “minimized” and where the research offers a prospect of direct benefit to children participating in the study;¹⁶
- allowing research where the risks are “minimized” and where the research offers a prospect of direct benefit to children with the same condition (not necessarily those participating in the research).¹⁷

A further complication arises in connection with the general ethical and legal expectation that parents will act in their children's 'best interests' (understood not simply in terms of medical interests but also taking into account wider welfare factors¹⁸) when making decisions about their medical care. In the UK, although there is no case law that specifically applies this approach to clinical research decisions, the Medical Research Council has suggested that it would be reasonable to do so.¹⁹ The question therefore arises as to whether it can ever be considered to be in a child's best interests to experience discomfort, or be exposed to even minimal risk, where the primary aim is to obtain knowledge for future children, rather than to benefit that child's health.

By contrast, it has also been argued that children should be seen as having a *right* to be involved in clinical research, especially where they are living with a serious condition for which there is currently no effective treatment. In such cases, it has sometimes been suggested that 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.

Questions 7-10

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)?
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?

How should research in children be encouraged?

Background ([skip to questions 11-13](#))

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. However, these ethical concerns have not been the only factors inhibiting research in children: 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.²⁰

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 Europe²¹ and the US:²² 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. By 2013, the US approaches had resulted in 481 changes in labelling on medicines used for children,²³ while the more recent European regulations led to 77 such changes by 2011, along with the authorisation of 31 new medicines for paediatric use, and the approval of 72 new paediatric indications for medicines already authorised.²⁴ Concerns have, however, been raised as to whether these incentives are sufficiently well targeted: in particular whether they 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.²⁵ 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).²⁶

Awareness is also increasing about the potential for involving young people themselves to influence clinical research proposals as they affect children. The Paediatric Committee of the European Medicines Agency, which is responsible for reviewing companies' paediatric investigation plans (proposals for carrying out studies in children) has recently published a 'concept paper' on the possible involvement of children and young people in their work.²⁷

Questions 11-13

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

What should happen when the research is over?

Background ([skip to question 14](#))

Ethical questions also arise as to what should happen when a clinical research project involving children is over. Such questions may arise both in terms of access to treatment in future (where the research is a clinical trial of a new medicine), and in terms of how children and their parents continue to be involved in the research at a policy level.

In clinical trials of new medicines, the decision may be taken not to proceed further with the research because of concerns about the safety or effectiveness of the medicine in the research group as a whole – but this may be a source of major anxiety for individual children and their families if they have seen considerable benefit from the medicine. There may also be practical or financial reasons why research funders decide not to pursue a particular research avenue. The question then arises as to whether there is any scope for children who have benefited from the new medicine to continue obtaining it.

In research more generally, there is a growing awareness that research participants value being treated as ‘partners’ in research (rather than simply as research ‘subjects’) and, for example, may be interested in finding out more about the results of research in which they have participated, even where this is unlikely to be relevant for their own health care.²⁸ In the case of longitudinal research, it is possible for such ‘partnership’ to be more active: the Avon Longitudinal Study of Parents and Children, for example, which has collected information and biological samples from thousands of parents and children to form a substantial research resource, involves study participants in its governance arrangements – for example through membership of its Ethics and Law Committee.²⁹

Question 14

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

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.

How to submit your response

Please email your response to Kate Harvey (kharvey@nuffieldbioethics.org), with 'Children and clinical research' in the subject line. If possible, responses should be in the form of a single Word document, with question numbers clearly indicated.

Please ensure that you also include a completed response form with your submission, which can be found on [page 12 below](#) or downloaded from our [website](#).

If you would prefer to respond by post, please send your submission to:

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Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3JS

Telephone: +44 (0)20 7681 9619

Website: <http://www.nuffieldbioethics.org/children-and-research>

Closing date for responses: 31 October 2013

For more information about the Working Party, or the Nuffield Council, please follow the links listed below:

[Terms of reference of the Working Party](#)

[List of Working Party members](#)

[Terms of reference of the Council](#)

[List of Council members](#)

Before submitting your response, please make sure you have filled in the [respondent's form](#) telling us how we can use the information you have given us. We will not publish your name without your express permission.

Respondent's form

Please complete and return with your response by **31 October 2013**. We will **not** publish your name without your express permission.

Your details:

Name: _____

Organisation (if applicable): _____

Email: _____

About your response:

Are you responding personally (on your own behalf) or on behalf of your organisation?

Personal Organisation

May we include your name/your organisation's name in the list of respondents that will be published in the final report?

Yes No, I/we would prefer to be anonymous

If you have answered 'yes', please give your name or your organisation's name as it should appear in print (this is the name that we will use in the list of respondents in the report):

May we quote your response in the report and make it available on the Council's website when the report is published?

Yes, attributed to myself or my organisation No
 Yes, anonymously*

*If you select this option, please note that your response will be published in full (but excluding this form), and if you wish to be anonymous you should ensure that your name, and any other identifying information, does not appear in the main text of your response. The Nuffield Council on Bioethics cannot take responsibility for anonymising responses in which the individual or organisation is identifiable from the content of their response. **Obtaining consent to publish a response does not commit the Council to publishing it. We will also not publish any response where it appears to us that to do so might result in detriment to the Council's reputation or render it liable to legal proceedings.**

Why are you interested in this consultation? (Tick as many as apply)

- Personal interest – child/young person
 - I have taken part (or been invited to take part) in research at least once
 - I have a long-term health condition
- Personal interest – parent
 - My child has taken part (or been invited to take part) in research at least once
 - My child has a long-term health condition
- Other personal interest (please state): _____
- Professional interest – work in clinical research
- Professional interest – work for, or represent, a charity or support group
- Professional interest – work for, or represent, a governmental or non-governmental organisation
- Academic interest
- Legal/regulatory interest
- General interest
- Other (please state): _____

Please let us know where you heard about the consultation:

- Received notification by email
- Newspaper, radio or television
- Nuffield Council on Bioethics website
- Twitter
- Other website (please state): _____
- Other (please state): _____

Using your information

We ask for your email address in order that we can send you a link to the report when it is published and notify you about activities related to this project. (Please note that we do not make your email address available to anyone else, and we do not include it with the list of respondents in the report.)

May we keep your email address for these purposes?

- Yes
- No

Would you like to receive our newsletter by email which provides you with information about all of the Council’s activities?

- Yes
- No

References

- ¹ See, for example, Conroy S, McIntyre J, Choonara I *et al.* (1999) Unlicensed and off label drug use in neonates *Archives of Disease in Childhood Fetal Neonatal Edition* **80(2)**: F142–5; Conroy S, Choonara I, Impicciatore P *et al.* (2000) Survey of unlicensed and off-label drug use in paediatric wards in European countries *BMJ* **320(7227)**: 79–82; Mukattash TL, Millership JS, Collier PS and McElnay JC (2008) Public awareness and views on unlicensed use of medicines in children *British Journal of Clinical Pharmacology* **66(6)**: 838–45; and Ward RM and Kern SE (2009) Clinical trials in neonates: a therapeutic imperative *Clinical Pharmacology & Therapeutics* **86(6)**: 585–7.
- ² *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112; for more detail on the law in England and Wales with regard to consent to treatment, see: Department of Health (2009) *Reference guide to consent for examination or treatment: second edition*, available at: <https://www.gov.uk/government/publications/reference-guide-to-consent-for-examination-or-treatment-second-edition>.
- ³ See, for example, Medical Research Council (2004) *MRC ethics guide: medical research involving children*, at page 24, and Hunter D and Pierscionek BK (2007) Children, Gillick competency and consent for involvement in research *Journal of Medical Ethics* **33(11)**: 659–62.
- ⁴ The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended, generally referred to as the ‘Clinical Trials Regulations’.
- ⁵ The UK Clinical Trials Regulations transpose the EU Clinical Trials Directive into UK law. The Directive itself is silent on the age at which ‘minors’ become adults, and member states of the EU therefore have discretion in how this is determined in national law. However, EU Regulation 1901/2006 defines the ‘paediatric population’ as encompassing those aged under 18, and the recommendations of an EU *ad hoc* group on the implementation of the Directive states that ‘minors’ should ordinarily be understood as those under 18, with the exception of where national legislation specifies an earlier age of majority: see European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraphs 5.2 and 5.4.
- ⁶ See, for example, Royal College of Paediatrics and Child Health: Ethics Advisory Committee (2000) Guidelines for the ethical conduct of medical research involving children *Archives of Disease in Childhood* **82(2)**: 177–82.
- ⁷ European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraph 7.
- ⁸ See, for example, the discussion in Baylis B and Downie J (2006) The limits of altruism and arbitrary age limits *American Journal of Bioethics* **3(4)**: 19–21.
- ⁹ See, for example, Baines P (2011) Assent for children’s participation in research is incoherent and wrong *Archives of Disease in Childhood* **96(10)**: 960–2; and Sibley A, Sheehan M and Pollard AJ (2012) Assent is not consent *Journal of Medical Ethics* **38(1)**: 1–3.
- ¹⁰ Coyne I and Harder M (2011) Children’s participation in decision-making: balancing protection with shared decision-making using a situational perspective *Journal of Child Health Care* **15(4)**: 312–9.
- ¹¹ World Medical Association (2008) *Declaration of Helsinki*, available at <http://www.wma.net/en/30publications/10policies/b3/>. The 1996 version, while superseded by later revisions, is cited in the EU Directive and UK Clinical Trial Regulations.
- ¹² CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: http://www.cioms.ch/publications/layout_guide2002.pdf.
- ¹³ Council of Europe (1997) *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (Convention on human rights and*

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- biomedicine*), and its *Additional protocol* concerning biomedical research (2005), available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>.
- ¹⁴ US Department of Health and Human Services, Code of Federal Regulations, 45 CFR 46.404 & 46.406, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.406>.
- ¹⁵ US Department of Health and Human Services, Code of Federal Regulations, 45 CFR 46.405, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.405>.
- ¹⁶ Interpretation of the Clinical Trials Directive in Clinical Trials Regulations: The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031 as amended, Schedule 1, Part 4, paragraph 10.
- ¹⁷ Interpretation of the Clinical Trials Directive by EU *ad hoc* group: European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraph 12.
- ¹⁸ See, for example, *Re T (a minor) (wardship: medical treatment)* (1996) 35 BMLR 63 (Court of Appeal).
- ¹⁹ Medical Research Council (2004/2007) *MRC ethics guide: medical research involving children*, at page 29.
- ²⁰ Gennery B (2000) Clinical research in children: a pharmaceutical industry view *Paediatric and Perinatal Drug Therapy* **4(2)**: 67–70.
- ²¹ Council Regulation (EC) 1901/2006 on medicinal products for paediatric use, as amended by Council Regulation (EC) 1902/2006. These requirements may be waived where appropriate: for example where the disease or condition for which the medicine is being developed only arises in adults, or where use of the medicine is likely to be ineffective or unsafe in children. Where information from the ‘paediatric investigation plan’ is included in a new medicine’s ‘summary of product characteristics’, then the developer of the drug is granted a six-month extension of the supplementary protection certificate (effectively extending the benefit of the patent by six months). For ‘orphan’ medicinal products, this incentive takes the form of an extra two years’ market exclusivity in addition to the ten years’ market exclusivity that is already granted on authorisation of an orphan medicine.
- ²² 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.
- ²³ FDA (2013) New paediatric labeling information database, available at: <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>.
- ²⁴ European Commission (2013) *Better medicines for children – from concept to reality: general report on experience acquired as a result of the application of Regulation EC No 1901/2006 on medicine products for paediatric use*, at paragraph 4.3 (summaries of product characteristics changed in 65 products authorised at national level and 12 authorised centrally) and 4.2.
- ²⁵ Choonara I (2000) Clinical trials of medicines in children *BMJ* **321(7269)**: 1093–4 (with reference to the US regulations).
- ²⁶ European Commission (2013) *Better medicines for children – from concept to reality: general report on experience acquired as a result of the application of Regulation EC No 1901/2006 on medicine products for paediatric use*, at paragraph 5.5; see also: Wall Street Journal (18 February

2013) Families push for new ways to research rare diseases, available at:
<http://online.wsj.com/article/SB10001424127887324432004578306364187833702.html>.

- ²⁷ European Medicines Agency (2012) Concept paper on the involvement of children and young people at the Paediatric Committee (PDCO), available at
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132555.pdf.
- ²⁸ See, for example, the discussion in Nuffield Council on Bioethics (2011) *Human bodies: donation for medicine and research*, available at: <http://nuffieldbioethics.org/donation>, at paragraphs 7.70–1.
- ²⁹ Avon Longitudinal Study of Parents and Children (2013) *Ethics*, available at:
<http://www.bristol.ac.uk/alspac/participants/ethics/>.