Workshop: 9 December 2011

Children, medicines and clinical trials

Background paper

NB: The opinions expressed in this paper do not necessarily represent the views of the Nuffield Council on Bioethics.

I Summary and scope

1 This paper provides an overview of the ethical challenges that face those seeking to test new medicines for use in children, and the diverse roles and responsibilities of the many organisations and individuals concerned in ensuring that such trials are appropriately facilitated and managed. Particular attention is focused on two areas: how the benefits and risks of research may be balanced in an acceptable manner; and the role of children, parents, clinicians and investigators in determining whether research participation is appropriate for a particular child. While the paper is primarily concerned with clinical trials, it also refers at times to other forms of medical research involving children that do not fall into the definition of 'clinical trials', and which are hence not covered by the same regulatory system.

II Background: the need for clinical trials in children

2 Historically, there have been few paediatric clinical trials of medicines that are prescribed to children. Children (from neonates to adolescents) are perceived as constituting a vulnerable population in need of special protection to ensure that they are not exploited in research, and these ethical concerns are discussed at length later in this paper (see sections V and VI). However, practical and commercial concerns have also

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1 Throughout this paper, the terms 'children', 'minors', and 'the paediatric population' will be used interchangeably to refer to those under the legal age of majority (usually 18), reflecting the approach taken in EU instruments and other guidance. However, the Clinical Trial Regulations specifically define those of 16 and above as 'adults' and hence those provisions in the UK Regulations that apply to 'minors' do not apply to young people aged 16 and 17. The final section of this paper discusses some of the ethical and legal complexities that arise in connection with children under 16 who have the capacity to understand what is involved in trial participation.

2 Defined in the Clinical Trials Regulations as: "any investigation in human subjects, other than a non-interventional trial, intended (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products, (b) to identify any adverse reactions to one or more such products, or (c) to study absorption, distribution, metabolism and excretion of one or more such products, with the object of ascertaining the safety or efficacy of those products."
played a part in limiting the number of trials that have taken place involving children. Aspects of clinical trials, such as discomfort, pain, fear, and separation from familiar surroundings, may be much harder for children to cope with than for adults, and additional concerns may arise as to the potential effects of the medicine being tested on growing or developing organs, and the impact of what would be routine research procedures in adults such as the taking of blood tests. The pharmaceutical industry has in the past shown reluctance to study medicines in children, arguing that there are limited financial returns from what is perceived to be a comparatively small market, that it is difficult to organise clinical trials in children, and that there are concerns over possible toxicity.

As a result, however, the data regarding dosage-requirements, efficacy and safety of particular medicines in children are often very limited. In many cases, children are prescribed medicines that are either not licensed for use at all, or are being used 'off-label', that is outside the terms of the product licence (for example where the medicine has been given market authorisation for a different clinical indication, age group, dose or route from that prescribed). Two studies in 1999 (in the UK) and 2000 (across a number of European countries) found that 90 per cent of newborns in intensive care and 46 per cent of children in general paediatric wards received either unlicensed or off-label prescriptions. The fact that a medicine is unlicensed or prescribed off-label does not, of course, mean that no information is available as to its possible effects: in the UK for example, the British National Formulary for Children (BNFC) provides prescribers with evidence-based guidance and expert opinion, and the General Medical Council advises that it may not be necessary for doctors explicitly to draw attention to this issue when seeking consent for treatment if current practice supports the use of off-label prescribing. However, public awareness of the off-label use of medicines for children appears to be low with one study in Northern Ireland finding that 86 per cent of people were not aware of the practice. A German study reported that nine per cent of the parents of chronically ill children, and 20 per cent of those of healthy children, would refuse treatment with an off-label medicine.

A common approach for using medicines off-label for children has been to use data from clinical trials involving adults and to adjust the dose according to the child’s weight.

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3 The total blood volume in a 0.5kg premature neonate, for example, may be as low as 45 ml: see Ward RM and Kern SE (2009): Clinical trials in neonates: a therapeutic imperative, Clinical Pharmacology & Therapeutics 86(6): 585–7. More generally, blood tests may of course be distressing to children.
7 General Medical Council (2008) Good Practice in Prescribing Medicines (London: General Medical Council), paragraph 22.
Although doctors have pursued this approach for many years, studies have indicated that off-label or unlicensed prescription has nevertheless been associated with adverse reactions and increased risk of mortality in some cases. For example, the use of the antibiotic chloramphenicol in newborns and premature babies was ceased following the identification of ‘grey baby syndrome’,\(^{11}\) the symptoms of which include low blood pressure, and blue colouring of lips, nail beds and skin, and which can often lead to death. Impaired metabolism of chloramphenicol in the paediatric population was identified as the cause.

5 The principal problem with transferring data from adults to children is that children are not simply ‘small adults’. In addition to their smaller weight and the dynamics of growth and maturation of organs, changes in body proportion and other developmental changes must also be considered, as these factors affect how pharmaceuticals are absorbed, distributed, metabolised and excreted. As a result, dosages extrapolated from adult data (or from data from older children to newborns) may potentially be either dangerously high, or too low to be effective.\(^{12}\) Practical problems may also arise with the administration of medicines to children where trials have only taken place in adults: for example, a young child may not be able to take a medicine if it is difficult to swallow and there is no syrup formulation available.\(^{13}\) More fundamental problems arise in connection with illnesses that arise only in childhood, where no data at all may be available from adult trials.

6 Examples of ineffective and harmful interventions being used in children before they have been assessed by clinical trial have led to an increased interest in conducting paediatric clinical trials.\(^{14}\) Indeed, some have argued that there is a “moral imperative” to study medicines in children in order to provide them with equality of access to both current and future medicine.\(^{15}\) One paediatric pharmacologist has described clinical care that involves the use of a medicine in the absence of data indicating that it will probably achieve its therapeutic goal, as the equivalent of "conducting thousands of studies with an N=1" and concluded: "Our most vulnerable pediatric population deserves better care than this."\(^{16}\)

### III Roles and responsibilities

7 It was suggested above (see paragraph 2) that the factors hindering research on the effect of medicines on children include: ethical concerns as to the proper protection of children; practical concerns over the appropriate management and adaptation of trials to

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meet children's needs; and commercial influences affecting the decisions and priorities of pharmaceutical companies. These very different factors demonstrate how many organisations and individuals potentially have a role to play in determining what research takes place and who takes part in it.17

8 Governments and other regulatory bodies set down the regulatory environment that influences the policies, priorities and decisions of pharmaceutical companies with respect to paediatric clinical trials. Similarly they set down over-arching standards with the aim of ensuring that the welfare of any child involved in clinical trials is adequately protected. Professional associations may set down more detailed, and sometimes more stringent, requirements based on their own professional norms and ethics. At the level of individual research proposals, companies, investigators and research ethics committees scrutinise both the scientific validity of the proposed research, and whether the potential risks and benefits are appropriately balanced. The role of scrutiny at this level is to determine whether it is appropriate for a particular research project to go ahead: whether an invitation to participate would constitute a 'reasonable choice' for children and their parents. Finally, there is a separate decision-making process at the level of the particular child: children, parents, clinicians treating the child, and the investigator concerned all have a role to play in determining whether participation would be the right choice for this child in his or her own particular circumstances.

9 The rest of this paper covers three of these areas. First it considers briefly what regulatory action has been taken both within Europe and in the United States to incentivise or even mandate pharmaceutical companies to carry out more clinical trials in children. Second, it considers the approaches taken by a range of regulatory and professional bodies in determining how children should be protected in research, with particular reference to how 'risk' and 'benefit' should be defined and balanced. Third, it considers the question of decision-making at the level of the individual child participant, considering the roles of the various different parties involved and how any disagreements should be managed.

IV Promoting clinical trials in children

10 As a result of the growing pressure for better data on medicines used in children, there have been a number of changes in legislation that have either set requirements to conduct paediatric clinical trials or provided incentives to encourage their practice.

11 In the European Union, the Regulation on Paediatric Medicines, which came into force in January 2007, aims to increase both the availability of medicines specifically adapted and licensed for paediatric use, and the information available to prescribers.18 For companies wanting to market a new medicine or to change an existing marketing authorisation, there is now a requirement that data from paediatric studies (carried out in


18 Council Regulation (EC) 1901/2006 on medicinal products for paediatric use, as amended by Council Regulation (EC) 1902/2006. Note that some of the specific provisions only came into force a further 18 months after the main Regulation.
In accordance with a pre-agreed 'paediatric investigation plan' or PIP) must be included in the application. Age-appropriate formulations of medicines must also be developed. (These requirements may be waived where appropriate: for example where the disease or condition for which the medicine is being developed only arises in adults, or where use of the medicine is likely to be ineffective or unsafe in children.) The Regulation further requires the publication of information on paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and in 2009, the European Commission published guidance relating to this information.19

In addition to these requirements, the Regulation also provides financial incentives to pharmaceutical companies in order to make it easier for prescribers to obtain paediatric data about both new and existing medicines. Where information from the PIP is included in a new medicine's 'summary of product characteristics', then the developer of the drug is granted a six months' extension of the supplementary protection certificate (effectively extending the benefit of the patent by six months). For 'orphan' medicinal products, this incentive takes the form of an extra two years' market exclusivity in addition to the ten years' market exclusivity that is already granted on authorisation of an orphan medicine. For off-patent products, a new category of marketing authorisation called the 'paediatric use marketing authorisation' (PUMA) has been developed with the aim of encouraging the development of new paediatric formulations of older products. A PUMA, if granted, will provide ten years' market protection.20

In the USA, similar approaches have been in place for some time. Since 1997 the government has provided financial incentives to the pharmaceutical industry to conduct paediatric clinical trials through legislation that offers an additional six-month market exclusivity to patents for all paediatric formulations of products that have been trialled in children.21 More recently, the Paediatric Research Equity Act (2003) gave the Food and Drug Administration (FDA) the authority to require paediatric studies of a new medicine if the FDA determines either that the medicine is likely to be used in a substantial number of children, or that it would provide a meaningful benefit for children over existing treatments.22 By 2009, these combined 'carrot and stick' approaches had resulted in over 300 changes in labelling on medicines used for children.23 While the European changes are much more recent, there is some optimism that they will have a significant impact in improving care for children.24

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19 European Commission (2009) Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006 [2009] OJ C28/1.
24 See, for example, Vassai G (2009) Will children with cancer benefit from the new European Paediatric Medicines Regulation? European Journal of Cancer 45(9): 1535–46,
Regulating to protect children taking part in trials

In addition to taking action both to require and to incentivise pharmaceutical companies to increase the amount of information available as to the effects of medicines on children, governments and other regulatory bodies also have a role in setting standards to ensure that children who are invited to take part in such trials are appropriately protected. Such standards are set at a high level (for example through legislative requirements, professional standards and international declarations and conventions), and are then interpreted and implemented at local level through the individual scrutiny of particular research proposals. Within the EU, Article 4 of the Clinical Trials Directive sets out minimum standards for paediatric clinical trials: these have been implemented in the UK through the Clinical Trials Regulations 2004. Professional guidance within the UK on paediatric research more generally includes guidance from the General Medical Council (GMC), the Medical Research Council (MRC) and the Royal College of Paediatrics and Child Health (RCPCH). Advice on the interpretation of the Directive has been issued by an EU ad hoc group, and international statements on the standards to be met in all forms of research include the World Medical Association’s Declaration of Helsinki, the Council of Europe’s Convention on Human Rights and Biomedicine (known as the Oviedo Convention) and its Additional Protocol, and the International Ethical Guidelines for Biomedical Research involving Human Subjects published by the Council for International Organizations of Medical Sciences (CIOMS) in association with the World Health Organization. Individual research proposals are scrutinised at local level in the UK by Research Ethics Committees.

The Clinical Trials Directive makes general provision for all clinical trials in the EU, and includes specific provision for clinical trials in minors, setting out both overarching requirements to protect minors, and procedural safeguards to ensure that such requirements are considered on a case-by-case basis for each proposed trial. Article 4

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25 Directive 2001/20/EC 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.


30 European Commission (2008) Ethical considerations for clinical trials on medicinal products conducted with the paediatric population.


of the Directive specifies that trials involving minors may be undertaken only if the consent of the parents or a legal representative has been obtained, where the consent "must represent the minor's presumed will". In addition, the minor must receive information, appropriate to their ability to understand, from staff with paediatric experience regarding the trial, its risks and its benefits. The explicit wish of a minor, who is capable of forming an opinion and assessing this information, to refuse participation or to be withdrawn from the trial must be "considered" by the investigator, and no incentives or financial inducements are to be given except compensation. The trial must be "designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage" and "some direct benefit for the group of patients [must be] obtained". Additionally, the Directive requires that a clinical trial may be conducted only when it is essential to validate hypotheses generated from adult clinical trials or other research methods, and when it is of direct relevance to a clinical condition in the child subject or the research is of the nature that it can only be conducted in minors. The research ethics committee (REC) scrutinising the research protocol must either include direct paediatric expertise or have taken the advice of those in the field of paediatrics.

16 The Clinical Trials Regulations 2004 transpose the Clinical Trials Directive into UK law, albeit with some subtle but significant differences of language and emphasis (discussed below). Among both the various sets of professional guidance relevant to those wishing to carry out paediatric trials in the UK, and the key international ethical codes and conventions in this area, a number of differing stances on the ethical involvement of children in research may similarly be discerned, in particular with regard to risks and benefits, and the role of the minor concerned in making the decision about participating in, or withdrawing from, a research project. The rest of this section concerns the differences, and the associated ethical arguments, between these various forms of guidance with respect to risks and benefits, while the final section of this paper will return to the question of the proper role of the minor in deciding whether or not to participate in a trial.

**Balancing risks and benefits**

17 The question of how risks and benefits may legitimately be balanced, and indeed how they are to be defined, is central in determining the ethical acceptability of a particular research project. Yet, significant differences in approach are found between relevant international ethical declarations, the legislation governing clinical trials in the EU, UK and United States, and various sets of professional guidelines applicable to research in the UK. Different challenges also arise in connection with research projects that are quite distinct from a child's medical care (where there is clearly no expectation of immediate personal benefit), and research such as a clinical trial of a new medicine where there is usually both potential for the child participant to receive direct benefit from the new medicine, and also for benefit to others in the future.

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34 Both the Directive and the UK Regulations use the term 'obtained' in connection with 'benefit', despite the inevitable lack of certainty as to the outcome inherent in any trial.
Until relatively recently, these two categories of medical research were widely described as 'non-therapeutic', or as 'therapeutic' (or 'clinical') research. However, this terminology has become less popular, not least because of fears that references to 'therapeutic research' could add to existing (and perhaps inevitable) confusion between the aim of research (defined as an attempt to derive generalisable new knowledge) and the aims of any treatment which the child may be receiving within the research protocol for their own medical condition. The terms 'therapeutic' and 'non-therapeutic' research have therefore mainly been replaced in regulations and codes of practice with references to research that may, or may not, offer the possibility of benefit to a particular child. It has been suggested that it would add further clarity to distinguish, within any particular research protocol, those procedures that are potentially beneficial (such as the administration of a new medicine) and those procedures that are purely undertaken for research processes (such as blood tests or other forms of monitoring that would not otherwise be undertaken for therapeutic purposes). Although the primary aim of research may indeed be to attempt to derive generalisable new knowledge, it is nonetheless very clear that many parents (particularly those of severely ill children) see access to new, as-yet unlicensed medicines as offering their child their only hope of medical benefit. In such cases it will be particularly important to distinguish between what is being undertaken that may be of clinical benefit to the child, and those procedures that are additionally taking place in order to meet research objectives.

The concept of ‘minimal risk’ is used in a number of international declarations, and also in the regulations governing clinical trials in the United States, as a threshold for determining whether a research project that has no likelihood of benefiting the minor participant is ethically acceptable. Such an approach recognises that it is difficult to ‘balance’ risk to one child with benefit to another, and hence sets a maximum threshold of acceptable risk in order to protect the child subject. Thus the 2008 version of the Declaration of Helsinki permits such research only where it entails “minimal risk and minimal burden” (along with additional protections). The Additional Protocol to the Oviedo Convention similarly requires that research that does not have the potential to produce results of direct benefit to the health of the research participant must entail “only minimal risk and minimal burden for the individual concerned”. In the United States, regulations governing paediatric research interventions distinguish between research

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35 See, for example, the 1996 version of the Declaration of Helsinki which makes this distinction: http://www.jcto.co.uk/Documents/Training/Declaration_of_Helsinki_1996_version.pdf.
39 See, for example, the efforts to which parents of severely-ill children may go to obtain a new (investigative) medicine outside a clinical trial if for whatever reason the child is not eligible to participate in the trial itself: Pinxten W, Nys H and Dierickx (2010) Access to investigational medicinal products for minors in Europe: ethical and regulatory issues in negotiating children’s access to investigational medicines Journal of Medical Ethics 36: 791–4.
40 World Medical Association (2008) Declaration of Helsinki, Article 27 (applying to all legally ‘incompetent’ subjects, hence making no distinction between minors and adults with reduced capacity).
41 Council of Europe (2005) Additional protocol to the Convention on human rights and biomedicine, concerning biomedical research, Article 15(2) (again making no distinction between minors and incapacitated adults).
interventions that offer a “prospect of direct benefit” to the child participant, and those that do not. Where no prospect of direct benefit exists, research may only go ahead if it poses “minimal risk” or risks that are no greater than a “minor increase over minimal”.42

Where research does offer prospect of direct benefit, then the US Regulations permit risks that are “justified by the anticipated benefits to the subjects”, thus potentially allowing for high risks (for example of as-yet unknown side-effects) where the potential for benefit for the subject is also thought to be high.43 The approach taken in Europe by the EU Directive, however, distinguishes much less clearly between research that may offer prospect of direct benefit to participants, and that which does not. As described above, the EU Directive permits only research that will obtain "some direct benefit for the group of patients". While the Directive itself does not define specifically what is meant by the ‘group’ of minor patients concerned, the EU Commission's ad hoc group that developed implementing guidelines for the Directive defines 'group' as "children affected by the same disease, or a disease which shares similar features and for which the medicinal product could be of benefit".44 Thus, on this interpretation, the Directive does allow for research that is unlikely to benefit the children participating, as long as it aims to benefit other children with the same or similar condition in the future. However, in contrast to the Declaration of Helsinki and the Oviedo Convention, the Directive does not itself specify a threshold of permitted risk for child subjects45: rather it requires that the trial be designed to “minimise pain, discomfort, fear and any other foreseeable risk” and stipulates that “both the risk threshold and the degree of distress” should be defined and constantly monitored. The Directive thus appears to leave the definition of acceptable risk either to national governments, or to local scrutiny of specific research proposals. It also makes no distinction as to risk between trial participants who may themselves be likely to benefit from the research, and those who do not.

In the United Kingdom, the Clinical Trial Regulations have interpreted 'group' much more narrowly, requiring that "some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial" [emphasis added].46 The UK Regulations thus only allow research that aims to benefit at least some of the minors actually participating in the trial. It should be reiterated here that the EU Directive and the UK Clinical Trials Regulations are applicable only to clinical trials of new medicinal products, and do not aim to provide a governance framework for other forms of medical research on children. Nevertheless, circumstances do arise in which it might be thought ethically appropriate to involve children in clinical trials, and yet where the requirement that those participating "obtain" direct benefit could be hard to meet. These include, at one end of the spectrum, vaccine trials on healthy children where risks are assessed as very low.

44 European Commission (2008) Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, paragraph 12.
45 Article 2 of the Directive requires for all trials that: "the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients".
but chance of direct benefit is similarly low, and at the other, Phase 1 trials on children suffering from rare childhood diseases where no other way of carrying out the research is possible and the very uncertain possibility of benefit to the child is thought to be the child's 'only hope', despite potentially very severe risks.\(^{47}\)

22 Guidance on research in general from a number of different professional and regulatory bodies within the UK clearly envisages circumstances in which it would be appropriate to involve children in research that is unlikely to benefit them personally. The RCPCH comments that "a research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal";\(^{48}\) the GMC states that children can be involved in research that "does not go against their best interests or involves only minimal or low risk of harm";\(^{49}\) and the MRC specifies that "the researcher must be satisfied that the research is not contrary to the child participant's interests".\(^{50}\) These approaches are not, however, universally endorsed: it has, for example, been argued that any form of research that involves "having unnecessary pain inflicted upon one" is counter to one's well-being, and that hence \textit{any} such research carried out on individuals who are unable to consent for themselves potentially breaches the overarching requirement in the Declaration of Helsinki that "the well-being of the individual research subject must take precedence over all other interests", however minimal the risk or discomfort may be.\(^{51}\)

23 While most regulatory systems, international statements and professional guidelines do allow for the possibility of children incurring some degree of risk without benefit to themselves in the research context, a number of different approaches are taken to describing or defining that risk. As noted above, many limit such risks either to 'minimal' or to a 'minor increase over minimal', while the EU Directive, and also the UK Regulations,\(^{52}\) make reference simply to 'minimising' risks. The recommendations of the EU \textit{ad hoc} group on the implementation of the Directive, however, do use the language of 'minimal risk' and 'minor increase over minimal risk', suggesting that the latter is acceptable where there is benefit either to the individual or to the group, and where the benefit to risk balance is "at least as favourable as that of available alternative approaches".\(^{53}\) "Greater than minor increase over minimal risk", on the other hand, is only permitted where there is benefit for the individual concerned, and that benefit "is especially favourable in relation to available alternative approaches for the individual's condition.\(^{54}\)


\(^{48}\) Royal College of Paediatrics and Child Health: Ethics Advisory Committee (2000) Guidelines for the ethical conduct of medical research involving children \textit{Archives of Disease in Childhood} 82:177–82.

\(^{49}\) General Medical Council (2007) 0-18: guidance for all doctors, paragraph 37(a).

\(^{50}\) Medical Research Council (2004/2007) MRC ethics guide: medical research involving children, paragraph 4.3.


\(^{52}\) The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended, Schedule 1, Part 4, paragraph 14.

\(^{53}\) European Commission (2008) \textit{Ethical considerations for clinical trials on medicinal products conducted with the paediatric population}, paragraph 12.

\(^{54}\) \textit{ibid.}
The circumstances in which 'minor increase over minimal risk' is permitted vary between jurisdictions and conventions. The US regulations permit such risk where the research does not offer participants the prospect of direct benefit but where "the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition, which is of vital importance for the understanding or amelioration of the subjects' disorder or condition". This approach has been criticised on the basis that it may potentially allow greater 'net risk' (i.e. risk that is not justified by the possible benefits) in circumstances where the research does not offer prospect of direct benefit. It is therefore argued that a minor increase in 'net risk' should also be permitted in cases where direct benefit to the child participant is expected. In contrast to the current US approach, the EU ad hoc group guidance does not distinguish between benefit to the individual and benefit to the wider group (such as children suffering from the same disease): this approach has equally been criticised on the basis that it is hard to see what the associated requirement that the benefit to risk balance is "at least as favourable as that of available alternative approaches" can mean in the context of group, as opposed to individual, benefit. Concern has been expressed that this lack of clarity as to the circumstances in which research involving 'minor increase over minimal risk' is lawful within the EU may lead to the 'shopping' of trials to those EU countries that have adopted a less stringent approach.

A final issue arises in connection with how these various thresholds of acceptable risk are to be defined and understood - and indeed the extent to which researchers and ethics committees interpret them in very different ways, leading to conflicting views on the ethical acceptability of particular research protocols, and even of routine procedures used in multiple research projects such as blood sampling and various forms of scanning. The US Regulations define risk as minimal where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life" or "during the performance of routine physical or psychological examinations or tests". The first of these definitions (the 'daily life' definition) has been strongly criticised on the basis that it is impossible to identify and describe the risks encountered by a normal healthy person: "the risks encountered by the typical person are no more familiar to us than anything about the typical person". It has therefore been argued in the United States that only the second part of the current US definition should be used, and that regulatory bodies should take responsibility for producing, and regularly updating, guidance on how routine medical procedures used in research should be categorised.

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56 Wendler D (2008) Is it possible to protect pediatric research subjects without blocking appropriate research? *Journal of Paediatrics* 152: 467–70: an acceptable increase in 'net risk' could, for example, be a new treatment whose risk/benefit balance is very slightly worse than that of the standard treatment, where the new treatment is much cheaper and hence other healthcare users may benefit from the cost savings.
58 ibid.
60 Resknik DB (2005) Eliminating the daily life risk standard from the definition of minimal risk, *Journal of Medical Ethics* 31: 35–8, at 37.
61 ibid.
26 Such an approach would be very close to that used by CIOMS/WHO whose guidance avoids the use of the term 'minimal' in favour of specifying that "the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them." In the EU, guidance on what procedures might constitute 'minimal' risk, 'minor increase over minimal risk' and 'greater than minor increase over minimal risk' is provided in an Annex to the EU ad hoc group guidance.

VI Deciding whether to participate in a particular trial

Who decides?

27 Once a particular clinical trial has been authorised, a further layer of decision-making comes into play, in which doctors, researchers, parents and children are potentially all involved in deciding whether any particular child should be enrolled in the trial. Under the common law in England and Wales, young people aged 16 and above are presumed to have the capacity to give or withhold consent themselves in connection with proposed medical treatment (although their parents may retain the right to provide a legally-valid consent on their behalf up to the age of 18). Although case-law has not addressed whether this presumption of capacity should also apply with relation to research in general, the Clinical Trials Regulations specifically define a minor as being under the age of 16. Young people aged 16 and 17 in the UK are therefore entitled to give, or withhold, consent for themselves if invited to participate in a clinical trial. This emphasis on the autonomy of 16 and 17 year olds contrasts with the position taken at EU level: EU Regulation 1901/2006 defines the 'paediatric population' as encompassing those aged under 18, and the recommendations of the EU ad hoc group on the implementation of the Directive states that 'minors' should ordinarily be understood as those under 18, with the exception of where national legislation specifies an earlier age of majority. The EU Directive is itself silent on how 'minors' should be defined.

28 In the UK, children under 16 who are deemed to be 'Gillick competent' - that is, those who are judged to have "sufficient understanding and intelligence to enable them to understand fully what is involved in a proposed intervention" - will also be judged to have the capacity to consent to that particular intervention in the context of their own

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64 The term 'parents' is used here to refer to anyone with parental responsibility for a child.

65 European Commission (2008) Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, paragraphs 5.2 and 5.4
treatment. However, there is no equivalent case-law on the involvement of children in research, and views differ as to whether it would be appropriate to apply the concept of Gillick competence to the involvement of older children in research in general. As far as clinical trials are concerned, however, the law is clear: the UK Regulations require written "informed consent" from a person with parental responsibility for the minor before the minor may participate in the trial. Moreover, minors do not have any legal right of veto: the explicit wish of "a minor who is capable of forming an opinion and assessing the information" to refuse participation or withdraw from a trial must only be "considered" by the investigator.

**How should minors be involved in decision-making?**

While the law in the UK is clear that children under the age of 16 have the legal right neither to veto their own involvement in a clinical trial, nor to consent to participation without the formal consent of a parent, this does not, of course, mean that they are therefore not involved in deciding whether they should be enrolled in a clinical trial. The abilities of even quite young children to participate in decisions about both medical treatment and research are increasingly recognised, and the importance of obtaining the ‘assent’ or acquiescence of the child before proceeding with research is widely emphasised in professional guidance. While the EU Directive does not use the term ‘assent’, it specifies that the parent’s consent “must represent the minor’s presumed will”, and the EU ad hoc group guidance on the Directive emphasises that investigators should actively seek assent from child participants. Indeed, the ad hoc group guidance suggests that children as young as three may have “the emergent capacity to agree”, and that from this age up some form of assent should ordinarily be sought.

In order for such assent to be meaningful, information about the trial, tailored to the needs and abilities of the child, clearly needs to be available, and the UK Regulations follow the EU Directive closely in requiring that before research can go ahead "the minor has received information according to his capacity of understanding, from staff with experience with minors, regarding the trial, its risks and its benefits". The requirement that such information is provided by specialist staff emphasises the important role

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68 The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended, Schedule 1, Part 4, paragraphs 4 and 7, echoing Article 4(c) of EU Directive 2001 20 EC.
70 See, for example, Royal College of Paediatrics and Child Health: Ethics Advisory Committee (2000) *Guidelines for the ethical conduct of medical research involving children* *Archives of Disease in Childhood* 82: 177–82.
potentially played by doctors and researchers, as well as parents, in maximising a child's ability to participate meaningfully in the decision-making process.\footnote{See, for example, the work of Priscilla Alderson who argues that healthcare teams may have to “test and stretch their own abilities to inform, and involve, and thereby increase the competence of their patients”: Alderson P (2007) Competent children? Minors’ consent to health care treatment and research \textit{Social Science \\& Medicine} 65: 2272–93.}

31 While the emphasis in the Directive and the UK Regulations on the importance of involving children in decisions is very much in line with current good practice and professional guidance, the fact that the law in the UK applies a single cut-off point of 16 years when determining legal capacity to consent to involvement in a clinical trial, regardless of the abilities of younger children, is more controversial. Difficulties may particularly arise in two circumstances: where a child wishes to participate in research \textit{without} the consent of his or her parents (this may arise for example in research related to sexual health\footnote{Most commentary on such research, however, appears to relate to research governed by the common law, rather than clinical trials covered by the Clinical Trials Directive and UK Regulations: see, for example, Hunter D and Pierscionek BK (2007) Children, Gillick competency and consent for involvement in research \textit{Journal of Medical Ethics} 33: 659–62.}), and where a child does not wish to participate, despite his or her parents' consent. The approach taken in both the Directive and the UK Regulations, that a minor’s wish to refuse should only be “considered” contrasts both with standard professional practice and international conventions. The EU \textit{ad hoc} group, for example, states that if a minor wished to withdraw from a trial “the child’s should be respected”;\footnote{European Commission (2008) \textit{Ethical considerations for clinical trials on medicinal products conducted with the paediatric population}, paragraph 7.} the CIOMS guidance similarly states that “a child’s refusal to participate or continue in the research will be respected”.\footnote{CIOMS (2002) \textit{International ethical guidelines for biomedical research involving human subjects}, available at: http://www.cioms.ch/publications/layout_guide2002.pdf, Guideline 14.} Guidance issued by the MRC describes as a “key ethical principle” the requirement that “a child’s refusal to participate or continue in research should always be respected”.\footnote{Medical Research Council (2004) \textit{MRC ethics guide: medical research involving children}, p6.}

32 Such statements of principle do not appear to rest on any requirement that the child should have the capacity to understand fully what is involved in the trial: they therefore appear to apply not only to older children who may be Gillick competent, but also to much younger children who are able to express a preference even if their understanding of what is at stake is relatively limited. Similarly, provisions in the Declaration of Helsinki and in the Additional Protocol to the Oviedo Convention forbidding research involvement if the potential participant "objects" apply generally to “incompetent” persons or “persons not able to consent”: no distinction is made between adults and minors, and hence no distinction is made between minors who do or do not have the capacity to understand the particular research project. The idea that even very young children should effectively have a veto on research involvement has, however, been criticised for failing to give proper emphasis to the rights and responsibilities of parents, and potentially of thereby delaying the development of vital childhood drugs.\footnote{John T, Home T, Savulescu J, Stein A and Pollard AJ (2008) Children’s consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research? \textit{Archives of Disease in Childhood} 93: 379–83.}
The recognition, on the other hand, that older children may well have the cognitive abilities to understand what is at stake in a clinical trial raises the fundamental question of quite what it is that makes (all) children a ‘vulnerable population’ in need of protection. Research carried out with children between the age of 8-12 with attention deficit/hyperactivity disorder (ADHD), for example, demonstrated significant capacity to understand the nature of the research project, what was involved (for example the function of informed consent and the rules on confidentiality), and the nature of their own role in the research (“I thought you were supposed to be learning from me!” in response to information from the interviewer). Such understanding in adults would be taken as clear evidence that the adult had the capacity to make their own decisions about participation in the research. It has therefore been suggested that it is helpful to separate out task specific capacities (for example to understand what procedures are involved in a trial) from the wider competence and maturity necessary to make a decision for oneself. Thus it is argued that “children present a unique category of ill people, whose capacities, competence and autonomy must be considered using a development perspective.” The GMC similarly offers reasons to justify children being treated as a vulnerable group, regardless of their individual intellectual capacities, commenting that children “may be vulnerable because they cannot always recognise their best interests, express their needs or defend their rights.”

This issue of ‘best interests’ is discussed further in the following section of this paper in the context of how parents should make decisions about their child’s research involvement. However, in line with the GMC statement that children may not always recognise their own ‘best interests’, concerns have been expressed that permitting Gillick competent children to make their own research decisions before the age of 16 “might expose children to harm”: it is argued that, unlike medical treatment, research is not designed primarily to benefit the child, and it is right to protect them from making potentially harmful decisions, in the same way that it is right to prevent them from smoking, drinking or gambling before the legal age of majority. The use of comparisons to activities harmful to health, such as smoking and drinking, however, appears to ignore the additional protective layer of ethical and scientific scrutiny: as discussed in Part V of this paper above, the role of such scrutiny should be to ensure that any invitation to participate in a research project represents a reasonable choice for the children concerned.

As the above discussion demonstrates, the proper role of children under the age of 16 in giving or withholding consent to research participation is the subject of considerable academic disagreement, despite the widespread consensus of the importance of ‘appropriate’ involvement. Indeed, the fact that in practice (if not in law for clinical trials within the UK), a child effectively has a veto over research suggests that the difference

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80 ibid, at S36.  
81 General Medical Council (2010) Good practice in research and Consent to research; and General Medical Council (2007) 0-18 years: guidance for all doctors, paragraph 36.  
between ‘assent’ and ‘consent’ may be less clear-cut than generally understood. \textsuperscript{83} However, recent empirical research in Canada suggests that, in practice, most researchers in fact operate a ‘family decision-making model’ where researchers and clinicians work with the whole family to maximise understanding and come to an agreed decision. \textsuperscript{84} The authors argue that a change in legal requirements to reflect such a model would encourage more thoughtful and ethical research practice.

**How should parents decide?**

36 Even where children are actively involved in deciding whether or not to participate in a clinical trial, parents still retain ultimate responsibility for providing a legally valid consent. There will, of course, also be cases, for example in trials involving neonates and babies, where parents must decide whether or not to enrol their child in a trial without any involvement by the child in the decision. There is continuing debate over what is involved in providing such a ‘proxy’ consent on behalf of a child.

37 A parent’s rights in connection with their child are not absolute: in England and Wales parents must act in accordance to the ‘welfare principle’: that a child’s welfare or best interests must be paramount. \textsuperscript{85} Thus, in deciding whether or not to consent to medical treatment for their child, parents are required to consider what course of action would be in his or her best interests. While there is no case-law that applies these principles to research, the MRC has suggested that in the absence of such case-law, “the principles applying to medical treatment in England, Wales, Scotland and Northern Ireland might reasonably be applied to research.”\textsuperscript{86} Where the research in question is a clinical trial, the UK Regulations explicitly authorise parents to consent on behalf of their child. However, the Regulations do not provide any basis on which the decision to consent should be made, other than that the parent’s consent “shall represent the minor’s presumed will”. \textsuperscript{87} It therefore seems reasonable to assume that although parents are explicitly empowered to consent under the Regulations, they are still required to meet the ordinary legal requirement to act in their child’s best interests.

38 This paper has already highlighted some of the arguments around the extent to which procedures involved in research may or may not benefit the child (see paragraphs 17 – 18). In some cases, particularly where a child is seriously ill and no other treatments are available, parents may consent to their child being enrolled in a clinical trial of a new medicine purely in the hope that the medicine may turn out to benefit their child. In other

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\textsuperscript{83} Indeed, the term ‘assent’ has been used variably to refer, on the one hand, to the acquiescence of very young children, and, on the other, to the informed agreement of children who potentially have the capacity to consent for themselves: see discussion in Baylis B and Downie J (2006) The limits of altruism and arbitrary age limits American Journal of Bioethics 3(4): 19–21.

\textsuperscript{84} Gibson BE, Stasiulis E, Gutfried S, McDonald M and Dade L (2011) Assessment of children’s capacity to consent for research: a descriptive qualitative study of researchers’ practices Journal of Medical Ethics 37: 504–9.

\textsuperscript{85} See, for example, Department of Health (2009) Reference guide to consent for examination or treatment, paragraph 19. Similar principles apply in Scotland.

\textsuperscript{86} Medical Research Council (2004/2007) MRC ethics guide: medical research involving children, p29.

\textsuperscript{87} The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended, Schedule 1, Part 4, paragraph 13. This requirement is clearly not intended to mean that the parents' decision should be based simply on the child's wishes, since the Regulations require only that a child's objection be "considered".
cases, for example where healthy children are involved in vaccine trials, any possible benefit to the child will be much less direct. Moreover, clinical trials may often involve additional procedures, such as blood tests or scans, undertaken with the aim of generating additional research data, rather than to influence the individual child’s care. It is not entirely clear in what sense such procedures can be said to be in the child’s ‘best interests’. The situation with respect to clinical trials is potentially exacerbated by the wording of the UK Regulations which require that “direct” benefit be obtained for the group of children participating in the trial before the trial may be approved. The use of the term “direct” in this context suggests that incidental or ‘collateral’ benefits, such as additional monitoring and health checks, may not be sufficient to count when determining a child’s best interests.88

39 Where an adult makes their own decision to participate in research, accepting some degree of risk and discomfort in order to benefit others, this may be understood and praised as an altruistic act. The question of whether it is acceptable to make such 'altruistic' decisions when acting as a proxy decision-maker for another person, who is not deemed legally competent to make that decision for himself or herself, is much more controversial. Indeed, it has been argued that "on a conceptual level, we should recognise that one person cannot volunteer or command the altruism of another. While parents may have the moral authority to volunteer their child for research, a child's altruism is not something they are in a position to offer or negotiate."89 On the other hand, there is unease at the idea that the requirement to act in children’s ‘best interests’ should apparently exclude any consideration on the part of the decision-maker of the interests of others. It has recently been argued that the notion of what can ‘benefit’ a person, or be in their ‘best interests’ should be widened so that it includes the notion of “contributing to a valuable project”;90 a similar approach is found in the argument that there are benefits in living in a society where good research is prioritised.91 Others, by contrast, find these attempts to broaden the notion of ‘benefit’ unhelpful, but see no ethical difficulty in moving away from the idea of best interests altogether and instead applying the test of whether a procedure would be contrary to a child’s interests.92

40 Qualitative research across a number of different countries investigating how, in practice, parents actually make decisions about research participation suggests that the approaches taken fall into two broad categories: “being a good parent”; and “being a good citizen”. The first category included consideration of factors closely bound up with the child’s medical best interests such as:

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• whether the research would give the child access to free, enhanced or more convenient healthcare, including treatment that would not be available outside the research context; 93
• how novel the treatment was (seen positively as offering hope where other treatments had failed, or negatively as involving high risks); and
• how they thought the child would cope.

Factors associated with “being a good citizen”, on the other hand, included seeing participation as a social responsibility, for example as a way of reflecting the altruism of other children who had participated in research in the past and hence helped improve healthcare for their own child. 94

41 Similarly, a recent UK study looking at the experience of parents being invited to consider enrolling their child in a clinical trial as part of their treatment for leukaemia found that discussions about the option of entering the trial were firmly embedded in clinical practice. Discussions about the trial took place in the context of making the best decision about the child’s care in the light of uncertainty: cited examples included a doctor saying “if I wasn’t [happy for the child to be enrolled in either ‘arm’ of the trial] I’d be giving you the one that I thought was better.” 95 Most of the parents who commented on the scientific rationale of the trial, as opposed to their own child’s treatment options, were positive about the possibility of helping families in other situations. One parent interviewed, for example, commented that “at every opportunity that we’re able to give something back in terms of information or supporting them in some way we will do it… This is such a massive ordeal that anything we can do to make it easier for someone else we will do.” It therefore seems to be the case that, in practice, some parents do feel able to take a wider view, in addition to considering what is best for their own child.

42 Finally, studies on how parents make decisions on research participation highlight how very difficult many parents find these decisions, and hence how significant the role of the investigator and/or physician involved may be. One study that sought to examine parents’ involvement in the consent process, for example, found that the majority of parents appeared to prefer the physician to take responsibility in the decision-making process, with 38 per cent of parents making their decision together with the investigator, and 41 per cent allowing the physician to decide. 96 Such statistics suggest that not only children, but also their parents may potentially be vulnerable when making decisions about research, and highlight again the importance of clarity as to which procedures in a clinical trial constitute treatment for the child, and which are primarily designed to gather research data.

VII Questions the Nuffield Council might address

93 The consideration of access to free healthcare arose particularly in countries with a universal freely accessible health system.
This aim of the workshop is to consider whether the Nuffield Council might play a useful role in addressing these ethical issues, by establishing a Working Party to consider them and make recommendations, or by any other means. Ethical questions arising out this background paper relate to: the role of the regulatory environment in encouraging paediatric trials: the question of how risks and benefits may ethically be balanced; and the role of all concerned in determining whether a child should be enrolled in a particular trial. They include:

**Regulatory environment**

- To what extent does the regulatory environment affect the number and conduct of clinical trials in children and thus affect the delivery of better treatments and medicines to children? What are the respective responsibilities of regulators and pharmaceutical companies?

**Balancing risk and benefit**

- In what sense are children vulnerable with respect to research participation? How should they be protected, and by whom?

- To what extent should children be permitted by law to undergo research procedures that are not designed to offer them personal medical benefit?

- What, if any, limits should there be on children being involved in clinical trials that do have the potential to offer them personal benefit? Are any risks too high?

- How can risks be most usefully categorised and/or defined, both to enable consistent decision-making by those scrutinising research, and to support individual parents and children in deciding whether or not to participate once a project has been approved?

- In what circumstances should ‘minor increase over minimal risk’ be permitted?

**Roles of parent, child and health professional in determining involvement**

- Should parents be allowed to ‘volunteer’ their children for research that is not designed personally to benefit them? How helpful is the concept of ‘best interests’ in considering research involvement?

- What should be the respective roles of the doctor, the investigator, the parent(s) and the child in deciding whether or not to participate in a particular trial?

- Is it helpful to separate out ‘consent’ from parents and ‘assent’ from children? Would it be more meaningful to move towards a model of family decision-making, in law as well as in practice?
• To what extent are children able to make their own judgments about altruism, even where they are not judged competent to give a legally binding consent for themselves?