Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees

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Background

The British Paediatric Association, the forerunner of the Royal College of Paediatrics and Child Health (RCPCH), first published guidance in relation to research involving children in 1980\(^1\). Prior to this time little clinical research involved children. The 1980 guidance initiated a sea change, stating ‘research involving children is important’, ‘should be supported and encouraged’ and ‘research which involves a child and is of no benefit to that child (non-therapeutic research) is not necessarily either unethical or illegal’. Updated guidance was issued by the RCPCH in 2000\(^2\). Both documents have been cited extensively.

The need for updating

There are now many sources of detailed information for researchers, and the purpose of this paper is not to duplicate this material. The principles that underpin previous guidance remain valid, but there have been changes in their interpretation, scope, and application. Since the last RCPCH guidance the National Institute for Health Research (NIHR) has transformed the environment for research in the UK, changes in the regulation of clinical trials have facilitated research involving children, and the European Union approval of the Paediatric Regulation in 2007 has led to an increase in children’s medicines research\(^3,4\). There have been significant changes in the regulation and governance of research, with responsibility falling to a number of agencies in the UK, most recently principally to the Health Research Authority established in December 2011 ‘to protect and promote the interests of patients and the public in health research, and to streamline the regulation of research’\(^5\). There has been an increase in the diversity of health professionals involved in research, and the use of qualitative methodologies. Novel issues, many consequent on powerful new technologies, have emerged. There is a greater focus on involving children and their parents more actively in the design, review and conduct of studies. The ways in which society views clinical research have also continued to evolve. The Declaration of Helsinki that sets out the ethical principles that underpin medical research involving all human subjects has had two notes of clarification and seven amendments, the most recent in 2013\(^6\).

In recognition of these changes, a working party led by the RCPCH was established with representatives from the Royal College of Nursing, Ethics and the Law Advisory Committee of the RCPCH, National Research Ethics Service, Medicines & Healthcare Regulatory Agency, General Medical Council, Medical Research Council, WellChild, Medicines for Children Research Network (MCRN), NIHR Paediatrics (non-medicines) Speciality Group, and NIHR MCRN Young Person’s Advisory Group. The remit was to provide updated practical guidance on ethical issues in relation to research involving children. Here we provide a summary of the areas considered.

Children’s rights and interests

Children require considered protection, but this should not preclude the claim of other rights, including the right to the highest standard of health care, and to be informed, express their views, and influence decisions made about them [United Nations Convention of Rights of Child 1989]\(^7\). The current version of the Declaration of Helsinki makes no specific provision for children\(^6\) but does include a stipulation that special consideration is required for research involving vulnerable populations, and accepts the authority of legally authorised representatives to make decisions on their behalf. As the biology of many diseases and the responses to treatments differ in children and adults, conclusions extrapolated from studies in adults often have limited relevance and may even be harmful. The NIHR MCRN Young Persons Advisory Group strongly supports the view that
children should be offered the opportunity to participate in research, adding the comment that their care should ‘be assured by research’ (appendix). Without information from research there will be continuing uncertainties in the care that children receive. Of note also is that experimental treatments are not necessarily better than existing treatments; a Cochrane review has concluded ‘Society can expect that slightly more than half of new experimental treatments will prove to be better than established treatments when tested in RCTs, but few will be substantially better’. The RCPCH supports the conduct of ethical research in children that has the objectives of understanding, preventing and treating disease, and preserving health. All protocols for research involving human participants must have received approval by a Research Ethics Committee before the study begins.

**Research importance and risk**

Every research study must be preceded by a careful assessment of predictable risks and burdens in comparison with possible benefits to the individual and the population affected by the condition. Measures to minimise risk include appropriate research design, delivery by personnel trained in the procedures to be used and experienced in caring for children, and methods to reduce the volumes of blood or tissue required. Blood sampling is often regarded as a concern in relation to the pain, burden and risk of research participation. However effective anaesthetic creams are now available and sampling from indwelling lines placed as part of clinical care is painless, but expert knowledge is required of the use of these medications and the volume of blood that it is safe to take. The obligation to monitor safety, if necessary by an independent Data Monitoring Committee continues throughout a study, with actions to be taken if concerns arise or conclusive evidence of benefit emerges, set out in advance.

The importance of the research in scientific, psychological or social terms should be justified as part of the research protocol. Peer review is the most accepted mechanism used to judge research quality, whether the methodology is sound, and whether it is likely to deliver meaningful results. Studies that are of poor methodological quality are unlikely to produce reliable results and should be deemed inherently unethical. Research Ethics Committees have responsibility for determining whether research is ethical, that the rights and safety of participants are protected, and that high quality peer review has taken place.

Research should ideally carry no greater than minimal or low risk. However research that involves greater than minimal risk may be acceptable if the interventions involve diagnostic procedures or treatments that are important for the individual child, and are likely to provide information that will improve understanding or treatment of the condition. Many phase 1 investigational medicinal product studies do not achieve regulatory approval because of concerns about safety and efficacy. In general therefore medicines should be tested in adults first, with testing in children deferred until phase 3 trials. Exceptions are situations where the condition is life threatening and no alternative therapies exist, the condition is life limiting and all accepted therapies have failed, or where the condition has no adult analogy and the impact is significant.

Risk should be quantified as objectively as possible and contextualised in relation to the child’s life (e.g. describing the dose of radiation in terms of years of exposure to natural background radiation), and if applicable, the child’s experience of the condition. The risk of the disease, treatments and clinically required procedures, should be clearly distinguished from the risk of the research.
Researchers or regulators may categorise a study as ‘high risk’, whereas the family may consider a risk to be reasonable if the child or other children are likely to benefit. Seeking the views of children affected by the condition and their parents about the research and the risks and burdens they regard as acceptable and reasonable is important.

**Consent, assent and dissent**

The voluntary consent of a research participant who has been provided with appropriate information, or the consent of a person legally authorised to act on their behalf, remains fundamental to the conduct of research. Formal consent must usually be obtained and documented before enrolment and should be re-affirmed, although not necessarily in writing, at each research encounter. This is especially relevant to those studies conducted over long periods in which the child’s legal status changes or where their capacity to understand information about the study matures. For children lacking capacity to provide appropriately informed consent for research, this must be obtained on their behalf from a parent, or legally authorised representative; the child’s active affirmative agreement (assent) should also be sought. By the age of seven, many children are able to give assent and lack of objection should not be construed as assent. In those with capacity, consent may be withdrawn at any time without reason and without penalty.

The acquisition of capacity is a developmental continuum and children over 12-14 years of age may have near adult capacity. This poses potential difficulties in law. The legal test for capacity as it applies to medical treatment for those under 16 years of age, is the ability to understand what is involved and the consequences (so-called Gillick or Fraser competence)\(^1\). As there is no direct case or statute law in the UK covering non-clinical trial research, it has been presumed that the test of Gillick competence applies. In most instances the child’s assent or consent should be underpinned by parent consent, but this can be problematic where sensitive subjects such as sexual health, contraception, and adolescent behavioural studies are involved and there is a duty to preserve confidentiality. In such cases the need for parental assent or consent should be carefully considered\(^2\).

The Medicines for Human Use (Clinical Trials) Regulations 2004 are the current legal basis for consent in *Clinical Trials of Investigational Medicinal Products* that involve children\(^4\), though likely to be superseded by new European Union regulations in the near future. Here, a minor is defined as a child of less than 16 years of age. A person with ‘Parental Responsibility’ or a legally authorised representative is required to provide consent on behalf of a ‘minor,’ even if s/he has evidential capacity, and the assent of the ‘minor’ should also be sought. Consent must be obtained from those over 16 years, and from participants reaching the age of 16 during the course of a study.

Dissent is refusal to grant, or subsequent withdrawal of consent or assent. Dissent is not necessarily legally determinative, other than for *Clinical Trials of Investigational Medicinal Products*, especially if it places a child at risk of significant harm. However in the context of research dissent should be respected, even if parent consent continues.

**Research involving pregnant women**

Research involving enrolment during pregnancy may require the involvement of the newborn baby in the research protocol. There is an explicit legal requirement for a person with ‘Parental Responsibility’\(^13\) to provide consent on the behalf of a newborn baby, but lack of clarity in current guidance as to whether antenatal enrolment of a mother should be followed by additional formal
written agreement for her baby to participate in any postnatal component of the study. In many circumstances the involvement of the baby may involve no more than the use of routinely collected clinical data, or a simple procedure such as obtaining the baby’s weight or length, or sample of urine from the nappy. Alternatively it may involve a non-trivial procedure, such as a scan, blood sample, or additional out-patient attendance. The principle to be followed is that of consent as a continuing process as discussed above. The mother should have opportunity to discuss the study again with the researcher, and her ongoing agreement obtained for the participation of her baby if there are further active interventions. It is recommended that there should be formal documentation if the baby is to be involved in more than non-trivial procedures. Whether her ongoing agreement for her baby to be involved will be documented in writing should be made explicit in the research protocol and the Research Ethics Committee approved information sheets.

Research in pregnancy may involve ‘minors’ (mothers less than 16 years of age). Here practice in relation to consent should be based on the competence of the mother to understand the issues involved (Gillick/Fraser competence)\(^ {11} \). The researchers should consider whether the consent or assent of the mother’s mother or father, or other legal representative, is also necessary. Researchers aiming to recruit pregnant women may find it helpful to discuss these issues with experienced researchers and relevant parent groups at the planning stage.

**Research in urgent or emergency situations**

Research is needed to improve care in urgent and emergency situations but should only be undertaken in these situations if absolutely necessary and if non-emergency research will not resolve the uncertainties. The Mental Capacity Act\(^ {14} \) makes provision for research in incapacitated adults in emergency situations. It can be argued that similar considerations apply in this situation in children, and criteria that justify proceeding without initial informed consent have been developed\(^ {15} \). Children are particularly vulnerable to being excluded because of the difficulty in obtaining appropriately informed consent under these circumstances\(^ {16} \). The child, even if normally competent to make decisions, will be unable to do so, and parents, even if present, may find themselves in a position of ‘situational incapacity’ where their capacity is compromised by the extreme stress of the situation, the time-critical nature of the intervention, or their own condition, such as a mother after delivery under general anaesthesia. If enrolment were only possible with parental consent this would preclude the participation of many infants and children in emergency research. This is clearly undesirable and hence the concept of ‘deferred consent’ has arisen\(^ {17} \). Here enrolment in emergency situations without parental consent is acceptable, if followed by explanation and information as soon as possible afterwards when formal written consent for ongoing involvement is sought, and that it is made clear that refusal for continued participation or withdrawal can take place at any time. Deferred consent is based upon the ethical principles of standard informed consent with the difference that the process is split temporally. Recent research has emphasised that parents are not necessarily averse to considering research participation for their children in such circumstances\(^ {18,19} \). However if no parent is available, the concept of ‘substituted acceptance’ might apply. Here someone else is consulted to confirm eligibility and provide consent as a ‘legal representative’. This may be the doctor primarily responsible for child’s treatment if she or he is not involved in study as a researcher. Consideration should be given to providing general information in advance if appropriate (e.g. information about newborn resuscitation research could be provided in antenatal clinics or at booking). In all cases a Research Ethics Committee must agree that the study is fully justified and that the parent/carer is provided with good information at the right time and is then able to decide whether or not to give consent for ongoing involvement.
For Clinical Trials of Investigational Medicinal Products there was no exception formerly for emergencies and consent had to be given on behalf of a minor before recruitment by a person with parental responsibility or a legal representative. The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations that came into force 2008 allows minors to be entered into a trial prior to informed consent being obtained provided that urgent action is necessary, it is not practicable to obtain informed consent prior to enrolment, and the intervention is approved by a Research Ethics Committee.

Research with particularly vulnerable children

Children with life-threatening illnesses, looked-after children, their families, and bereaved families require a robust evidence base for both physical and psychosocial aspects of care. However evidence remains limited and largely focussed on aspects such as symptom relief. The fear of intruding on children that are especially vulnerable, and their families, and the perceived need to provide them with extra protection has led to reluctance to involve them in research. However there is now considerable evidence that families and young people who participate in research find it beneficial rather than harmful, with opportunity to speak about illness and death, express painful emotions, and obtain release from isolation. There is also evidence of a ‘maturational effect’ of life ending illnesses where children and young people express a wish to benefit others, and benefit themselves from such ‘meaningful’ encounters. Research in these sensitive areas, including qualitative studies, requires review by Research Ethics Committees that have the necessary knowledge, and expertise.

Sedation for research procedures

Sedating active infants and children may be essential for some procedures such as certain forms of respiratory function testing which of themselves are of minimal risk. Oral sedation in healthy infants and children carries minimal additional risk and is usually associated with no more than occasional vomiting or short-lived disturbance of sleep. Children born preterm and other at-risk groups such as those with respiratory problems or other co-morbidities may require short-stay observation facilities as they are at greatest risk of adverse effects from sedation. General anaesthesia for research purposes is normally unacceptable except where the potential benefit outweighs the risks (e.g. where a tissue biopsy, imaging study or other investigation is required to assign treatment in a clinical trial of a life-threatening or progressive illness). Researchers must justify the use of sedation, and provide evidence that appropriate monitoring will be in place during the procedure, and that they possess the necessary competences and skills to carry out the procedures and to deal immediately with any adverse effects. The protocol must demonstrate the importance of the study, and evidence of a rigorous risk benefit analysis. Research Ethics Committee review is, again, always required.

Unexpected findings detected during research investigations

With increasing use of new technologies unexpected findings may emerge in the course of a research study, for example from a blood test, imaging, or other investigation. The spectrum of possible findings will have varying implications, treatability and severity. Researchers have a moral responsibility and clinician researchers may have a ‘duty of care’ towards research participants. Before carrying out the investigation investigators should consider how to address such findings and, if appropriate, explain the possibility of an unexpected finding, the course of action should this occur, such as arranging for the involvement of a senior paediatrician or the participant’s General
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Practitioner, or taking no action. This process should be made explicit in the study protocol, and in the Participant Information Sheet. As clear guidance and consensus on how Health-Related Findings should be addressed are lacking, the Medical Research Council and Wellcome Trust have provided a framework to help investigators decide on the best approach.\textsuperscript{32}

**Commercial sponsorship, payment of researchers, and conflicts of interest**

Commercial sponsorship and partnership provides an important source of research development, support and funding and is a major component of UK government strategy for biosciences. Sponsorship from companies whose products are harmful to children, such as tobacco, alcohol or armaments, is in the view of the RCPCH, unacceptable. However a controversial area for the RCPCH and its members and fellows is sponsorship from the manufacturers of breast milk substitutes\textsuperscript{33}. A working party of the RCPCH\textsuperscript{34} considered these issues carefully and concluded ‘Collaboration with commercial companies is important for the care of children and their families. For example it is necessary that paediatricians should collaborate fully with research to produce drugs and other products, such as breast milk substitutes to the highest scientific standards. The College should support this process and be legitimately involved in it.’ This report and recommendations were accepted by RCPCH Council and remain valid to this time.

Sources of research funding and potential conflicts of interest should be declared and transparent. In England the Health Research Authority through the National Research Ethics Service has responsibility for ensuring that research ethics review is independent of sponsors, funders, and academic institutions. All sponsorship arrangements should be transparent, accountable and subject to appropriate scrutiny. Clinical trials must be registered, the results published or otherwise made available, and the data disclosed within a reasonable timescale, if requested.

Financial incentives for recruitment may exert undue influence on researchers and compromise the scientific validity of a study. Financial incentives for recruiting or referring children are unacceptable. Advertisements may be helpful for recruitment and are acceptable provided that they present a truthful, balanced account of risks and potential benefits, and receive Research Ethics Committee approval.

**Payments for participation of children in research**

A ‘reimbursement’ is payment of expenses incurred through involvement in a research study. ‘Compensation payments’ additionally reward participants for the time and effort of involvement in the study. ‘Appreciation payments’ are small tokens given after study completion. ‘Incentive payments’ are designed to encourage enrolment through promise of financial gain.

Reimbursement of costs incurred through research participation, such as travel costs, is appropriate. Compensation for time spent in research participation is often offered in adult studies but controversial in children’s studies because of the concern that they may undermine the voluntariness of consent, exploit weak and vulnerable subjects and create selection bias\textsuperscript{35}. However evidence that they have these consequences or that they increase risk-taking behaviours is limited. The situation is further complicated in countries in which sections of the population have limited access to healthcare on financial grounds and where research may provide ‘free access’ to a treatment they might otherwise not be able to receive.
Guidance over payments in clinical trials or other research is complex and inconsistent. The EU Clinical Trials directive prohibits incentives or financial inducements but does permit ‘compensation’ without further specification. The Medicines for Human Use (Clinical Trials) Regulations 2004 has the same prohibition for children and their families, but appears to specify that compensation applies in the event of injury or loss.

The UK NIHR Medicines for Children Research Network has investigated young people’s views on whether or not the offer of an appreciation payment would influence their decision to take part (appendix). Their view was that participation in simple, quick and non-invasive studies should be altruistic and payment would not be expected. For invasive clinical studies they expressed strong concern that any payment other than reimbursements and tokens of appreciation would be an inducement, and hence unacceptable. They considered a small token of thanks for participation in research reasonable. The nature of any token of thanks should be in proportion with the age of the child, approved by the Research Ethics Committee, and made clear in the Parent/Patient information sheets.

**Student research**

Research undertaken by undergraduate or postgraduate students, and trainees, can provide valuable educational opportunities, but poor research serves neither student nor participant well. Students cannot be expected to undertake major research projects nor is it justifiable to recruit participants to a study that will not produce meaningful results. However when well integrated into the activities of a large research group, student research can provide valuable contributions to wider goals and patient benefit, for example through acquiring pilot or feasibility data, assisting a qualified researcher with measurements, consulting user groups, and conducting systematic reviews or meta-analyses that are an essential prelude to the design of adequately powered high quality clinical trials. It is the supervisor’s responsibility to ensure that extravagant claims about the research are avoided, and that there is clarity about the reasons for the project (e.g. how a small, preliminary, or pilot study carried out by a student fits into a wider research strategy to benefit patients or improve knowledge or understanding). This information and the review and approvals process that the research has received, must be made clear to participants and parents. The supervisor should attend with the student to present the study to the Research Ethics Committee.

**Researcher competencies**

It is a requirement for anyone involved in clinical research in the National Health Service (NHS) to have received training in Good Clinical Practice (GCP), the standard to which all research should be conducted. This is laid down in the Research Governance Framework for Health and Social Care 2005 that covers research in the NHS in England. Researchers working with children must be appropriately qualified by education, training and experience and able to demonstrate that they have the necessary competencies. These include an understanding of physiology, growth and development, the pharmacological properties and side effects of any medicines involved, and the methodological, ethical and legal principles underpinning the study. They must be proficient in the techniques required, possess the necessary skill and knowledge to seek informed voluntary consent from participants and their parents, demonstrate professional integrity, openness and transparency in presenting relevant conflicts of interest to subjects and parents, and maintain complete and honest research records. There have been significant changes in research regulation and governance in the UK and around the world since the last RCPCH guidance was issued. It is
the responsibility of researchers to ensure that they understand the regulatory framework that governs the conduct of any study to which they contribute.

**Research involving UK paediatricians conducted in other countries**

Researchers based in the UK may lead or be involved in research in other countries. Research regulatory frameworks differ from country to country. The Nuffield Council of Bioethics provides guidance on research in developing countries, recommending that in addition to evaluation of scientific validity, and ethical acceptability, the relevance of the study to the healthcare priorities of the country where it is being conducted should be considered. UK Research Ethics Committees are able to provide a view without delivering a formal opinion, and researchers might find it useful to consult a committee experienced in children's research for advice, particularly in complex studies, or when they have personal uncertainties. In addition to meeting local requirements where these exist, UK paediatricians should conduct research in accordance with the UK's ethical principles and the Declaration of Helsinki, placing the wellbeing of the child foremost.

**Concluding remarks**

The ethical principles underpinning the participation of children in clinical research have evolved over the last decades, and will continue to evolve. Recent positive developments are greater involvement of young people and parents in all aspects of research, and appreciation that regulation, while providing protection for participants and researchers alike, and consistency of processes, is also crucial to benefit health and wellbeing through facilitation of high quality research. Efforts to reduce uncertainties in care through carefully conducted, methodologically rigorous, closely regulated, ethical research is an imperative that every clinician should uphold. Confidence in conduct to the highest ethical standards will help move clinical research from the exception to the norm, a necessary pre-requisite to improve children's life-long health, and further understanding and treatment of common illnesses and rare diseases.

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**Contributor statement**

Members of the RCPCH Working Party held a series of face-to-face meetings and corresponded by email. The first draft of the paper was prepared by NM; all authors contributed to subsequent revisions. The final draft was reviewed and approved by representatives of RCPCH Council and all authors.

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Royal College of Paediatrics and Child Health.

**Competing interests**

NM was Science and Research Vice-President of the RCPCH 2009-2014, is current President of the Neonatal Society, a research society founded in 1959, and Chair of the BMJ Ethics Committee.
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in the last five years NM has held research grants awarded by the National Institute of Health Research, Welcome Trust, Medical Research Council, Acton Medical Research, Child Growth Foundation, Department of Health, Westminster Medical School Research Trust, Healthcare Quality Improvement Partnership, HCA International, and Bliss.

AG is current RCPCH Science and Research Vice-President, and has held grants and received honoraria from various ventilator manufacturers.

VL provides ethics advice as a member of a Data Monitoring Committee that reviews information from an international trial of long acting beta agonists in asthma. The trial involves four sponsors co-ordinated by a company who convened the DMC at the request of the US Food and Drug Administration.

Appendix
NIHR MCRN Young Person’s Advisory Group Feedback
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Introduction

The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) felt it was important to consult with members of the MCRN Young Persons Advisory Group (YPAG) in the revision of the RCPCH ethical guidance document on involving children in research, last updated in 2000. We wanted to hear young peoples’ views on some of the proposed changes to the guidance, and highlight the key ethical issues faced by researchers today. The ethical issues were broken down into:

- Children’s Rights
- Risks involved in research
- Consent, assent, dissent
- Research in emergency settings
- Payments for participating in research

25 members of the group responded, 15 via email 10 via a face to face meeting. Those in the face to face meeting however only focused on certain questions due to time restraints.

Here are the key findings to the following questions:

What are your thoughts on the statements below? Please consider:

- Do they make sense?
- How important are these statements (give a score between 0-10, where 0 means ‘Not at all important’ and 10 means ‘Extremely important’)
- Do you think there are other ethical concerns about involving children in research that researchers should be aware of?

Children’s Rights

Children have a right to be offered the opportunity to participate in research designed to reduce uncertainties in their care; where uncertainties exist there may be greater risk to the child’s wellbeing by not participating.
Collective response:

18 out of 25 young people responded to this statement. Overwhelmingly all the young people felt this statement was very important (mean score 8-10) and that young people should be offered the opportunities to get involved in research. As one young person said:

“From my own experience in a clinical trial I know that many young people are willing to improve medicines of the future by getting involved in research. Young people like myself welcome the opportunities to participate in research because it is so vital for the progression of modern medicine. Uncertainties and risks are to be made clear to the child and parents when approached to take part in research and it is up to the child and parents to evaluate such risks and decide on whether or not to take part”

One young person offered a slightly unique perspective:

“Perhaps it is not a child’s right to participate in research. Rather, it is the right of all young people to have their care to be assured by research – that is to say, that all medicines and practices for young patients should be researched with young people”.

Statement: Every child has a right to be safeguarded and protected in research by allowing participation **only** in research that is well designed, well regulated, and where risk is minor, or reasonable.

Collective response:

20 young people responded to this statement. This was viewed as an extremely important statement (mean score 9-10) but the young people challenged the view that research participation may involve greater risks but may result in more benefits to the child, however this was based on the context of research and the type of research:

“Extremely important – research should not adversely affect the child’s health and participation should not put them in any danger. However, sometimes a greater risk may be outweighed by more benefits”.

“The child and family should be given the opportunity to evaluate the level of risk themselves. Researchers may categorise the trial as ‘high risk’, whereas the family may consider it to be a reasonable risk if the child is likely to benefit from the research”
Risks and benefits in research

Most interventions in medical practice and research involve risks and burdens to participants. Outweighing the risks versus the benefits of taking part in research is something young people and families have to consider before they take part. To help, we can classify risk of procedures as minimal, low and high. Here are some examples of procedures:

- **Minimal:** such as questionnaires, simple measurements, single urine sample, extra tube of blood when sample already being taken for clinical care
- **Low:** (cause brief pain/discomfort) blood test, injection, intravenous cannula (drip tube for short time)
- **High:** taking a tissue sample e.g. of kidney, muscle, liver or an invasive test such as putting an intravenous or arterial tube to check the heart/organs (nearly always needs pain relief/anaesthesia)

High risk procedures are generally only allowed if the research is part of the care/diagnosis

Here are some statements that talk about risk v benefits of taking part in research. Firstly look at statements A and B, then comment on these and score. What do you think of statement C?

A. *Research that carries greater than minimal risk may also be acceptable provided that is carries a prospect of direct benefit to the child.* For example, if a blood test was needed as part of research in a study (e.g. to measure the level of a new drug in the blood) it could only be ethical if that information (level in the blood) was directly helpful to the child (e.g. because a low level might mean a higher dose was needed or a high level might mean it was dangerous)

B. *Research that involves greater than minimal risk but has no direct benefit to the child may be acceptable, but only if: the additional risk is minor; the child is already familiar with the interventions used (i.e. having regular bloods taken) for their condition; and the research will produce further knowledge of a particular condition and some understanding of how the condition can be treated.* Using the above example of the research blood test (to measure the level of a new drug in the blood) this statement suggests it could be ethical if that information (which might help doctors check how children metabolise – break down – the drug) gave helpful knowledge for children in general or about the disease and doesn’t have to directly benefit the child.
Collective response:

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<tr>
<th>18 young people responded to this statement. Overwhelmingly in response to both A and B all young people felt that as long as children and families were fully informed of the possible risks in advance then whatever the risks involved they are able to make an informed decision:</th>
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<tr>
<td>“The child and parents must be fully informed of the risks associated with the procedures in advance”</td>
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<tr>
<td>Some went so far to say that children and families should be informed that not all research will have direct benefits to the child but may have benefits for other children in the future:</td>
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<td>“I do not believe that every aspect of a trial should carry a prospect of direct possible benefits to the child. When signing up to the trial the child and the family should understand that the trial has the possibility of helping them directly but is not being done solely to help the individual”.</td>
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C: Gaining advice from appropriate user groups of children and families about the importance of the research and level of risk involved is important?

Collective response:

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<th>20 young people responded to this statement. Unsurprisingly all members agreed with this statement (mean score 10) and felt it was invaluable to obtain the views of children and families in the design and outcomes of a trial. Some comments include:</th>
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<td>“This is very important because it makes sure that the trial is viable even with higher risks involved ad it means the trial can be adapted to make it better for patients and families which means that it is more likely that people will participate”</td>
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<tr>
<td>“This is vital for the research to improve and is the only way to gain a full understanding of what levels of risk are truly reasonable in research”</td>
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<tr>
<td>“Researchers may be surprised by the willingness of patients and families to get involved and help in research, especially if they raise more awareness in research”</td>
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</tbody>
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**Consent, assent and dissent**

The voluntary informed consent of research subjects, or those legally authorised to act on their behalf (i.e. parents) remains fundamental to the conduct of research. The legal test for measuring capacity for those under 16 is called Gillick competence, which means measuring the ability to understand what is involved and its consequences but this only applies to medical treatment, this does not apply to research.
Gaining consent, and assent in research that involves medicines

Please comment on the following statements about agreeing (or not) to take part in research (please also score)

Consent for participation of a child (under 16 years of age) should be sought from a person with legal “Parental Responsibility”; a competent child should also be asked whether they agree to participate; such agreement is known as assent

Collective response:

18 young people responded to this statement (mean score 8). All of the young people who responded to this statement agreed that a person with legal ‘parental responsibility’ should consent for their child to participate and that the child should also be asked whether they agree to participate. However, some young people queried what was meant by competence and how is this be measured?

“I do wonder how competence of a child’s understanding will be measured?”

“If a young person opposes the parent’s decision there is a dilemma. How do you assess the competence of the young person to assess if they are making the right decision?”

In the context of research, refusal to grant informed consent or assent should be respected and normally granted even if parental consent continues

Collective response:

18 young people responded to this statement (mean score 7). All young people agreed that the young person’s wishes should be respected:

“It is extremely important that the child taking part in the study agrees to it and not just the parents and the study should not take place if the child is not happy to be a part of it”.

“Ultimately the child is the main person affected by the trial so should be the one to decide whether or not they want to participate”

Research in emergency situations

Research in emergency situations is a problem because of the difficulties of obtaining informed consent. The child, even if normally able to make decisions, will be unable to do so because of their condition (e.g. very unwell, unconscious, head injury). Parents, even if present, may not be able to make a careful decision because the situation is unexpected, urgent, time is pressing and they will be very stressed. Examples of such research include new treatments for severe asthma, research in looking after sick newborn babies, research in meningitis (infection of lining of brain) but not doing research in these emergency cases means that children might not benefit from advances in treatments.
Please comment on the following statements:

Statement: Research in emergency situations can be essential but should only be undertaken if comparable non-emergency research is not possible.

Collective response:

20 young people responded to this statement (mean score 7). All members agreed with this statement and valued the importance of research in emergency settings, some even went as far to say that it was vital and the issue of deferred consent/assent was mentioned:

“Parents and child may be unable to make informed consents decisions but the professionals should be trusted to keep the family’s best interests at heart”.

“If the emergency research is the only research than can be undertaken then it should, but the parents and child still need to be asked for consent and assent when well

Statement: In research in certain emergency situations, it may be acceptable to undertake the research without first asking for consent, provided a Research Ethics Committee agrees that the study is fully justified (e.g. the disease, child’s condition, level of risk and benefit) and the parent/carer is provided with good information at the right time and is then able to decide whether or not to give consent for on-going involvement in the study.

Collective response:

Most members agreed (mean score 7) that research in certain emergency situations is acceptable as long as the parents and possibly the young person can withdraw from the study once they receive all the information:

“In emergency situations I think the research can be undertaken, however if when capable the child doesn’t want to take part then their information shouldn’t be used”.

“Yes I agree but the patient and family should later be asked if they wish to continue in the trial and if they disagree their information should be deleted”.

Two young people felt that consent should be sought first:

“I think that consent should be at least taken from a ‘next of kin’ rather than go ahead without any consent”.

Payments for participation

Statement: It is reasonable to give a small token of thanks for participation in research; this should be in proportion with the age of the child, and approved by the Research Ethics
Committee; the Parent/Patient Information Sheet should explain that a token of appreciation will be provided at the end of the period of participation

Collective response:

20 young people responded to this statement (mean score 8). The majority of members agreed with this statement but felt that researchers needed to explain what was meant by small token of thanks, and this needed to be clear in patient information sheets. The group felt that any talk of payments might be seen as bribing or incentivising young people’s participation, but it seemed acceptable when a small token of thanks (age appropriate i.e. teddy, certificate, vouchers) was acceptable.

Do you think there are any other ethical issues of involving children and young people in research that are not covered above?

Collective response:

Only four young people commented on this section. Two young people felt it was important for researchers to be aware of the amount of time a young person may lose from their education or social life by taking part in trials, so researchers have to be flexible and work around children.

One young person felt the Gillick system should be applicable in research and one made a comment that it was unethical not to involve children in research.