



Foreword

Medical research involving children is important for the benefit of all children. It leads to innovations in healthcare that can substantially improve their health and quality of life. Furthermore, the scientific opportunities for developing better methods of preventing and treating diseases that affect children or begin in childhood have never been greater.

The Medical Research Council (MRC) believes that research involving children should be supported, encouraged, and conducted in an ethical manner. We want to ensure that research participants, their parents and the general public can be confident that medical researchers work ethically with children.

We recognise that while many other organisations have published guidance on medical research involving children, this is a vital area in which we must provide support and guidance to MRC researchers. The previous MRC guidance *The ethical conduct of research on children*¹ (1991) has been replaced by the following updated guidelines. They outline the practical, ethical and legal issues that researchers need to consider when carrying out studies involving children. Our aim has been to set out general principles that can be applied in most situations rather than to cover every possible eventuality. The guidelines are intended to be concise and easily readable, and include a glossary defining some of the key terms used (see Section 7).

We refer to guidance from The Royal College of Paediatrics and Child Health,² the Department of Health³ and British Medical Association⁴ throughout this document. These organisations can all provide further useful information.

This guide complements guidance on other research-related topics produced by the MRC, all of which is available at the MRC website, www.mrc.ac.uk. Any changes to MRC guidance are highlighted on the site as they arise.

Contents

1. Introduction	4	5. Children, ethics and the law	21
1.1 Purpose	4	5.1 Consent	21
1.2 General ethical principles	5	5.1.1 What is valid consent?	21
1.3 Summary of key ethical principles relating to research involving children	5	5.1.2 When should consent be sought, and who should seek consent?	21
2. Why do we need research involving children?	7	5.1.3 Who can give consent, and who should you seek consent from?	22
2.1 What would be the consequences of not carrying out research on children?	8	5.1.3.a Provision in law for children to consent	23
3. What has limited research so far, and what are the challenges?	9	5.1.4 Assessing the competence of a child to consent	27
3.1 Difficulty in reaching consensus about including children in research	9	5.1.4.a Children unable to consent to involvement, and parental consent	28
3.2 Methodological challenges	10	5.1.4.b Seeking legal advice	30
3.3 Expense of developing new treatments	11	5.1.5 How best to seek consent	30
3.4 Weak licensing and regulation arrangements for paediatric versions of pharmaceuticals	11	5.1.6 Seeking consent – a summary	32
4. The way forward – ethical considerations	13	5.2 Confidentiality	34
4.1 Does the research need to be carried out with children?	13	5.3 Ethics committee review	35
4.2 Use of terms 'therapeutic' and 'non-therapeutic' research	14	5.4 Children's safety in relation to researchers	36
4.3 Benefit, harm and risk	15	5.5 Specific situations	36
4.3.1 Other considerations	17	5.5.1 Research involving human material	36
4.3.2 Minimising risk	19	5.5.2 The use of personal information	37
		5.5.3 Research involving very young children	37
		5.5.4 Emergency situations	37
		5.5.5 Including minority groups – equality in research	38
		5.5.6 Research in developing countries	39
		6. Summary	40
		7. Glossary	41
		8. Other MRC ethics guidance	44
		9. References	46

I. Introduction

I.1 Purpose

These guidelines are designed to be of use to researchers preparing proposals for MRC support for research involving children, and to those planning, undertaking or collaborating in such research. They will also be helpful to other researchers, and to doctors and other health professionals whose patients may be involved in research, to ethics committees, to others reviewing or supervising research, and to the public.

The guidelines take into account recent publications by leading organisations and professional bodies, which are referred to throughout. They should be read in conjunction with MRC guidance on different aspects of good practice in research with adults (listed in Section 8), the principles of which are also relevant to paediatric research.

I.2 General ethical principles

The MRC is committed to the highest ethical standards in medical research. The fundamental principles underpinning research on human beings and information relating to them have been elaborated and refined in various national and international guidelines: ⁵⁻¹²

- Participants' interests must prevail over those of science and society, where there is conflict.
- The research must have potential to generate scientific understanding that may be a basis for improvements in human health and wellbeing.
- There must be an acceptable balance of risk and benefit for participants.
- Researchers can only proceed if they have obtained voluntary informed consent from the participant to participate in research (special safeguards apply when this is not possible).
- An appropriate independent research ethics committee must review and approve the research proposal.

I.3 Summary of key ethical principles relating to research involving children

Children require special protection because they are less likely than adults to be able to express their needs or defend their interests – they may not have the capacity to give consent.

The following principles should guide all MRC-funded research involving children: ^{4,5}

- Research should only include children where the relevant knowledge cannot be obtained by research in adults (for guidance, see 4.1)

- The purpose of the research is to obtain knowledge relevant to the health, wellbeing or healthcare needs of children.
- Researchers can only involve competent children if they have obtained their informed consent beforehand.
- A child's refusal to participate or continue in research should always be respected.
- If a child becomes upset by a procedure, researchers must accept this as a valid refusal.
- Researchers should involve parents/guardians in the decision to participate wherever possible, and in all cases where the child is not yet competent. Exceptional circumstances where this is not possible are discussed in 5.5.4.
- Researchers should attempt to avoid any pressures that might lead the child to volunteer for research or that might lead parents to volunteer their children, in the expectation of direct benefit (whether therapeutic or financial).
- Research involves partnership with the child and/or family, who should be kept informed and consent to separate stages of the project. Obtaining consent is a continuing process, rather than a one-off occurrence. Children and their families are likely to appreciate some recognition of their role in this partnership, such as a certificate of participation.
- Researchers must take account of the cumulative medical, emotional, social and psychological consequences of the child being involved in research. Children with certain conditions may be exposed to a sequence of research projects. It is advisable to consider the risks of a particular research procedure in the context of the child's overall involvement in projects by different researchers.

2. Why do we need research involving children?

Medical research involving children is essential for advancing child health and wellbeing. Often it is not sufficient, scientific, or ethical to carry out research with adults and apply the findings to children. This may be because:

- The disease processes in children may differ from those in adults. Some childhood diseases have no close analogies in adults, therefore to understand these in any detail it is necessary to carry out research with children.
- The physiology of children is different from that of adults, and the pharmacokinetics of many drugs will vary with the age of the child. Treatments designed specifically to meet the needs of children ensure that age-related differences in drug handling and/or effects are recognised, that the doses needed for efficacy are understood, and that any adverse effects can be avoided.
- Many disorders can only be understood in the context of a child's growth and development. Examples include changes in the visual system following early squint, or the way the developing brain adapts to injury or damage in babies.
- Children are not small adults. For the therapy to be effective, its delivery must suit their needs. Use of adult formulations is often not suitable, eg, many children find it easier to swallow a liquid formulation than a tablet.

Research with children can also play a key part in increasing our understanding of some adult diseases that are thought to have their origins in early life. It enables the development of preventive intervention into the natural history of the disease. The findings of research involving children can therefore also be relevant for adults.

Research promoting the health of children can include investigation of:²

- Normal childhood development.
- Origins and causes of disease.
- Means of promoting health.
- Means of preventing, diagnosing, assessing and treating disease.
- Whether the beneficial results of research conducted in adults can be applied to children.

While we have a responsibility to protect children, we also have an ethical obligation to ensure that they receive the best treatment. Like adults, they should be given the opportunity to benefit from the results of successful research. Children should therefore have the opportunity to participate while, of course, being protected from any hazards that involvement in the research project might bring. The MRC's research on childhood leukaemia shows how valuable this involvement can be. Most children diagnosed with leukaemia in the UK are entered into the MRC's trials, and in the last 40 years the survival rate for children with acute lymphoblastic leukaemia especially has greatly improved – from less than five per cent in 1962 to 80 per cent at present.¹³

2.1 What would be the consequences of not carrying out research on children?

When research does not involve children, child-specific treatments for diseases are not developed and diseases with no close analogies in adults are not studied. This means that future generations of children miss the opportunity to benefit from the findings of that research. Progress in the clinical care of children will be impaired without research in this age group and children may be given treatments that are potentially unsafe. In addition, progress on understanding adult diseases thought to have their origins in early life will be hampered, limiting the possibilities of preventive intervention.

3. What has limited research so far, and what are the challenges?

Progress in research involving children has been limited primarily by:

- Difficulty in reaching consensus about including children in research.
- Methodological challenges.
- Expense of developing new treatments.
- Lack of legal enforcement for paediatric versions of drugs.

3.1 Difficulty in reaching consensus about including children in research

Current ethical principles for conducting research involving children have evolved from the Nuremberg Code which emerged after the Second World War. The Code set out statements of moral, ethical and legal principles relating to research involving human subjects, and included a bar on research involving children. Research was seen as a potential harm from which vulnerable people should be protected. Later, in 1964, the Declaration of Helsinki, drawn up by the World Medical Association, advised that research involving minors could be carried out where "the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons" and appropriate consent and assent had been obtained.

Today, organisations such as the Council for International Organizations of Medical Sciences play a vital part in considering how these ethical principles can be effectively applied. While research may have associated risks, it can also offer potential benefits to all participants, including children. Changes in the way we regard children include a growing recognition of the importance of listening to children's views and wishes, and of their autonomy. This can be observed in

attitudes towards research involving children. Earlier research tended to be on children, with children regarded as subjects of the research. Increasingly, research is conducted with children, who are involved as active participants.

3.2 Methodological challenges

Smyth and Weindling describe how the emergence of evidence-based healthcare has led to a greater awareness of the need to evaluate critically what is already known before making recommendations for clinical practice or embarking on further research.¹⁴ Studies have shown that in comparison to research on adults, research questions relevant to the health of children may not have been addressed at all, or only by small, poorly designed studies.¹⁵

Particular methodological challenges occur in research involving children. Childhood forms of many chronic diseases, eg, juvenile chronic arthritis, are uncommon and this may lead to difficulties in gaining statistical power to detect an effective treatment. Genetic disorders leading to severe disability or death are also rare.

Even for more common conditions challenges arise. In asthma, for example, the diagnosis may be subjective, which poses problems in establishing the clear inclusion and exclusion criteria required for clinical trials. Standard outcome measures in adults include death and quality of life, but for many conditions different outcomes are more relevant. Measurements of these outcomes have been determined for use in adults specifically and may not be relevant for children. Quality of life measures can be used, but should be focused on the child or family and validated and tested for reliability and responsiveness to change before being used; such instruments have not always been available.

It is therefore useful, and important, to consult children about outcome measures and other issues, when the research is being designed.

When carrying out research on children, it is important to assess both the short-term and long-term outcomes. For example, early treatment of premature infants at high risk of chronic lung disease with steroid drugs reduces this risk, but long-term studies show an increased risk of cerebral palsy.¹⁶

Investigations of cognitive, neurological and respiratory function can also pose challenges, eg, the inability of young children to understand and co-operate with the demands of complex tasks.

3.3 Expense of developing new treatments

Because of the expense of developing a new treatment, commercially funded research understandably focuses on treatment options that are likely to be profitable. Pharmaceutical companies have traditionally been reluctant to invest in developing child-specific treatments or adapting existing medicines to meet the needs of children. The main reasons are that the market is often small and that long-term follow-up of adverse effects is often needed because the risks associated with paediatric treatments are generally higher.¹⁷

3.4 Weak licensing and regulation arrangements for paediatric versions of pharmaceuticals

The National Audit Office recently reported that up to 90 per cent of medicines prescribed to children in hospitals were not licensed for that use.¹⁸ Consequently, there are potentially important public health benefits in improving the licensing of medicines and the testing of their safety for children. Currently in Europe there is no legal requirement for the necessary studies to be performed if the pharmaceutical company does not present the drug for use in children. However, the European Commission has proposed legislation on medicinal products for paediatric use.^{17,19}

This regulatory initiative takes its direction mainly from recent US legislation – the US Best Pharmaceuticals for Children Act 2002 and the related 'Pediatric Exclusivity' provision and 'Pediatric Rule'. The Pediatric Exclusivity provision grants an additional six months' patent protection or market exclusivity to companies that voluntarily test the relevant drug on children, which has been generally well received. The Pediatric Rule demands that companies test their products on children under certain circumstances, including the likelihood of: usage for a substantial number of children, meaningful therapeutic benefits, risk to children in the absence of licensing and usage in different paediatric age groups.

The European legislation will probably be finalised in 2006. Meanwhile, a co-ordinated UK strategy led by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Department of Health aims to begin to address the issue and raise awareness in the pharmaceutical industry of the need to take action now to ensure that products are appropriately labelled and formulated for paediatric use.²⁰ The resulting need for more research in paediatric pharmacology was highlighted in the Royal College of Paediatrics and Child Health (RCPCH) review *Safer and Better Medicines for Children*, which was commissioned by the MRC, the Department of Health and the Association of the British Pharmaceutical Industry.²¹

In addition to the above constraints, the increased complexity of regulation for paediatric and adult clinical research has become more burdensome for clinicians and researchers.

4. The way forward – ethical considerations

The following section outlines the key issues to consider when planning and conducting research involving children.

4.1 Does the research need to be carried out with children?

Research involving children should only be carried out if it cannot feasibly be carried out on adults. Therefore the researcher needs to assess beforehand whether the same potential benefit for children could be derived from studies on adults, which involves asking the following questions:

- Is the disease specific to children, with no close analogy in adults? For example, juvenile rheumatoid arthritis or Kawasaki's disease.
- Will the study increase understanding of the children's development and/or wellbeing with the aim of improving child health?
- Are the relevant pharmacokinetics of the treatment option being studied already known in adults? Is it expected that the pharmacokinetics for children and adults will differ? Is there a need to test this?
- Is the adult-style therapy shown or believed to be unpalatable or difficult to administer to children? Has the therapy previously been developed for adults and not tolerated by children?
- Is the adult disease believed to have its origins in early life? Will studies involving children shed light on the disease and its natural history and increase understanding of the possibilities of prevention?

If the answer to any of these questions is yes, children may ethically be involved in this research, and may benefit from it.

When a choice of age groups is possible, older children should be involved in preference to younger ones, although some research questions are specific to younger children and babies.²

4.2 Use of terms 'therapeutic' and 'non-therapeutic' research

The distinction drawn previously between therapeutic and non-therapeutic research is now regarded by many as unhelpful and potentially misleading. For example, clinical trials that involve medicines include both therapeutic elements – the medicine being given – and non-therapeutic ones – the taking of a blood sample. Moreover, the term therapeutic can cause confusion if it raises hopes of success whereas the outcome of the research may not provide a treatment that benefits the individual participant. Indeed, some 'therapeutic' research has been considered to be more hazardous than 'non-therapeutic' research. Consequently, the Declaration of Helsinki (2000) no longer uses these terms, setting out instead basic principles for all medical research and additional ones for research combined with medical care.

The guidelines from the RCPCH published in 2000 likewise avoid drawing this distinction, highlighting instead the principles that research involving children is important for the benefit of all children, and that a research procedure which cannot directly benefit the child is not necessarily unethical if the findings might benefit future generations of children. Research where there is no benefit to the individual child participant would have to be of minimal risk. This is a major step forward in thinking. The expectation is that children can now begin to reap the benefits of research designed with children in mind.

4.3 Benefit, harm and risk

In the past, the concern to protect children from the potential harms of research may have denied them potential benefits. To ensure that this vulnerable group are not exploited, the General Medical Council advises that it is important to assess carefully the potential benefits and harm to children at all stages of any research. As the benefits of research are not predictable, the researcher must be satisfied that the research is not contrary to the child participant's interests. The foreseeable risks should be kept as low as possible: the potential benefits from the development of treatments and furthering of knowledge must outweigh any foreseeable risks.²²

Risk - A potential harm; the characteristics of risk include the probability of its occurrence, as well as its magnitude and duration

Risks may be estimated as minimal, low or high:ⁱ

Minimal (the least possible) risk describes procedures such as questioning, observing, and measuring children, provided that procedures are carried out in a sensitive way, respecting the child's autonomy, and that consent has been given. Procedures with minimal risk include obtaining bodily fluids without invasive intervention, eg, taking saliva or urine samples. It is expected that research of minimal risk would not result in more than a very slight and temporary negative impact on the health of the person concerned.

Low risk describes procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress; eg, a blood test.

High risk procedures such as lung or liver biopsy, arterial or lumbar puncture, and cardiac catheterisation are not justified for research purposes alone with children. They should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned.

ⁱ Adapted from RCPCH guidance and Council of Europe guidance.

Research in which children are submitted to more than minimal risk with only slight, uncertain, or no benefit to themselves requires serious ethical consideration.

The RCPCH advises that assessment of potential benefits and harms includes considering the following:²

Assessing potential benefit for the participant and children as a whole

Magnitude – How severe is the condition that the research aims to alleviate and how common is it? How is the knowledge gained likely to be used?

Probability – How likely is the research to achieve its aims?

Beneficiaries – Is the research intended to benefit the child participants, and/or other children?

Resources – Will potential benefits be limited because the treatment is very expensive, or difficult to deliver?

Types of intervention – Might a new treatment or procedure replace one that is more invasive?

Timing – Might benefits be brief or long-lasting, immediate or not evident until years later?

Equity – Should a wider range of children be offered the potential benefits of participating in the research?

Assessing potential harms to the participant

Magnitude – How severe may the harms associated with the research procedures be?

Probability – How likely are the harms to occur?

Types of intervention – How invasive or intrusive is the research? (Psychosocial research should be assessed as carefully as physical research.)

Timing – Might adverse effects be brief or long-lasting, immediate or not evident until years later?

Equity – Are a few children who already have many medical problems drawn into too many projects simply because they are available?

4.3.1 Other considerations

The **assessment of risk** must be carried out by all involved in the research – the children where possible, the parents/guardians, the researchers and clinicians concerned and the research ethics committees. This assessment includes reviewing personal circumstances: generalisation can be controversial as children's responses vary, can be unpredictable, and alter as children develop; a procedure that does not bother one child can arouse severe distress in another. For example, many children fear needles. For them, low rather than minimal risk could be incurred by injections and venepuncture. However, the procedure may be made more acceptable with careful explanation of the effectiveness of local anaesthetic cream and an understanding of the reason for the venepuncture – so that the child may choose to proceed. Researchers sometimes underestimate high risk of pain if the effects are brief, whereas the child or parents may consider that the severe transient pain is not justified by the hoped-for benefit.

Careful consideration of consequences may be required to identify some risks or potential harm. For example, with research into serious genetic disorders that present in adult life, pre-symptomatic diagnosis in a child, while it may be beneficial, may also have harmful effects or implications which may affect the child's opportunities and freedom of choice.²³

Interim findings: as with adults, if evidence of harm emerges during the trial as a result of giving or withholding certain treatment, the interests of the child participants must be put before the requirements of the research. This must be taken into account by researchers and trial steering committees when deciding on 'stopping rules' for trials and in studies of new techniques.

Child volunteers: healthy volunteers should be treated in the same way as other child participants. Please see 5.1.4 for more information. It is ethical for a healthy child to participate in research as long as appropriate consent has been obtained, there is no more than minimal risk and the research is not against the child's interest.

Participation in more than one research study: as with adults, there may be situations where it could be argued that participation in more than one trial or study might be potentially beneficial – both for participants and for the research. The potential benefits and risks of doing so would need to be carefully explored by all concerned, and clearly understood by the child and family.²⁴

Equipoise: this is when there is genuine uncertainty among those who have considered the issue, including patients, about the relative benefits and risks of treatments or tests being compared. A clinical trial cannot be ethical unless there is this genuine informed uncertainty among the expert medical community and in an informed competent patient/participant.

4.3.2 Minimising risk

The National Academy of the Sciences provides guidance on how to minimise risk, summarised here:²⁵

Minimising risk in research involving children

- Is inclusion of children necessary to answer the scientific question posed by the research? What are the ages of the children to be included? Are any of the potential research harms age-dependent?
- Will potential child participants be screened for known vulnerability to the risks associated with specific elements of the research?
- What does the research require of children and their families? Is adherence to the research protocol a concern? If so, what are the risks of non-adherence?
- Are all the procedures or interventions necessary to answer the research question? Can the investigators collect the required information using procedures that the child participants will undergo as part of their normal therapy or monitoring?
- Have previous laboratory studies, animal research, studies with adults, or other data provided a sufficient basis for proceeding with research involving children?
- Does the study follow principles of sound research design?
- What are the theoretical risks involved with the research as proposed? Are data available to estimate the probability and magnitude of each risk as they relate to the categories of children to be included?
- Have the investigators provided data on the frequency of adverse events for the procedures at the site in question? For example, sedation for research procedures.

Continued...

Minimising risk in research involving children - *Continued*

- Are the investigators and other members of the research team qualified to perform each of the procedures or assessments specified in the protocol and recognise potential risks and adverse outcomes? Does the research team have appropriate skills and expertise in caring for children of the ages included in the study?
- Will research be performed in a setting that is 'friendly' to children of the ages included in the study? Is the setting appropriate for the physical, clinical, psychological and emotional needs of those age groups?
- For research that involves more than minimal risk, does the research protocol have an adequate plan for monitoring the safety of the child participants? Does the monitoring plan provide for the inclusion of professionals with the appropriate expertise in paediatrics?
- If the protocol presents the risk of a physical or psychological emergency, is the research setting equipped to respond? Are plans for responding to an emergency specified in the protocol?
- What are the stopping rules or 'endpoints' for early discontinuation of the research on the basis of strong findings about harms or benefits? Are they specific and appropriate?
- What happens to the data once they are collected? Where are research records stored, and who has access to them? What are the practices and procedures for maintaining the short-term and long-term confidentiality of the data?

5. Children, ethics and the law

5.1 Consent

5.1.1 What is valid consent?

Consent – The voluntary agreement of an adult or competent child, based on adequate knowledge and understanding of relevant information, to participate in research

Consent is legally valid and professionally acceptable only where the participants (or their parental guardian) are competent to give consent, have been properly informed, and have agreed without coercion.²²

In the UK, there are now two legal systems running in parallel. The common law applies to research not involving the Clinical Trials Regulations. As of May 2004, the Medicines for Human Use (Clinical Trials) Regulations apply to research involving investigational medicinal products (see Glossary). Researchers need to familiarise themselves with the Regulations.²⁶

5.1.2 When should consent be sought, and who should seek consent?

Research with children must normally only be carried out with the consent of the parent/guardian and/or child depending on the competence of the child. A summary of what is required in different circumstances is given below and in the flow diagram in 5.1.6. The physical integrity of children is protected by law and unless they or their parent/guardian agrees, it is not lawful to do anything that involves touching them.

Consent should be sought before a child is examined, treated, cared for or involved in research. The clinician responsible for the child's treatment needs to ensure that

processes are in place and adhered to that ensure that the child and/or parent/guardian have given their informed consent. However the task of seeking consent can be delegated to another suitably trained and qualified health professional who understands the procedure(s) for which consent is being sought.

As indicated in 5.1.5, the process of obtaining consent entails far more than a signature on paper. Verbal informed consent can be as valid as written consent for research, unless the Clinical Trials Regulations apply. It is vital that the person seeking consent records in writing that it has been given verbally. It may nevertheless be useful to obtain a signature from the participant or parent where this seems appropriate. It is important to note that under the Clinical Trials Regulations, verbal consent is not valid. The consent must be in writing unless the person giving consent is unable to write or otherwise mark the consent document.

Informed consent is only one possible result of the informed choice process; the other possible result is the informed choice not to participate.

Possible exceptions – Some research based on observation, on information collated from notes and tests already performed for therapeutic purposes, and public health research may be permissible without consent.² Further information on the use of personal information in medical research is available from the MRC guidance *Personal information in medical research*.¹¹

Research linked to medical care in an emergency; the handling of this depends on whether the proposed study falls under the Clinical Trials Regulations. For further information please refer to 5.5.4.

5.1.3 Who can give consent, and who should you seek consent from?

The law regarding the child's right to consent has developed differently in Scotland than in England, Wales and Northern Ireland – as outlined in 5.1.3a and 5.1.4a below. Generally, where children have sufficient understanding and intelligence to

understand what is proposed, it is their consent and not that of their parent/guardian that is required by law.

Ethically it is important to involve children as much as possible in decisions about their own health, wellbeing and healthcare. The United Nations Convention on the Rights of the Child states that the child has a right to be informed, to express a view and to influence a decision.²⁷ Methods used to facilitate the consent process should be appropriate to the age and understanding of the child. The Department of Health provides very useful guidance on consent for both patients and clinicians, including guidance for children and for parents/guardians explaining what they have a right to expect.³

5.1.3.a Provision in law for children to consent

England, Wales and Northern Ireland

Where the Clinical Trial Regulations apply, a minor is defined as someone under the age of 16.

Where the common law applies – all situations not covered by the Regulations – the law states that the age of majority is 18. Whilst not considered to have fully reached adulthood, young people between the age of 16 and 18 are presumed to be competent to give consent. No statute governs the rights of those under the age of 16 to give consent for medical treatment or research. However, case law provides the example of the Gillick case with respect to treatment.²⁸ This case determined that where a young person has sufficient understanding and intelligence to understand fully what is proposed, and use and weigh this information in reaching a decision, he or she can give consent to treatment and consent from parents is not legally necessary – although parental involvement should always be encouraged. The term "Gillick competent" is used to describe a young person's ability to make a decision regarding consent.

In the absence of case law dealing specifically with research, the Gillick principles might reasonably be applied here, although the threshold for understanding will vary according to the complexity of the research. However there is continuing uncertainty about the application of these principles to research in general and, in the case of law covered by the Clinical Trials Regulations, it will be those Regulations that apply and not the Gillick case law.

Scotland

As in England, Wales and Northern Ireland, where the Clinical Trials Regulations apply, a minor is defined as someone under the age of 16.

Also as in England, Wales and Northern Ireland, in Scotland a person reaches majority at the age of 18.²⁹ However, Scottish statute makes legal provision for young people, where they are considered to be competent, to consent to medical procedures or treatment. Under Scottish statute young people aged 16 and above are presumed to be competent to give consent until proven otherwise, having legal capacity to enter into any transaction, which includes "...the giving by a person of any consent having legal effect."³⁰

Young people under the age of 16 can also give legally binding consent to participate in medical research as long as they are believed by the medical practitioner to be competent: "...a person under the age of 16 years shall have legal capacity to consent on his own behalf to any surgical, medical or dental procedure or treatment where in the opinion of a qualified medical practitioner attending him, he is capable of understanding the nature and possible consequences of the procedure or treatment."³⁰ Interpretation of Scottish law has been that a young person's competency allows them to refuse as well as consent to treatment.

It is not entirely clear whether this Scottish statute covers consent to participate in research, but as discussed above, in the absence of law dealing specifically with research, the principles of Scottish law relating to consent to procedures and

treatment might reasonably be applied. At the same time, it is vital to recognise that the threshold for understanding will relate to the complexity of the research being undertaken.

Additional protection for children participating in clinical trials

The Medicines for Human Use (Clinical Trials) Regulations 2004 have been law since they came into force on 1 May 2004 and regulate trials in the UK.²⁶ These regulations transpose European Union Directive 2001/20/EC into UK law.³¹ The Regulations offer additional protection for a minor (a person under the age of 16 years) who is being considered for a clinical trial. This additional protection comes at a time when more children are expected to be asked to participate in clinical trials, as part of an international initiative to provide medicines for children that are fully licensed (see 3.4 for more information). The regulations specify that for a minor to participate in a clinical trial, a person with parental responsibility or a legal representative must give informed consent and may withdraw the young person at any time.

Key provisions for the protection of minors within the Medicines for Human Use (Clinical Trials) Regulations 2004 (*Regulation 15 and Part 4 of Schedule 1*) – extract from MHRA adviceⁱⁱ

The Regulations provide additional protection for a minor (a person under the age of 16) who is a candidate for a clinical trial. They require, among other provisions, that:

- an ethics committee considering the trial must receive advice on the relevant field of paediatric care; and
- a person with parental responsibility or a legal representative must give informed consent and may withdraw the young person at any time; and, in relation to the minor himself:
- staff with experience with young persons must inform him/her of the risks and benefits of the trial according to his capacity to understand;
- the investigator must consider his or her explicit wish to refuse to participate or to be withdrawn from the trial at any time;
- the clinical trial relate directly to an illness from which he or she suffers or that can only be carried out on minors; and
- the trial must aim to provide some direct benefit for the group of patients involved.

5.1.4 Assessing the competence of a child to consent

While normally increasing with age, competence is considered not to depend primarily on age, but rather on the ability to understand and weigh up options. It can be influenced by the way information is presented – many children will be competent if information is presented in an appropriate way and they are supported through the decision-making process. The Central Office for Research Ethics Committees (COREC) provides a useful template for designing patient information sheets and seeking assent/consent from children and young people.³³ A child's ability to consent develops as he or she learns to make increasingly complex and serious decisions, which can be experience and/or age-related.

For people to be able to have the capacity to take a particular decision they must be able to:³⁴

- Comprehend and retain information material to the decision, especially the consequences of having or not having any intervention.
- Use and weigh this information in a decision-making process.
- Reach and communicate a decision.

Even if the child is competent, it is still normally good practice to involve the family in the decision-making process. It is particularly desirable to obtain parental consent for younger children or for procedures that carry any risk or discomfort. If the competent child specifically asks for the family not to be involved in the decision-making process and they cannot be persuaded otherwise, their privacy should be respected.

For further information please see 5.2.

ⁱⁱ Extract from MHRA Description of the Medicines for Human Use (Clinical Trials) Regulations 2004.³²

5.1.4.a Children unable to consent to involvement, and parental consent

If the child is deemed incompetent to consent to participate in research, then he or she should normally not participate without the consent of a person with parental responsibility. A person with parental responsibility may legally consent to treatment on an incompetent child's behalf. If the child is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative. If the child does not assent, this should be respected.

Legally, the researcher need only obtain consent from one person with parental responsibility. However, it is good practice and in the best interests of the child to involve others close to the child – for example, a second parent – in the decision-making process. Where opinions are strongly divided and agreement cannot be reached, it would be advisable to exclude the child from the research study unless a treatment option is only available as part of that programme. In such a case, every effort should be made to overcome the disagreement without a decision having to be referred to the courts.

If the parents are themselves under 16 years of age, they will only be able to give valid consent on behalf of their child if they are competent to take the decision in question.

Parents/guardians can consent to research procedures that offer potential benefit to the child. If the research is thought not to offer potential benefit to the child, parents/guardians can still consent provided the risks are sufficiently small to mean that research can be reasonably said not to go against the child's interests.

Guidance on the law regarding parental consent is available from the BMA.⁴ A summary of country-specific differences follows:

England, Wales and Northern Ireland

The Children Act 1989 and The Children Act (Northern Ireland) Order 1995 make provision for parental rights in respect of their child, including the right to give consent to medical treatment.^{35,36} Case law shows that a person with parental responsibility or the court can overrule a competent child's decision to refuse potentially beneficial treatment if it is felt to be in the best interests of the child or young person.

Scotland

The Children (Scotland) Act 1995³⁷ makes provision for cases where a young person aged under 16 is not competent to give legally valid consent. Parental rights enabling parents to carry out parental responsibilities include "safeguarding and promoting the child's health, welfare and development, providing direction and guidance to the child in a manner appropriate to the stage of the child's development and acting as the child's legal representative." Most of these last until the young person is 16 years old or shows competency to make their own decisions. Interestingly, in this Act it is stated that a child of 12 years or more should be presumed to be of sufficient age and maturity to form a view. The parental responsibility to provide guidance continues until the young person is 18. Case law suggests that a parent cannot overrule the decision of a competent child; however this has not yet been added to statute.

The Adults with Incapacity (Scotland) Act 2000³⁸ covers the treatment and welfare of people over the age of 16 who are unable to give consent.

In the absence of case law dealing specifically with research, the principles applying to medical treatment in England, Wales, Scotland and Northern Ireland might reasonably be applied to research.

5.1.4.b Seeking legal advice

Researchers should seek legal advice if in any doubt regarding authority to proceed.

5.1.5 How best to seek consent

The RCPCH provides guidance on how best to seek consent:²

For consent to be freely given researchers must:

- Offer families no financial inducement although expenses should be paid.
- Exert no pressure on families.
- Give them as much time as possible (a few days for a major study, if at all possible) to consider whether to take part in the project.
- Encourage families to discuss the project with – for example – their relatives, primary health carers – or an independent counsellor where available.
- Tell them that they may refuse to take part, or may withdraw at any time even if they have signed a consent form.
- Say that they need not give a reason for withdrawing (although their reason may help the researchers and other children in the study).
- Assure them that the child patient's treatment will not be prejudiced by withdrawal from research.
- Encourage parents/guardians to stay with the child during procedures.
- Respond to families' questions, anxiety or distress throughout the study.

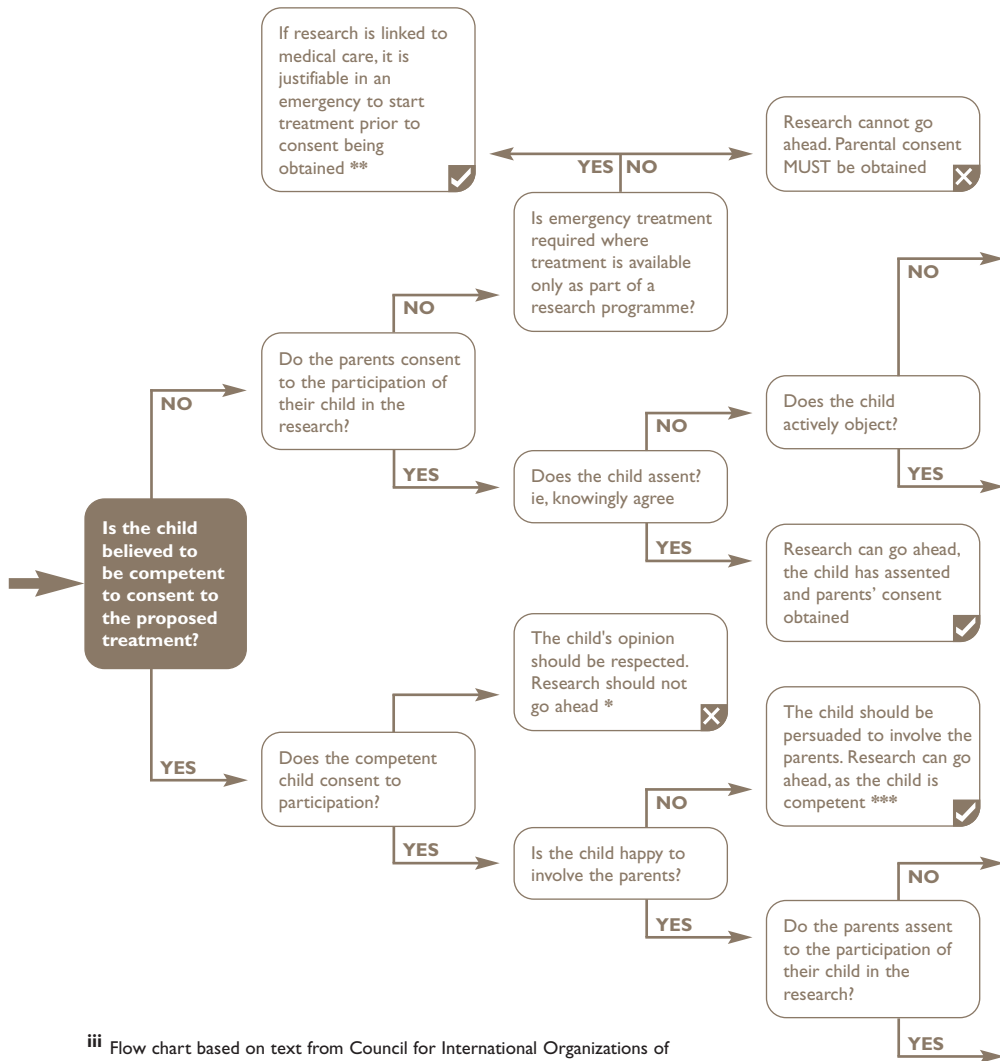
For consent to be informed researchers must discuss with families:

- The purpose of the research.
- Whether the child stands to benefit directly and if so how; the difference between research and treatment.
- The meaning of relevant research terms and any implications of consent (eg, placebo, randomised double-blind trial).
- The nature of each procedure, how often and for how long each may occur.
- The potential benefits and harms (both immediate and long-term).
- The name of a researcher whom they can contact with their enquiries.
- The name of the doctor directly responsible for the child's care.
- How the child can withdraw from the project.

Researchers must also:

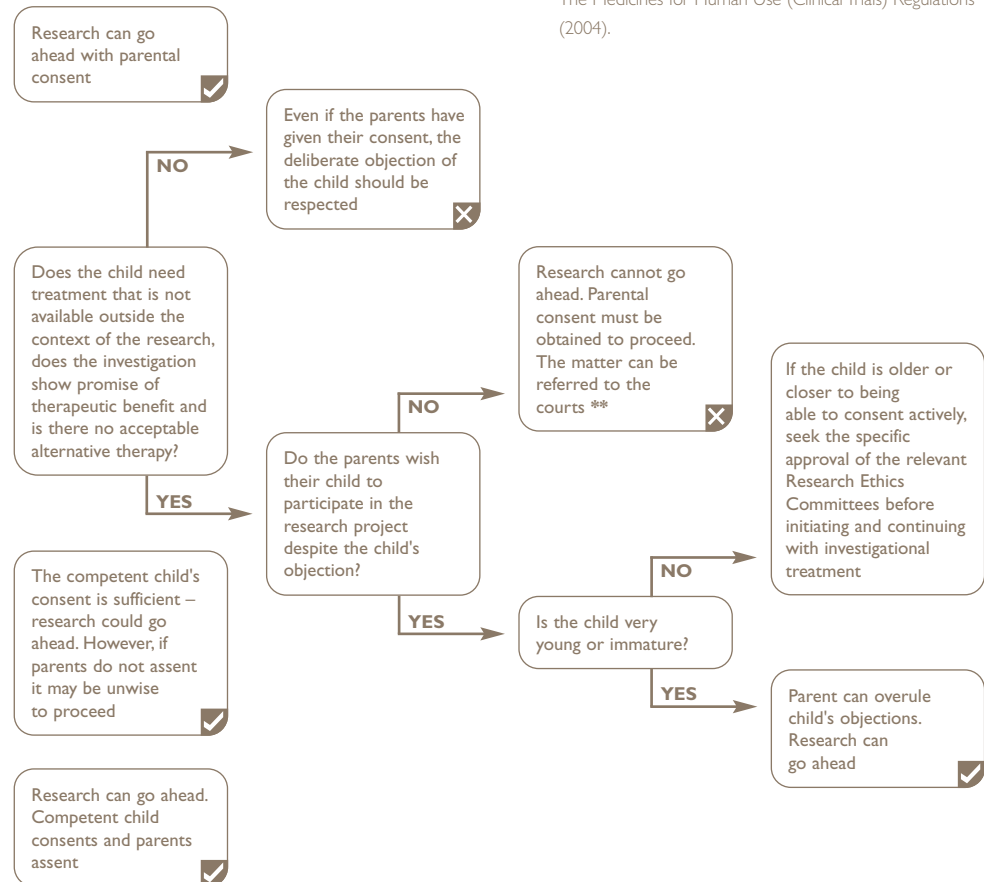
- Willingly explain and answer questions throughout the project.
- Ensure that other staff caring for child subjects know about the research, and can also explain it if necessary.
- Give clearly written patient information leaflets setting out all relevant information for families to keep (guidance on this can be found on the COREC website³³).
- Report the results of research to the families involved wherever possible.

5.1.6 Seeking consent – a summaryⁱⁱⁱ



ⁱⁱⁱ Flow chart based on text from Council for International Organizations of Medical Sciences *International ethical guidelines for biomedical research involving human subjects*.⁵

- ✓ Research can go ahead
- ✗ Research cannot go ahead



- * In England, Wales and Northern Ireland parents may overrule the child's decision if it is felt to be in the best interests of the child.
- ** Where parents refuse to give their consent, the courts can overrule if it is felt to be in the best interests of the child.
- *** The researcher must obtain the permission of the parent/guardian in accordance with local laws or established procedures eg, in the UK participation of a minor in a clinical trial requires parental consent under The Medicines for Human Use (Clinical Trials) Regulations (2004).

Seeking consent is not a single response but a *process*. The child should be provided with information appropriate to his or her increasing ability to make decisions about complex and serious issues. It is helpful for researchers to produce child-friendly information in a form appropriate for the relevant age groups – this could make use of pictures or videos. More than one version may need to be produced if research covers a wide age range, such as eight-18 years. Where the research project lasts a number of years, the child and/or parent/guardian may need to be approached periodically to ensure they still consent to the child's involvement in research. For example, where a parent has consented to follow-up studies throughout the life of the child, the child must be given the opportunity to decide for himself/herself, once competent to do so, whether he or she wishes to continue his or her involvement.

5.2 Confidentiality

Medical professionals have a duty of confidentiality to all patients including children. Legally competent children are entitled to expect that information about themselves will not be provided to a third party, including their parent/guardian, without their consent. However, it is important that wherever possible the parents/guardians are informed, and young people should be encouraged to involve them unless it is not in their best interests to do so. If competent children do not wish to involve their parents/guardians this should be respected. Disclosure can only be justified if there is reasonable cause to suspect that the child is suffering or is likely to suffer significant harm as a result of non-disclosure. Any decision to disclose confidential information to a third party must be relayed to the competent child before disclosure.

To facilitate both the child's healthcare and longer term research, general practitioners (GPs) should be notified of all research on their paediatric patients. The consent form should request consent to inform and update GPs of the child's involvement. If a participant is likely to resist information being provided to parents/guardians and family practitioners because the research is of a sensitive

nature, eg, investigating smoking habits or sexual health, advice should be sought from the Research Ethics Committee that assesses the protocol.

Children who lack competence to consent to participate are nevertheless entitled to confidentiality. The researcher will have had to request the parent/guardian's consent to the child's involvement in research. Any intention to disclose information to anyone else should be discussed with both the parent/guardian and the child, taking into consideration whether disclosure to a third party is necessary in the interests of the child's health. Public health research may require the use of anonymous data without explicit consent – for detailed guidance on this researchers should consult the MRC guidance *Personal information in medical research*.¹¹

Researchers working with children have important responsibilities in relation to child protection. Where researchers have reasonable cause to suspect that a child is suffering or likely to suffer significant harm, they have a clear responsibility to liaise urgently with those responsible for the child's clinical care with a view to making a referral to social services. Again, a decision to disclose information should, wherever possible, be discussed with the child before disclosure, in terms appropriate to the child's capability to understand.

All researchers need to be aware of relevant data protection legislation and the rights of the child (and their parents/guardians in some circumstances) to access their health records. Fuller guidance on confidentiality issues is available from the Department of Health, the British Medical Association and the General Medical Council.^{3,4,39}

5.3 Ethics committee review

The Council of Europe Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research provides guidance regarding the role of the ethics committee in research.⁹ According to this guidance, every research project must be submitted for independent examination of its scientific merit, including assessment of the importance of the aim of research and ethical acceptability to an

ethics committee. An examination of the ethical acceptability is necessary to protect the dignity, rights, safety and wellbeing of the research participant. The assessment should draw on an appropriate range of expertise adequately reflecting professional and lay views, therefore a professional opinion should be sought for any research involving children. The ethics committee must be satisfied that dependent persons and vulnerable groups will not be subjected to undue influence.

Whilst the Council of Europe protocol is a legal instrument, it has not so far been transposed into UK law. However, the Medicines for Human Use (Clinical Trials) Regulations 2004, which transpose Directive 2001/20/EC into UK law, require that an ethics committee considering a trial involving minors must receive advice on the relevant field of paediatric care.^{29,30} A "minor" is defined as a person under the age of 16.

5.4 Children's safety in relation to researchers

Any individual recruited by the MRC to work directly with children will undergo security screening, including criminal records review. This includes nurses, survey interviewers and some individuals involved in a clinically invasive capacity, eg, phlebotomists. The MRC expects its grant-holding institutions to do likewise. Security screening is complementary to other good recruitment practices and not a substitute for them. Staff involved in MRC's recruitment process are responsible for ensuring that standard checks are still made.

5.5 Specific situations

5.5.1 Research involving human material

Please refer to the MRC guidance *Human tissue and biological samples for use in research*.¹²

Further guidance will be issued when the Human Tissue Bill, and equivalent legislation in Scotland, become law.

5.5.2 The use of personal information

Please refer to the MRC guidance *Personal information in medical research*.¹¹

5.5.3 Research involving very young children

A parent/guardian's informed consent is necessary for the involvement of babies in research. When a baby is seriously ill and a decision about treatment is required quickly, the pressure on parents is high and the difficulty of obtaining truly informed consent is recognised. The RCPCH provides detailed guidance relating to research involving babies.⁴⁰

5.5.4 Emergency situations

Under common law, provided that the specific approval of a research ethics committee has been obtained for the project overall, it is ethical to carry out research involving children on occasions of extreme urgency without obtaining prior consent. However, there is a lack of clarity in the law about this if the research does not have the potential to benefit the child in question. If in doubt, it would be advisable to seek legal advice in potentially contentious circumstances.

Research involving children in an emergency situation may be needed when treatment is available only as part of a research programme. Ethically, if the research does not have the potential to produce results of direct benefit to the individual participant, the Council of Europe recommends that it should only be carried out if it has the aim of contributing or improving understanding of the individual's condition so that it could ultimately confer benefit upon the patient or others with the same condition, and that it entails only minimal risk.⁹

Research involving children in emergency situations should be carried out only where research of comparable effectiveness cannot be carried out on persons in non-emergency situations. The parents and child must be informed about the research as

soon as possible afterwards and their consent for future involvement sought. It must be made clear that the child (or parent on behalf of a child not yet competent) can withdraw from the study at any point.

The Council of Europe provide further guidance on research in emergency clinical situations.⁹

Under the Clinical Trial Regulations, consent must be given on behalf of a minor prior to participation in a trial of an investigational medicinal product in all circumstances; there is currently no exception for emergency situations. However, it is possible for someone other than a parent to give consent as a “legal representative”, if the parent is unable to do so. This could be the doctor primarily responsible for the person’s treatment (if not involved in the trial) or, if they are not available, a person nominated by the healthcare provider.⁴¹

5.5.5 Including minority groups – equality in research

As with adults it is important to include minority groups in research involving children to ensure that they as a group receive a share of the potential benefits of research.

Researchers should be sensitive to cultural issues and particularly to participants’ specific concerns and values. For example, whether acceptance of research is necessary from someone in the extended cultural group as well as the immediate family, or whether participants undertake religious fasts that may affect when they can take medicines.

When seeking consent where the child or parent needs an interpreter, an independent interpreter is preferable to a family member.

Where the child has a disability, particular care should be taken to ensure that information is provided in a suitable form. Specialist colleagues may be able to act as

facilitators or advocates where the child has particular needs. Children with specific impairments such as learning difficulties should not be excluded from participating in research, but equally should not be over-researched because of their condition.

5.5.6 Research in developing countries

Please refer to MRC guidance on *Research involving human participants in developing societies*.

6. Summary

Children should be included in medical research only if:

- The relevant knowledge cannot be gained through research with adults.
- It is approved by the appropriate Research Ethics Committee/s.
- Either the participant has given consent where competent, or consent has been given on his or her behalf by a parent or guardian and the participant does not object or appear to object in either words or actions.^{iv}

^{iv} See 5.5.4 for guidance on emergency situations, when this might not be possible.

7. Glossary

The definitions provided here apply as they are used in the above guidelines.

Assent

A child's affirmative agreement to participate. Failure to object should not be construed as assent.

Burden of disease

The impact of disease on the individual and on society due to loss of duration and quality of life. Measures include (i) 'morbidity burden', ie, the prevalence of a condition, the range of its severity and the age distribution of the population suffering from the condition, and (ii) the financial burden to society in meeting the obligation to support the individual; for example, in terms of net public expenditure on health services and on social services.

Child

In the UK, a person under the age of 18. "Young person" is a term often used to describe older children in this age group. The competence of children to consent is discussed in Section 5.

Clinical Trials Regulations

The Medicines for Human Use (Clinical Trials) Regulations apply to research involving investigational medicinal products (see below). In such studies, informed consent is strictly defined as follows and only consent meeting this definition will suffice:

"A person gives informed consent to take part, or that a subject is to take part, in a clinical trial only if his decision –
 (a) is given freely after that person is informed of the nature, significance, implications and risks of the trial; and

(b) either –

- (i) is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or
- (ii) if the person is unable to sign or to mark a document so as to indicate his consent, is given orally in the presence of at least one witness and recorded in writing.”

Confidentiality

The duty of persons to whom personal information has been given not to share the information with any unauthorised person. For more information about what this involves in practice, see 5.2.

Competence

The ability of a person, given the necessary information, to understand the nature and the consequences of the proposed procedure or treatment, and to use that information to make a valid choice in accordance with their own fundamental values. Please refer to 5.1.4.

Consent

The voluntary agreement of an adult or competent child, based on adequate knowledge and understanding of relevant information, to participate in research. For further information please refer to Section 5.

Family

A group of individuals who together form a social structure; a family may or may not include biological relatives.

Harm

That which adversely affects the interests or welfare of an individual. This may be physical harm, discomfort, anxiety, pain, and psychological disturbance or social disadvantage (ostracism).

Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.³¹

Off-label

Term used to describe a medicine used for an indication, dose, or route of administration outside the terms of the product licence.

Parent/guardian

The term "parent/guardian" is used in these guidelines to describe those with legal responsibility for the child. The Children Act 1989, the Children (Scotland) Act 1995 and the Children (Northern Ireland) Order 1995 set out who has parental responsibility in their respective jurisdictions. The Adoption and Children Act 2002 s 11(2) has recently extended the definition of those with legal responsibility for the child to include unmarried fathers who have entered into a legally binding Parental Responsibility Agreement.⁴²

Risk

A potential harm; the characteristics of risk include the probability of its occurrence, as well as its magnitude and duration. For more on assessment and minimising risk see 4.3.

8. Other MRC ethics guidance

The MRC produces a wide range of ethics guidance for researchers, which is available at www.mrc.ac.uk and includes the following:

- MRC interim guidance on ethics of research involving human material derived from the nervous system (June 2003).
- MRC policy on antiretroviral therapy (ART) for people infected with HIV and involved in AIDS research in developing countries – General guidance notes for consideration (2002).
- MRC guidance on reviewing research proposals (2001).
- Ethical conduct of research on the mentally incapacitated (1993) – to be revised following the introduction of English legislation. This guidance is no longer applicable in Scotland, following the introduction of the Adults with Incapacity (Scotland) Act 2000.
- Good research practice (2000).
- Personal information in medical research (2000) – also available as Executive Summary (2000). New guidance on Health and Social Care Act 2001: "Section 60" added – January 2003.
- Human tissue and biological samples for use in research: operational and ethical guidelines (2001).
- Policy and procedure for inquiring into allegations of scientific misconduct (1997).
- Research involving human participants in developing societies: ethical guidelines for MRC-sponsored studies (2004).

- Responsibility in the use of animals in medical research (1993).
- The MRC's terms and conditions for research grants and training awards involving stem cells (2003).
- Cluster randomised trials: Methodological and ethical considerations (2002).
- MRC guidelines for good clinical practice in clinical trials (1998).
- Health Technology Assessment in surgery (2003).

Additional guidance available by post includes:

- Principles in the assessment and conduct of medical research and publicising results (1995).

9. References

1. *The ethical conduct of research on children*. London: Medical Research Council (MRC), 1991.
2. Royal College of Paediatrics and Child Health: Ethics Advisory Committee. 2002. "Guidelines for the ethical conduct of medical research involving children". Reprinted from *Archives of Disease in Childhood* 82 (2): 177-182.
3. Department of Health: Consent guidance webpages. www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Consent/ConsentGeneralInformation/fs/en
4. *Consent, rights and choices in healthcare for children and young people*. London: British Medical Association, 2001.
5. *International ethical guidelines for biomedical research involving human subjects*. Geneva: Council for International Organizations of Medical Sciences, 2002.
6. Declaration of Helsinki: ethical principles for medical research involving human subjects. Amended by the 52nd World Medical Association (WMA) General Assembly. Ferney-Voltaire: WMA, 2000.
7. *International Guidelines for ethical review of epidemiological studies*. Geneva: Council for International Organizations of Medical Sciences, 1991.
8. *MRC guidelines for good clinical practice in clinical trials*. London: MRC, 1998.
9. Additional protocol to the Convention on Human Rights and Biomedicine on Biomedical Research. Strasbourg: Council of Europe, 2004.
10. Declaration of professional ethics. Voorburg: International Statistical Institute, 1985. www.cbs.nl/isi/ethics.htm
11. *Personal information in medical research*. London: MRC, 2000.
12. *Human tissue and biological samples for use in research: operational and ethical guidelines*. London: MRC, 2001.
13. Stiller C., Quinn M., Rowan S. 2004. "Childhood cancer". In: *The health of children and young people*, chapter 13. Office for National Statistics. www.statistics.gov.uk/children/downloads/child_cancer.pdf
14. Smyth R.L., Weindling A.M. 1999. "Research in children: ethical and scientific aspects". *Lancet* 354 (suppl II): 21-24.
15. Campbell H., Surry S.A.M., Royle E.M. 1998. "A review of randomised controlled trials published in *Archives of Disease in Childhood* from 1982-96." *Archives of Disease in Childhood* 79: 192-197.
16. Halliday H.L., Ehrenkranz R.A., Doyle L.W. 2004. "Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants" (Cochrane Review). In: *The Cochrane Library*, Issue 2. Chichester, UK: John Wiley & Sons, Ltd.
17. *Better Medicines for Children: proposed regulatory actions on paediatrics medicinal products*. European Commission (EC) consultation document. Addendum to ref 18. Brussels: EC, 2002. http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/feb/cd_pediatrics_en.pdf
18. National Audit Office Report (HC 255 2002-2003). *Safety, quality, efficacy: regulating medicines in the UK*. London: the Stationery Office, 2003.
19. Smith Robert N. 2000. Meeting report – A European conference on clinical research in children: ethical, scientific and regulatory issues. Section: "Research, the rights of the child and legal considerations in paediatric clinical research". *International Journal of Pharmaceutical Medicine*; reprinted from: *Archives of Disease in Childhood* 16:15-29.
20. Medicines and Healthcare products Regulatory Agency/Department of Health: Strategy on Medicines for Children, July 2004. <http://medicines.mhra.gov.uk/ourwork/licensingmeds/children/paediatricstrategydoc.pdf>
21. *Safer and Better Medicines for Children – Developing the Clinical and Research Base of Paediatric Pharmacology in the United Kingdom*. Royal College of Paediatrics and Child Health Review (commissioned by the MRC, the Department of Health, and the Association of the British Pharmaceutical Industry), May 2004.
22. *Research: the role and responsibilities of doctors*. London: General Medical Council, 2002.
23. *Testing for late onset genetic disorders*. London: British Paediatric Association, 1996.
24. Brocklehurst P. 1997. "Randomised controlled trials in perinatal medicine: 2. Recruitment of a pregnant woman or her newborn child into more than one trial." *British Journal of Obstetrics and Gynaecology* 104 (7):765-7.
25. *Ethical Conduct of Clinical Research Involving Children*. The National Academy of the Sciences USA, 2004.
26. The Medicines for Human Use (Clinical Trials) Regulations. 2004. www.legislation.hms.gov.uk/si/si2004/20041031.htm
27. UN Convention on the Rights of the Child. General Assembly resolution 44/25 of 20 November 1989, entry into force 2 September 1990 in accordance with article 49. www.childrenslawcentre.org/UNCRC_hearing.htm
28. Gillick v West Norfolk and Wisbech. London: House of Lords, Gillick v West Norfolk and Wisbech AHA (1986) AC 112, [1985] 3 WLR 830, [1985] 3 All ER 402, HL
29. Age of Majority (Scotland) Act 1969 s 1.
30. Age of Legal Capacity (Scotland) Act 1991. (c. 50)
31. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. http://europa.eu.int/eur-lex/prl/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf

32. Medicines and Healthcare products Regulatory Agency: Description of the Medicines for Human Use (Clinical Trials) Regulations 2004. http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/ctdregs_shortdesc.pdf
33. Central Office for Research Ethics Committees. www.corec.org.uk
34. *Seeking Consent: Working with children*. Department of Health, 2001. www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4007005&chk=xFifXP
35. Children Act 1989 (c. 41). www.hmsso.gov.uk
36. Children Act (Northern Ireland) Order 1995. www.northernireland-legislation.hmsso.gov.uk
37. Children (Scotland) Act 1995. www.hmsso.gov.uk
38. Adults with incapacity (Scotland) Act 2000. www.scotland-legislation.hmsso.gov.uk
39. *Confidentiality: protecting and providing information*. London: General Medical Council, 2004.
40. *Guidance safeguarding informed parental involvement in clinical research involving newborn babies and infants*. London: Royal College of Paediatrics and Child Health, 1999.
41. Department of Health/MRC: Clinical Trials Toolkit. 2004. www.ct-toolkit.ac.uk
42. The Adoption and Children Act 2002. www.hmsso.gov.uk/acts/acts2002/20020038.htm

