

41. British Medical Association 011113

## **Nuffield Council on Bioethics - Children and clinical research: ethical issues**

### **British Medical Association response**

The British Medical Association (BMA) is an independent trade union and voluntary professional association which represents doctors and medical students from all branches of medicine all over the UK. With a membership of over 152,000 worldwide, we promote the medical and allied sciences, seek to maintain the honour and interests of the medical profession and promote the achievement of high quality healthcare.

The BMA welcomes the opportunity to respond to the Council's call for evidence on the ethical issues associated with clinical research involving children. There is an ethical and practical imperative to increase and improve paediatric research to help develop and test treatments, interventions and services specific to the needs of children and young people. Without research to continually drive innovation and advance medical practice there is a danger that paediatric medicine will stagnate leading to the continuation of medical treatment based on untested and possibly suboptimal interventions, with the inherent risks that entails. Research can improve the health and well being of children, help to tackle adult ill health which has its origins in childhood development, and improve the life-chances of future generations. The BMA has recently updated its publication *Growing up in the UK – Ensuring a Healthy Future for our children*, which highlights the importance of making improvements to child health and outlines the Association's support for a "life course" approach.<sup>1</sup>

Children and young people are a potentially vulnerable population and, for the BMA, the primary consideration in any decisions relating to their involvement in research should be the promotion and protection of their interests. It is not, however, a homogenous group. The needs and capacities of neonates and very young children for example differ significantly to those of adolescents, and researchers need to be aware and take account of the special needs of children at different stages of their development. Where children have the capacity to govern their own interests, they should be able to influence decision-making commensurate with their level of competence, through providing their consent or assent for participation in research wherever possible. Where decisions are made on behalf of a child who has insufficient understanding to either consent or assent, this should be made by a person with parental responsibility with reference to the best interests of the child in question.

As the professional association for doctors, the BMA produces practical guidance on issues of medical ethics. The BMA does not have established policy in relation to many of the issues the Council has raised in its call for evidence document, which seek to explore some of the philosophical complexities associated with paediatric research. This response has been informed by comments from individual members of different BMA committees following an internal consultation process.

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<sup>1</sup> British Medical Association (2013) *Growing up in the UK – Ensuring a healthy future for our children*. London: BMA. <http://bma.org.uk/working-for-change/improving-and-protecting-health/child-health/growing-up-in-the-uk> (accessed October 2013).

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

There is a range of potential obstacles which can inhibit the recruitment of children to medical research. Although attitudes to research are generally positive amongst the general public, some parents may have pre-existing concerns or misconceptions about research in general, that their child would be used as a “guinea pig” for example, which can make approaches to enrol a child on a particular study difficult. Other barriers to parental consent can include a lack of understanding of the particular aims of individual studies and the often complex issues and technical aspects of research, such as randomisation and equipoise. Similarly, obtaining consent or assent from children can be challenging, depending on the age and competence of the child in question. The inflexibility of study designs or methodology can also affect both recruitment and retention to studies, as can fatigue resulting from using the same organisations and overuse of the same participants. Lack of awareness of the existence of potential studies may also be a problem in some cases, an issue which was highlighted in the recent House of Commons Science and Technology Select Committee inquiry into clinical trials.<sup>2</sup>

It is possible for many of these issues to be addressed and for reassurance to be provided through balanced and age-appropriate communication of what a study involves. Parents and children should have the opportunity to discuss any concerns or ask further questions. The BMA’s recommendations about the kinds of information that people involved in research need to be given are given below. These would apply whether the research participants are children or adults:

- why they have been asked to participate
- the purpose of the research and confirmation of its ethical approval
- whether the individual (if a patient) stands to benefit and, if so, the difference between research and treatment
- the risks of adverse events and arrangements for reporting these
- the meaning of relevant research terms (such as placebos, randomization and equipoise)
- the nature of each procedure, and how often or for how long each may occur
- the rights and safeguards for participants, including compensation if harm occurs
- how their health data will be stored, used and published
- if samples of human material are donated, what they might be used for
- the names of the researcher and the doctor responsible for their care

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<sup>2</sup> House of Commons Science and Technology Committee (2013) *Clinical trials*. London: The Stationery Office Ltd, p.29.

- that they can withdraw from the project at any stage and that such a decision will not adversely affect their healthcare.<sup>3</sup>

Encouraging confidence and addressing misconceptions regarding the purposes of clinical research more generally may be helped by publishing good practice or positive case examples. Parents and children should be reassured where needed about the strict regulatory structure in which research takes place and the safeguards which exist to protect participants. In the case of older children who have a chronic condition and their parents, barriers to consent and recruitment could possibly be fewer as they may be more likely to understand from their own experiences the potential benefits to the child and future patients which might be derived from involvement in research. Involving parents and children in the design of studies, wherever possible and relevant, could also help to encourage recruitment and retention.

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.)*

Ideally all parties should agree on participation and researchers have a responsibility to support parents and their children in working through any disagreements. In the case of research which may provide the chance of providing therapeutic benefit to a child, for example through early access to experimental therapies, the reasons for refusal from either child or parent should be sensitively explored. Researchers have a responsibility to ensure children and young people and their parents have the support and advice they need about their options, including explanations of the purposes, risks, and expected benefits of the research, and that they understand the consequences of agreeing or refusing to take part in a study. There may also be other practical considerations which may mean parental agreement and co-operation would still be necessary, irrespective of a child's consent. Similarly, on a practical level, co-operation from a child may be necessary to enable research to be undertaken.

As stated in the introduction to this response, children and young people should be involved in, and able to influence decisions about, their participation in research to the fullest extent possible and in line with their level of understanding. A 'Gillick competent' child must give unpressured and informed consent to be enrolled in research. The BMA acknowledges that, with the exception of clinical trials, there is a degree of uncertainty in the law over the rights a child has to consent or refuse consent for participation in research and the Association does not have an established view on how this uncertainty should be resolved. Generally though, for the BMA the primary consideration in any decisions relating to children and their involvement in research should be the promotion and protection of their best interests accepting that, in some circumstances, this may conflict with their autonomous wishes. On this basis, in cases where disagreement arises because a

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<sup>3</sup> British Medical Association (2012) *Medical Ethics Today: The BMA's Handbook of Ethics and Law*. Chichester: Wiley, p.595.

parent gives his or her consent for a competent child's participation but the child refuses, arguably this refusal should be respected and the child or young person should have the final say in the decision, unless this would clearly be significantly detrimental to the child interests. Similarly, in relation to decisions about withdrawing a child from a study, a competent child's decision to withdraw should be respected, without reason having to be given, unless this would be detrimental to the child's health.

Where a child lacks sufficient understanding to be deemed competent to provide consent, but is able to dissent, verbally or non-verbally, to participation or continuing in research this should usually be respected. Again, an exception to this would be where non-participation or withdrawal from a study would be clearly detrimental to the interests of a child.

With respect to clinical trials which fall under the scope of the Medicines for Human Use Regulations, legally, an explicit refusal need only be "considered" by researchers and is not necessarily determinative. Despite this, it would still be ethical best practice to respect the wishes of a child in the ways described above. This would also be consistent with guidance from the General Medical Council<sup>4</sup> and the ad hoc working party of the EU commission on the implementation of the EU Clinical Trials Directive<sup>5</sup>. For research which offers no potential benefit to the child, it is highly unlikely that a child's participation against their will would ever be in his or her best interests.

In cases where children who lack competence wish to participate in research but their parents object, a child's assent alone would not provide sufficient basis for enrolment on a study and parental consent would be required. Although in theory a competent child's decision to participate could be determinative, much would depend on the type of study and the risks and benefits involved. In the absence of a definitive legal position on the status of a child's consent in these circumstances, it could be argued that it would be best practice to apply the age threshold in the clinical trial regulations to all research such that, for children under 16, explicit parental consent would be required and therefore, where disagreements of this kind arise, a person with parental responsibility should make the final decision.

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

As the document acknowledges it is an accepted principle that where a child lacks the level of understanding required to be deemed competent to give consent for research, they should still be involved in the decision-making process; his or her assent should be sought alongside the valid consent of a person with parental responsibility. Children will have different levels of competence depending on their age and capacity to understand and weigh up the different issues involved in a decision. At one end of the spectrum, babies and very young children will have very

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<sup>4</sup> General Medical Council (2007) *0-18 years: guidance for all doctors*. London: GMC, para 38.

<sup>5</sup> *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population* (2008). [http://ec.europa.eu/health/files/eudralex/vol-10/ethical\\_considerations\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf) (accessed October 2013), pp.11-12.

little if any understanding of research whereas some children will have sufficient understanding to be deemed competent to provide full and valid consent. The concept of assent may help to formalise the decision-making capacity of children whose level of understanding lies between these extremes. It recognizes that this level of competence is a relevant consideration in research decisions and should be sought by researchers, whilst still distinguishing it from full consent to take part, which would still be required from a person with parental responsibility. Distinguishing the two is also important because while valid consent renders an intervention lawful, assent in the absence of valid consent does not.

While assent is a helpful concept, dissent is also important. Although children may not have the competence to make an informed refusal of participation, their objection, irrespective of how it is expressed, can in practical terms be a deciding factor as to whether a child should be enrolled or continue to participate in a study.

The differences between assent and consent need to be carefully explained to parents and children to avoid any confusion and so that everyone involved in the decision knows and understands the level of agreement to participate they are providing. Assent must never be used as a way of applying pressure on parents to consent or vice versa.

*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?*

A collaborative model can be helpful as it can strengthen trust and support for research proposals. Problems may arise where there is misunderstanding or a failure to communicate the specifics of the study clearly, problems which can then often be difficult to overcome. To avoid this it can help if protocols and proposals are written in simple everyday language targeted separately at children of different age groups and parents, and that the researcher has skill in communicating with both parents and children so as to be able to answer their questions and to offer reassurance and support if problems arise. Full explanation of what the research will entail, any possible side effects and the expected or predicted outcomes must all be made as clear as possible. Sometimes, a cooling off period for a decision is needed and further meetings also required.

*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?*

Differences in viewpoint between parents can result from a number of factors including background, ethnicity and religion and arguably there should be greater understanding about different parenting approaches and how they may impact on

research and decision making. Researchers need to consider any potential issues which may be relevant in advance of any approach to recruit children to a study and take the different views of those involved in the process, including children, into account at all times. If there are legal issues related to decision-making, which may conflict with any views held by parents, the legal position needs to be made clear.

*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?*

The BMA has general advice on payment to research subjects which emphasises that:

- Research ethics committees should look closely at the level of financial and non-monetary incentives when scrutinising the way research participants are recruited, in each individual protocol.
- Payment should not constitute an undue 'inducement'. Financial incentives should not be of a level as to encourage people to act against their own better judgement.
- The sum paid should be commensurate with the amount of time and inconvenience involved.
- Payments must never be for undergoing risk.
- Participants need to have accurate information about the risks and inconveniences involved.

The BMA does not have specific guidance on offering rewards to children for participation in research, although many of these key principles are relevant. In relation to clinical trials of new medicinal products offering incentives to either child or parent is prohibited in the EU Clinical Trials Directive and the Medicines for Human Use Regulations, a safeguard which reflects the greater potential for exploitation and the different dynamic which exists when recruiting children for research compared with recruitment of adults to studies. Offering a non-financial reward to a child as recognition of his or her involvement would not constitute an incentive or inducement to participation, provided it is given after a study has completed and is not a part of the consent process (although this may become problematic if potential study participants become aware before enrolment that rewards are given). The question refers to vouchers as a potential reward for children. Other, non-material ways of recognising the contribution of a child to a research project could include a certificate for participation in a study.

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

Although the BMA has not considered a definition of best interests specifically in relation to children and research, we do outline the various potential factors a consideration of best interests should cover in relation to treatment in our guidance, which may be relevant to a research context.<sup>6</sup> In general, for the BMA, “best interests” stands as an objective test as is possible of what would be in the actual best interests of a child and encompasses the full range of factors relevant to a decision. Among the factors which may be relevant in a best interest decision in relation to children and research could include:

- A child’s wishes, feelings and values (where these can be ascertained) including altruistic motivations
- his or her ability to understand what is proposed and weigh up the alternatives
- the potential to participate more in the decision, if provided with additional support or explanations
- physical and emotional needs
- where there is more than one option, which option is least restrictive of the patient’s future choices
- benefits, risks and potential harms of involvement
- the views about a child’s best interests of parents and others who are close to the child
- relevant information about religious or cultural background
- the views of health care professionals involved in providing care to the child or young person, and of any other professionals who have an interest in their welfare.

The term “best interests” is embedded in medical case law and medical practice. Its familiarity to health professionals and the fact that it can be used to encapsulate the different and sometimes competing factors at stake in the decision-making process, mean that, in some circumstances, it may be a helpful concept in relation to decisions about a child’s participation in research. The general public however may not have a well-developed understanding of the term and there is a responsibility on medical professionals to ensure that its meaning and application is communicated effectively to patients or research participants whenever it is used.

*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)?*

It is an accepted principle, set out in the Declaration of Helsinki and research legislation, that although the primary purpose of medical research is to generate new knowledge, the interests of individual participants should always prevail over the interests of science and society. This is particularly important in relation to children for whom immaturity makes it difficult for them to protect and promote their own interests. The rights and interests of individual children therefore should always be the paramount consideration, secondary to those of the potential, unidentified future beneficiaries of research. Without research however, medicine cannot advance and

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<sup>6</sup> British Medical Association (2010) *Children and young people tool kit*. London: BMA, p.19-20.

children and society will be denied the benefit that would accrue as a result of scientific progress. Where they are in tension it may be necessary to seek a working compromise between these two competing claims.

Where children have the opportunity to benefit from research, this is usually unproblematic as the risks that they undertake, intended in one sense to help to secure the improvements for later patients, would be offset by the benefit they may receive as a result of participation. The involvement of healthy child volunteers or the involvement of children in research that includes some risks but which offers no benefit at all however raises more difficult questions. For older children, who have sufficient understanding of the aims and importance of research, altruistic motivations and the personal benefit that can result from the feeling that their contribution now (through accepting a degree of risk, discomfort or inconvenience) could have a significant impact on future generations could be important considerations. Where this level of competence is lacking, balance can be achieved by only exposing these children to interventions with minimal risk and taking into account their own individual, special needs when making judgements on the acceptability of the potential harms, discomfort or inconveniences involved.

*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.*

Some types of research, such as notes-based studies, do not provide a direct benefit to the child but also involve no obvious harms to children. Provided appropriate consent has been obtained and the protocol has been approved by a research ethics committee, studies of this kind do not raise obvious concerns regarding acceptability.

Examples of other acceptable forms of research, which were cited by BMA committee members who were supportive of children being invited to studies where there would be no benefit to them, included research to ascertain aetiology, such as genetic studies, and also clinical research which may involve questioning and providing a narrative. Most studies which no more than involve “minimal risk” would be acceptable even where there is no personal benefit to the child from participation. However, much depends on how “personal benefit” is defined in this context and, for example, whether altruism could be considered a psychological benefit. A child who has experienced considerable suffering and wishes to help ensure others do not suffer similarly may be willing to tolerate 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 is important to distinguish between research studies which would and would not offer any potential benefits to participant children in the type of situation described. Exposing a child to high risk in a study which offered the participant child no benefit at all would be unacceptable, particularly if the research could instead be carried out on others with a more favourable risk-benefit profile.



If there are potential benefits to the participant child, this raises the question of what is meant by “too high” in this context and whether, for example, the research ethics committee would have weighed the risks against these benefits to a potential participant in making this assessment. It is likely that the type of situation described in the question would arise where enrolment in a research study would give an individual access to experimental treatments or interventions which are only available through the study, such that some potential therapeutic benefit to the child may result through their enrolment. In some situations individuals may have few, if any, other options. Therefore, even if the risks are high, there may be justification for approving their involvement on the grounds that it would be in a child’s best interests. This would need to be assessed and approved on a case-by-case basis. The research team would need to ensure that the potential benefits were not overstated and that both the parent and child (where possible) had considered all the options available to them, were fully aware of the risks involved and understood the relative costs and benefits as part of the consent process. In some highly challenging cases, legal involvement may be required.

*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?*

The BMA does not have an established view on the current regulations and their impact on the issues referred to in the question. Individual BMA committee members indicated that the regulations did perhaps strike the right balance, although concerns were raised about whether commercial interests in determining research priorities always resulted in the most beneficial outcomes for children.

The BMA is aware of concerns that the EU Clinical Trials Directive and Medicines for Human Use Regulations may not give sufficient weight to the autonomy of children and their rights to govern their own interests in decisions about their involvement in research. Under both pieces of legislation, a child (defined as under 16 in the UK and under 18 in other jurisdictions) should be given information about a trial appropriate to their level of understanding, but their explicit refusal need only be “considered” by researchers. This is contrary to guidance from the GMC and from the EU Commission working group on the application of the clinical trials directive which refer to the importance of assent and state a child’s objections should usually be respected. Although it is likely that the regulations are used in conjunction with best practice guidelines such as these, which then jointly provide the required level of protection, it raises questions as to whether the regulations themselves should be amended such that the significance of a child’s autonomous wishes in this respect are acknowledged in law.

*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?*

There are a range of factors which may be relevant when making the difficult decisions involved in identifying research priorities in children within a limited budget. Considerations may include, the severity of the condition and the risk of disability or mortality it poses to children; the prevalence of the condition; the existence of available treatment options and their safety and efficacy profiles; and where adult research suggests that data on younger groups would be helpful.

Although the BMA does not have considered policy on this issue, decisions would ideally be multidisciplinary and multi-stakeholder, including representatives of parents and children or young people. The types of individuals or organisations who should be involved in such decisions could include those with expertise in the conditions under consideration alongside research funders and commissioning bodies such as NICE. Decisions to prioritise a particular condition for research, and therefore focus funding less on others, would need to be clear, transparent and proportionate.

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

The BMA does not have specific policy on responsibilities in relation to the coordinating clinical research, although there would seem to be clear advantages in coordination, including avoiding duplication of effort and ensuring funding for research is effectively and efficiently directed and utilised. Some individual BMA committee members noted that it was important to ensure that collaboration on a national scale is monitored, particularly if studies require large numbers of participants or the condition is rare, and that caution should also be exercised where collaboration involves commercial interests.

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

The BMA encourages feedback from researchers and clinicians to participants after the completion of a study, should they wish to receive it, on the outcomes and results of the study. This may involve giving bad news to participants or their families, such as where an intervention provided as part of a study did not prove successful, which should be done carefully, ideally after seeking advice from any patient representatives who were involved in the research design at the outset. Depending on the study, continued contact and review with participants or their parents may be necessary so that late effects, whether physical or emotional, may be recognised and treated if possible. In the case of clinical trials, there may be circumstances where researchers, sponsors, or governments in the host country have a responsibility to provide post-trial access to an intervention which has been beneficial to a participant. As per the standards set out in the Declaration of Helsinki, these questions should be addressed in advance and information should be disclosed to participants during the consent process.

Researchers and sponsors of research also have a responsibility to ensure that the results of research are published or otherwise made available such that they are

open to public and scientific scrutiny. Individuals consent to take part, or give their consent for the participation of others, in medical research on the understanding that the risks they undertake will help to advance medical science and benefit future patients. Selective publication of research results betrays this altruistic motivation and, more generally, it distorts the scientific record and threatens the likelihood of people being willing to take part in research in the future.

In all research, there is an obligation on researchers to ensure the confidentiality of participants and to be alert to the risk of identification when publishing findings. This is particularly the case if the conditions investigated are rare, as patients may be identifiable even if obvious identifying details are removed. Patient consent must be sought for publication of case studies where individuals who have participated in research could be identified by themselves, or by people close to them. Research in children can raise other issues with respect to confidentiality in the long-term, partly because their health information, typically collected with the agreement of parents when the patients are young, may be stored for a long time and may be useful for projects that cannot currently be predicted. Children and young people may be unaware of the information kept about them and researchers have a duty to consider the long-term implications of future access to it. Protocols should specify the level of protection of educational records, for example, when studies are performed in schools and the information given to parents or legal representatives. This is particularly important when the information is very sensitive, such as that including issues of sexuality, mental health, illicit drug use or violence, or intellectual or physical impairment. Where personal information on a child is collected, stored, accessed, used or disposed of, a researcher should ensure that the privacy, confidentiality and cultural sensitivities of the subject are protected, subject to the usual exemptions (such as where there is a statutory duty to disclose or a public interest in doing so).