

1. Nigel Monaghan 300813

Nigel Monaghan

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. *Comment from Nigel Monaghan: The presumption that parents have a right to consent up to age 18 may no longer be true. 16 and 17 year olds can now also refuse treatment - The Mental Capacity Act 2005 states that those aged 16 or 17 should be treated as "being of age" i.e. presumed as able to consent for the purposes of both consenting to or refusing treatment – i.e. presumed able to consent or refuse for themselves. This presumption of being able to consent as if "of age" challenges the presumption that parents can still consent for a 16 or 17 year old who refuses treatment and is not judged to lack capacity.* 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.¹ 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.² 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.³

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. *Comment from Nigel Monaghan: This is entirely consistent with the Mental Capacity Act 2005.* (Most other European countries, by contrast, define 'minors' as those under the age of 18 in their legislation governing clinical trials.⁴) 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

1. Nigel Monaghan 300813

research is widely recognised.⁵ *Comment from Nigel Monaghan: The UN convention on the rights of the child states that children should be as involved as they can be in decisions made about them – the UK is a signatory to that convention.* The concept of assent, however, is used in quite diverse ways: from compliance by a child as young as three,⁶ to the active agreement of a teenager who would be considered competent to consent to their own treatment;⁷ and there is ongoing disagreement about how useful it may be.⁸ 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.⁹ *Comment from Nigel Monaghan: As someone who organises surveys of young children in schools I would avoid the use of assent for young children and use co-operating. We ask parents to consent to their child to be examined, but indicate to parents that we will not examine an uncooperative child.*

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. *Comment from Nigel Monaghan: The UN convention on the rights of the child states that children should be as involved as they can be in decisions made about them – the UK is a signatory to that convention.* 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. Nigel Monaghan 300813

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.)

If the child is competent then their views should not be overridden. The parent is there to assist and support the child in developing into an adult not to control their life.

Professionals need to be able to judge the competency of the child. The Mental Capacity Act provides a framework/test for doing this.

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

Assent implies approval or agreement (e.g. see Oxford Dictionary definition). In the context of adults this implies a considered response – equivalent to consent. By contrast co-operation has no such implications of a considered response. It is hard to see the difference between assent and consent unless a clear definition expressly highlighting the differences between co-operation assent and consent is used.

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?

Professionals are wise to tread carefully when getting involved in the 3 way relationship between parents and a child. Having said that the children should be as involved in the decision as they can be and the Mental Capacity Act does highlight the principles underpinning a "best interest" decision for adults. This might offer a way forward for exploring the best decision when parents have different views – what would the child want if they were able to make this decision – based on the child's beliefs, views and preferences?

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?

1. Nigel Monaghan 300813

One way to address this would be to ask whether any research has been done on this topic with members of the public and with research participants to identify from a list of options what is seen to be a strong expression of thanks without becoming undue incentive.

What research proposals should be regarded as ethically acceptable?

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

International conventions such as the Declaration of Helsinki,¹⁰ CIOMS guidelines¹¹ and the Council of Europe Oviedo Convention,¹² 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;¹³
- 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;¹⁴
- allowing research where the risks are "minimized" and where the research offers a prospect of direct benefit to children participating in the study;¹⁵

1. Nigel Monaghan 300813

- 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).¹⁶

A further complication arises in connection with the general ethical and legal expectation that parents will act in their children’s ‘best interests’ *Comment from Nigel Monaghan: This now has a specific meaning under the terms of the Mental Capacity Act 2005 and it is not “substituted judgement” - what the parents would want if they were their child.* (understood not simply in terms of medical interests but also taking into account wider welfare factors¹⁷) 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.¹⁸ 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. *Comment from Nigel Monaghan: This will depend on the beliefs and values of the child. If a child has experienced considerable suffering themselves and wishes to help ensure others do not suffer similarly in future they may be willing to suffer some minor additional discomfort.*

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. *Comment from Nigel Monaghan: It might be better expressed as a right not to be excluded from the opportunity to participate in research and as a right to be included.*

Questions 7-10

7. How helpful is the notion of the best interests of the child participant? How would you define ‘best interests’?

See Mental Capacity Act 2005 section 4 for mandatory minimum checklist which applies to treatment:

All relevant circumstances

Will the person have capacity sometime in the future in relation to the matter? If so, when?

The person’s past and present wishes and any statements made by them
The person’s beliefs and values
Other factors the person would consider if able to do so
Consult others if ‘practicable and appropriate’ eg. carers, relatives, an attorney, deputy or existing advocate

Must encourage and permit the person to participate in any act /decision done for him

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)?

Where possible by respecting the views of the children as people, not by using them as guinea pigs irrespective of their wishes.

1. Nigel Monaghan 300813

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.

If a child has experienced considerable suffering themselves and wishes to help ensure others do not suffer similarly in future they may be willing to suffer some minor additional 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 seem unwise to give research ethical approval to any study where the view was that the research risks are “too high”. The primary role of research ethical approval is to protect subjects from researchers.

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.¹⁹

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 Europe²⁰ and the US.²¹ 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,²² 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.²³ 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.²⁴ **Comment from Nigel Monaghan: The key ethical conflict is about the interests of the drug companies (profits) and those of the children (better treatments).** 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).²⁵

1. Nigel Monaghan 300813

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.²⁶

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?

I would question whether children are as involved as they could and should be in the decision making process.

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?

Priorities should be those for which treatment options are either not available or could be improved.

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

It should be possible to co-ordinate efforts, but commercial pressures may make this difficult. How much current company funded research does not get published?

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.²⁷ 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

1. Nigel Monaghan 300813

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.²⁸

Question 14

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

Any responsibility for providing any continuing access to new medicine should fall upon the research funders, not the research body or the NHS. Trials cannot become an alternative gateway to NHS funded care bypassing the main decision making process. If this occurred it is possible to foresee many trials for new treatments of questionable effectiveness promoted as a means of generating market share.

References

- ¹ *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>.
- ² 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.
- ³ The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended, generally referred to as the 'Clinical Trials Regulations'.
- ⁴ 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.
- ⁵ 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.
- ⁶ European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraph 7.
- ⁷ 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.
- ⁸ 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.
- ⁹ 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.

1. Nigel Monaghan 300813

- ¹⁰ 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.
- ¹¹ CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: http://www.cioms.ch/publications/layout_guide2002.pdf.
- ¹² 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 biomedicine)*, and its *Additional protocol* concerning biomedical research (2005), available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>.
- ¹³ 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>.
- ¹⁴ 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>.
- ¹⁵ 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.
- ¹⁶ 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.
- ¹⁷ See, for example, *Re T (a minor) (wardship: medical treatment)* (1996) 35 BMLR 63 (Court of Appeal).
- ¹⁸ Medical Research Council (2004/2007) *MRC ethics guide: medical research involving children*, at page 29.
- ¹⁹ Gennery B (2000) Clinical research in children: a pharmaceutical industry view *Paediatric and Perinatal Drug Therapy* **4(2)**: 67–70.
- ²⁰ 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.
- ²¹ 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.
- ²² FDA (2013) New paediatric labeling information database, available at: <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>.
- ²³ 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*

1. Nigel Monaghan 300813

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.

- ²⁴ Choonara I (2000) Clinical trials of medicines in children *BMJ* **321(7269)**: 1093–4 (with reference to the US regulations).
- ²⁵ 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>.
- ²⁶ 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.
- ²⁷ 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.
- ²⁸ Avon Longitudinal Study of Parents and Children (2013) *Ethics*, available at: <http://www.bristol.ac.uk/alspac/participants/ethics/>.