

Children and clinical trials workshop

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Academy of Medical Sciences, 41 Portland Place London W1B 1QH

Chair: Professor Steve Brown, Council member

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

Professor Steve Brown opened the workshop by identifying the key question to be considered: whether there are ethical and regulatory issues affecting paediatric clinical trials on which new light could be shed, and which if addressed could improve access to medicines for children? Is there a place for the Nuffield Council to offer analysis or guidance that would not otherwise be available?

Speakers and respondents were asked to address three sets of issues: what is different about children's trials; consent and decision-making; and questions of risk and benefit. The workshop was held under Chatham House rules, and the following note draws together the themes that emerged during presentations and discussion. While there was broad consensus in some areas, it should not be assumed that all present agreed with all points made.

A background paper was circulated in advance of the workshop, and where factual material was covered in that paper, it will not routinely be included in this note.

Session 1: What is different about children's trials?

Three speakers were asked to address the question: "*Are there good reasons to think that research that would be ethically acceptable if it involved adult research participants would be unethical if it involved children, even if non-exploitation and good proxy decision-making were assured?*" Comments were then offered, first from a respondent, and then from the floor.

What is different about children?

- Children are different because: they are developing and growing; they take their medicines differently; their understanding is different; they may assess risk differently; they suffer from different diseases; most are healthy; they play; they have parents (and may have siblings); and they are affected by their parents' choices.
- Particularly challenging research areas include emergency research: the common law requirement to seek legal advice 'if in doubt' in practice excludes children from such research. The Council of Europe provision that research is acceptable if it is minimal risk and may benefit children with the same condition is similarly problematic: what counts as a child in a 'similar condition' (how precise must the comparison be?) and how does the requirement of 'minimal risk' apply if the child is already at risk of dying (e.g. possible benefit of greater chance of life versus risk of death through use of blood clotting agent)? A decision as to whether or not to include a particular child in emergency research is complicated both because by definition parents haven't foreseen this eventuality, and because decisions about research involvement may be closely bound up with immediate clinical care decisions. UK law makes no specific provision for emergency research but does permit research to go ahead where a parent is unable to consent if a 'legal representative' (including a doctor involved in child's treatment if not involved in the study) consents: however, can someone other than a parent really provide meaningful consent? (Sample quote: "What do you mean I can't consent, but some bloke I've never met has ...").

Non-exploitation

- Is non-exploitation really possible?
- It may be oppressive or unethical **not** to invite children to participate. Young children and babies, for example, may be treated in intensive care units with equipment and multiple drugs, few of which have been tested in their age group or with their particular condition. Clinicians have to take risks in treating children without evidence – or in enrolling them in emergency trials!
- There is a tension between the rights of the child as an individual and the rights of children as a group. It is a balancing exercise for every child – we need to see the child as a moral reflective person who can be encouraged to consider what it is to be part of society. We know children are inherently altruistic – parents tend to temper this because they see the risks differently or on a more long-term basis. Should guidance similarly aim to temper this altruism?
- The 'protectionist impulse' can be two way: clinicians (and also researchers) may not feel comfortable in how to approach children appropriately.
- Is it acceptable to involve healthy children in studies of, for example: caffeine, paracetamol; swine flu vaccine; amoxicillin; gentamicin; methotrexate? On the one hand, there is possible future benefit to the child should they develop a particular condition, since quicker completion of studies in children may lead to better information for future care; there may be scientific benefits comparing the effects of medicines on healthy and sick children; and children are 'part of society'. On the other hand there is no immediate direct benefit to the child; there

are physical and emotional risks; children's lack of experience of life may make envisaging potential risk and discomfort difficult; results of pharmacokinetic studies in healthy children may be irrelevant for sick children; and some may argue that children have no societal obligations.

- The only situation in the UK where healthy volunteer trials in children take place at present is in vaccine trials where there clearly *is* some potential benefit although the child is healthy at present. Is it in fact useful to think of vaccine trials as 'healthy volunteer' trials given the child does have a risk of the disease? It is hard to imagine how any parent would expose their child if there is absolutely no chance of their getting that disease.
- Adult 'healthy volunteers' are compensated for their involvement. For children, the guidance is strict – you can't 'recompense' them, but you can 'reward' them, for example by a voucher or present afterwards. Is this a helpful or meaningful distinction?
- Trials in children are often motivated by companies' desire to obtain patent extension: thus paediatric trials may not necessary be prioritised by the relevance to children's diseases (the example was cited of researchers "running out of children with hypertension" to meet the regulatory requirement to test adult drugs in children unless a waiver applies).
- Problems of trial design: is it acceptable, for example, to take 15 blood samples from a child in a day because that gives the best results for the researcher?
- There are good reasons for a protective approach: some of the past scandals that have led to high levels of protection for research participants have taken place in children (e.g. injecting hepatitis virus into mentally disabled children at Willowbrook or the use of children with hydrocephalus as controls at Papworth in 1967).
- There are now a multitude of bodies regulating research in the UK: Health Research Agency, EMA, Ceres, Involve, NPSA, NRES ...
- Has the pendulum swung too far? - are we allowing *more* research than we should?

Proxy-decision-making

- If 'good proxy decision-making' is taken to mean decision-making that complies with legal and ethical requirements (for example regarding consent and assent and the child's developing autonomy), there is still a need for caution: the proxy is not the one taking the risks and no research is risk-free! It could even be argued that study intervention constitutes a battery on the child.
- There is considerable confusion over what is meant by 'assent'. Requirements for assent may lead to harmful tensions between parents and child where they analyse the issues differently. A compliant child may not actually be assenting, while a child who becomes competent during an extended study may find it difficult to reconsider their involvement.
- Proxies are likely to act with caution but in practice their understanding of factors such as risk, randomisation, or the nature of research may be weak; they may be

under severe stress; and they may feel that a decision to consent to research is the only 'parental' decision left to them.

- There is a need for further empirical work on the influences at play in research, including cultural, social and economic influences, and the role of powerful patient organisations.
- New issues arise in connection with studies looking at children's genes where there is a 'two-way' relationship: given that the results may be relevant also to adults, the role of the parent as a proxy decision-maker becomes further complicated. Where children have no genetic connection with a parent – are we opening a can of worms?

Relevant law

- Article 8 of the ECHR protects the right to private and family life (interpreted in *Pretty v UK* as including the “physical and psychological integrity of a person”).
- Article 3 prevents inhuman and degrading treatment.
- The case of *SvS* suggests that at times in treatment you may be allowed to act 'not against' the child's interests: but can this ever really be justified?

Possible ways forward

- 'Best possible consent' or 'imperfect consent', avoiding overly paternalistic approach (assuming study well-designed, peer-reviewed and ethically approved) and allowing for 'therapeutic optimism' (hope compatible with a valid consent).
- Children should be recognised as developing moral agents, and competent children should make up their own minds (consent not assent). There is considerable empirical evidence that children are much more capable than they are given credit for and many are keen to be involved (research involvement was cited as a 'reason to get up in the morning'). There are quite sophisticated ways of measuring children's understanding.
- Family decision-making should be the model for young children, avoiding the 'weasel words' of assent.
- Don't just transfer adult protocols to child trials. Trials can be designed to meet children's needs better and to minimise invasiveness: for example, by using Bayesian estimations you can avoid the burden of a high number of blood tests in one day, and seek fewer samples from more patients.
- Involve paediatricians and other professionals from the beginning.
- Ask children and parents.
- We need better ways of explaining risk to everyone, including adults!
- Things are getting easier - particularly in neonatal intensive care where there tends to be more time to consider issues (in some cases during pregnancy) and where the population is more standard than in paediatric intensive care.

Session 2: consent & decision-making

Presenters were invited to address the questions ***How should children's autonomy be recognised in the research context?*** and ***Can you be altruistic on behalf of your child?*** Comments were offered first by two respondents, and then from the floor.

Recognising children's autonomy

- Children are often seen as a 'vulnerable group' on the basis that they cannot understand complex information, are immature, can't always recognise their best interests, are not future-oriented, and need adult protection.
- However, the approach to children in bioethics is often quite confused: there is a lack of understanding of the ethical status of children (as seen for example in the fact that children under 16 cannot give their own legally-binding consent to a clinical trial, but at the same time ethical guidance suggests that their refusal to participate should be honoured), about what 'best interests' are etc. We don't have good tests of capacity in the sense of capacity across a number of domains; we tend to lump children together (and in extended trials even individual participants will themselves develop and change); and children who are very ill may be either increased in their capacity because of their experience of the illness, or depressed in their capacity because of the effect of the illness on them.
- Parents may feel 'abandoned' by doctors in making research decisions: they are usually guided through treatment decisions, but may then be left alone to make a research decision to avoid undue influence. If parents feel overwhelmed at being asked to decide, how can they realistically involve a child (e.g. a 7 year old with cancer) in decisions that go 'way over his head'? However, it is not always a struggle to decide: sometimes parents are excited to be asked, as are children, because they are interested in contributing and have sense of community with other patients with similar condition. So much depends on factors such as the clinical context, the time available to decide, and the type of trial: for example whether the research intervention is the main treatment or an 'add on'.
- A 'black and white' approach to children's competence may not be helpful. 15 year olds may welcome having their parents involved, even if judged to have capacity to decide for themselves, because of the benefits of parental support. This doesn't change overnight at 16: it is inappropriate for healthcare professionals to exclude the parents of a 17 year old from the consulting room unless this is in response to the child's wish - it is not a helpful way of 'respecting the child's autonomy'. As adults we like someone there with us – to remind us of what was said, support us, have someone to discuss the information with us. Being competent doesn't mean you don't need support (cf 'relational autonomy'). Indeed, parents can be a source of empowerment for children in making a decision – they can *support* their preferences and autonomy.

- Age is a very imperfect 'bar' given how much children vary. Where children are individually assessed for competence, the 'bar' is set much higher for children than for adults (which would strengthen the argument for allowing them to decide for themselves if judged competent and if they so wish).
- An emphasis on children's rights doesn't necessarily detract from a family model of decision-making. Clear legal messages are needed as safeguards to ensure that children's rights are not overlooked, and to entitle children to make their own decisions if they can and wish. However, arguing that the decision is ultimately for the competent child doesn't mean that they shouldn't have full support in reaching that decision. The law is about worse-case scenarios: we need both the law to protect rights **and** good practice in shared decision-making. In practice children do dissent, and at times restraint is used to require them to participate: legal parameters are thus clearly required to prevent abuse.
- Is it more helpful to think of 'beneficence' than autonomy? 'Assent' should be understood as promoting beneficence; we should move away from preoccupation with competence; it's often not so much about 'capacity' as about power, control and poor communication.
- There are several studies¹ in which most children prefer shared decision-making: "If we all make it together I think it's best because ... I have to make a bit of it because it's me that it's going to happen to, and they have to make it because they're my mother and father and they look after me. So if we both make it it's better' (11 year old). The assumption that children want to have independence and sole control is not right. But they do also like to be involved.
- Consensus and shared decision-making in families, after negotiation, is in practice a common position (with the possible exception of cancer where parents may perhaps not feel emotionally strong enough to share the information without burdening the child with their own sense of fear). In promoting a 'family' or 'shared' decision model, however, it is crucial to be aware of patterns of decision-making and parenting beliefs held by the families concerned, and the difficulties that may be involved in ensuring that all 'voices' in the family are heard. Parents may also seek to restrain a child's involvement, for example by withholding information, out of a desire to protect the child, even though they normally allow their children plenty of scope for decision-making in ordinary life. Where there is conflict, it is very important for clinicians and researchers to have the discretion to make adjustments in order to meet the particular needs of the child and the family.

¹ See, for example, Alderson P (1993) *Children's consent to surgery* (Oxford: Oxford University Press); Coyne I (2006) Consultation with children in hospital: children, parents' and nurses' perspectives *Journal of Clinical Nursing* **15**: 61-71; Coyne IT (2008) Children's participation in consultations and decision-making at health service level: a critical review of the literature *International Journal of Nursing Studies* **45**: 1682-9; Deatrick JA (1984) It's their decision now: perspectives of chronically disabled adolescents concerning surgery *Issues in Comprehensive Pediatric Nursing* **7**: 17-31; and Zwaanswijk M, Tates K, van Dulmen S *et al.* (2007) Young patients', parents', and survivors' communication preferences in paediatric oncology: results of online focus groups *BMC Pediatrics* **7**: 35.

- There is a real risk that processes designed to protect children just become boxes to be ticked. The more we put bureaucratic processes at the heart of the system, the less we involve children. We also need to balance protection with participation – children are sometimes excluded when they could have been involved. Taking account of children's preferences in every situation (a situational perspective²) will help adults to balance protection with shared decision-making.
- Children are morally capable, want to be engaged, and have moral views. The task is to try to elicit these views. In practice there is little engagement with children in this way, and also little awareness on how best to do so!
- Information needs to be clear and simple, in a format that engages children. It is important to explore children's (and parents') views about the trial and go beyond simply explaining risks and benefits to them. Informality is important: the discussion should be interesting and not perceived as being like a formal 'test' of whether the child understands. There is still far too little guidance for professionals in this area: they think they are using child-friendly language, but they're not. Non-verbal communication from child may be misinterpreted and lead to unnecessary exclusion.
- These communication problems are particularly likely to arise where professionals are not routinely working with children: paediatric practice by contrast is predicated on involving families and children, and it is very well accepted in paediatric practice that the same range of abilities are found in children as exist within an adult population. This may be a practical problem of training, rather than a conceptual one. Organisational context can also be highly influential in determining what happens in practice: for example play therapists provide a fantastic service, but may often not be available.
- Children and families need to be given more time and support. A 'genetic counselling' model might help here where one person is charged with taking account of the particularities of the child/family/kind of support/illness/treatment/risk etc, or where different set of experts involve the family in a non-time-constrained way.
- It is important to respect family context: it is hard to judge how families interpret things in the abstract, and this is often not the way we imagine! (In one example, parents said that in fact they felt involved and empowered by a particular discussion, even though the researcher observing them had gained the opposite impression.) There is a need for continuing research on how families do interpret this experience: for example, excluding practitioners whom the child knows and trusts from the discussion with the aim of avoiding undue influence may in fact lead to a loss of empowerment. If the child has a good relationship with the clinician, this may in fact enable them to make a decision that's right for them. Other children may feel freer to discuss with a nurse or play therapist rather than with their doctor.

² Coyne I and Harder M (2011) Children's participation in decision-making: Balancing protection with shared decision-making using a situational perspective *Journal of Child Health Care*, published online 9 August 2011, doi: 10.1177/1367493511406570.

Parental decision-making and altruism

- You can't be altruistic on behalf of someone else!
- However, the UK Clinical Trial Regulations place much tighter restrictions on what a proxy decision-maker can take into account than are the norm in other forms of parental decision-making. In general, parents may have 'overall goals' for their children (e.g. making them happy, prosperous, well-integrated, moral children ... developing into happy, prosperous, well-integrated, moral adults) and current goals (e.g. that the child should do well at school). Discrete decisions (e.g. that homework should be done **now**) may be directly or indirectly related to these goals. Other decisions may not be linked with these goals at all. Isn't it an acceptable 'parental goal' to bring your child up to be appropriately altruistic?
- The language of 'best interests' and the 'paramountcy' of best interests is denied by decisions we *de facto* allow parents to make every day (and indeed by the tax system since it's hard to see how taxing a child's money could be seen as being in their best interests). Where there is more than one child it is impossible to achieve this even in theory. Moreover, children's societal obligations are recognised in the UK by the criminal justice system where children may be held to be responsible for their own actions.
- How broad a definition of best interests can we take? Can it include being appropriately altruistic?
- Paternalism may be pure (where you have only the interests of the person at heart) or impure (where you act out of mixed motives - for example where something is good for the child but also best for the parent). In practice, parents often act out of impure paternalism, with concern for the child's best interests only providing part of the motivation.
- Parents have a persuasive role from when the child is quite young – we try to persuade them to do what is right. However, the current research ethics system may prevent trials taking place, thus taking it out of parents' power to take any role in persuading their child that it would be a good thing to participate, and then to consent on behalf of their child. Should the research ethics system prohibit certain projects to which proxies could legitimately consent on behalf of their child, on the basis that some proxies might make this decision in problematic ways?
- There is a difference between risks and burdens: burdens are predictable and reasonably certain (even if the effect on any particular child may vary from that on others) while in risk the magnitude of the possible negative event is what is usually of most concern. Parents are allowed both to force and persuade their children to take on quite large burdens in other areas, such as charitable obligations. It could be argued that there **are** some projects to which parents should consent on behalf of their children even if they involve more than minimal burden.

Session 3: Risk and Benefit

Three speakers were asked to address the questions: ***What level of risk is acceptable; Communicating risks to children;*** and ***Who should benefit?*** Presentations were followed by comment by a respondent, and then by open discussion.

Overview points on risk and benefit

- The ***quality*** of research is important: poor quality research prejudices all research.
- The value of clinical trials should not be underestimated: trials have led to 75% survival rates in childhood cancer, compared with 10% fifty years ago. Vaccine trials have led to routine vaccination and subsequent reductions in, for example, pneumococcal infections. The Medicines for Children Network has facilitated 300 studies involving 30,000 children.
- The RCPCH is currently revising its guidance on involving children in research, and is involving children and young people in that process.

Examples of particular trials

- Healthy infant vaccine trial, offering a new combination of vaccines, and earlier and broader coverage against forms of meningitis and pneumonia:
 - 4 blood samples over year (as well as initial immunisation)
 - Benefit: improved protection (individual and society – herd immunity)
 - Risk: discomfort of venepunctures (and very small risk)
- Pharmacokinetic study of a new antibiotic for serious infection in babies under 12 weeks:
 - Single dose, while receiving routine IV antibiotics; 4 blood samples over 8 hours
 - Benefit: improved information for other babies/children – little, if any, benefit for this particular child
 - Risk: of 'new' agent (new to this age group); discomfort of venepuncture.
- Pharmacokinetic study of a new hypertensive medicine in children aged 6 months to 18 years with high blood pressure:
 - Single dose; 8 blood samples over 24 hours
 - Benefit: improved information for other children (not this child)
 - Risk: new agent in this age group; discomfort
 - Researchers were able to recruit to the older group with no problem despite fears that it would be very difficult. Children were recruited through treating clinicians; attitudes expressed by those willing to participate included comments such as “blood pressure affects me and also my dad/friend ...”

- Newborn trial of licensed medicine currently used 'off-label' for seizures, with the aim of finding the optimal dose and defined pharmacokinetics in babies with hypoxic brain damage after delivery:
 - Inclusion criteria: babies who failed to respond to standard anti-convulsant medicine.
 - Benefit: possible improved outcome both for the child and for others
 - Risk: unforeseen adverse events; discomfort of blood sampling.
- Phase II study of a new agent for Duchenne Muscular dystrophy (seen as potentially 'curative' in that it allowed for some production of deficient protein, and hence lots of interest from affected families). Study involved dose-finding and also pharmacokinetic effects, and could last several months.
 - Benefit: possible improved outcome for child, and also for other children
 - Risk: disruption of being in a trial over a long period which can be hard for children to tolerate.

Assessment of risk

- Known risks can be measured – but how about unknown risks, such as unknown adverse reactions or long term risks? Reversibility is an important consideration here.
- Should you look at absolute risks – or at risk in relation to benefit? The latter is more intuitive, but the former may also be important: for example is a liver biopsy acceptable if it is unnecessary for treatment, and yet the results of trial will not be meaningful without the biopsy? How about muscle biopsies undertaken for research (not treatment) purposes in Duchenne muscular dystrophy: leads to increased loss of muscle function and is irreversible, but patients are keen because of the research potential?
- Is any risk acceptable in the context of life-threatening illness?
- Is 'minimal' risk a useful concept? 'Minimal' in whose view? – parents/ clinicians/ researchers all have different perceptions. Is vomiting minimal? – while it may usually be considered so, how about vomiting just after surgery which leads to other risks? In the US, 'minimal' risk is often defined through reference to activities in everyday life.
- One approach to risk is: hazard x probability. Should the focus of 'minimal' relate to the nature of the hazard or the degree of the probability?
- Risk may be assessed in different ways at different levels: at regulatory level it can only be a very blunt instrument, while RECs have the opportunity to look at the way that the risk fits in with the context of the research proposal, and can talk to researchers. However, even RECs only see one aspect of risk and don't see how in practice it is operationalised: there are a whole range of risks that people take into account and dispositions to risk-taking vary throughout the population. Much depends on the relationship between the researchers and parents.

- The approach of the EMA Paediatric Committee when considering questions of risk and benefit in paediatric investigation plans (PIPs) is often an intuitive reaction with risk weighed on one side and benefit on the other, decided by a democratic vote of the 27 representatives from member states. EMA are working on formal processes: it is not possible to legislate as to whether a particular process is acceptable/inacceptable; rather a system is needed to ensure issues are properly considered in a transparent way.

Research on communicating risk to children

- Even in areas like genetic services, it appears that communication with children (e.g. in terms of understanding the implications of carrier status) is often poor.
- There has been a general consensus for a long time that children under 11 can't understand abstract concepts like probability (following Piaget's theories of cognitive development). More recent work, however, suggests that if information is presented in an appropriate manner, younger children can cope.
- If risk is understood as the combination of the seriousness of an event and the likelihood of that event, then understanding of probability is key. From work with adults, it is known that the format in which probabilistic material is presented is key to understanding.
- Research³ has been undertaken with 106 children aged 7-11, from a wide range of academic abilities and socio-economic backgrounds, and with verbal ability scores ranging from 73-130 (median 100). Children were invited to play the 'cup game': identifying which cup was the most likely to be hiding the ball, with a 'temperature' gauge for them to indicate how confident they were in their own answer. Probability was expressed using a range of formats: verbal labels (e.g. often, seldom, sometimes), ratios, percentages, and pie charts.
- Format was found to be very important: pie charts were the best, with labels and percentages also quite successful. Pie charts were only shown one way (i.e. they were not used to test understanding with respect to an event *not* happening) in order to keep the magnitude of the risk the same between the various trial formats
- Age and verbal ability affected understanding for most formats, while gender was irrelevant. Feelings of certainty and reliability correlated well - i.e. children judged their own understanding accurately.
- This research was just a pilot scheme – but the results suggests that some 7-11 year olds *do* have the capacity to understand probability to a certain extent, so the onus is on clinicians to try! The next question to consider might be how children apply their understanding of probability to real situations.

³ Ulph F, Townsend E and Glazebrook, C (2009) How should risk be communicated to children? A cross-sectional study comparing different formats of probability information *BMC Medical Informatics & Decision Making* **9**: 26-41.

Who should benefit?

- Many different guidelines exist on how risk and benefit should be managed and balanced. At present, different countries pick and choose from amongst the guidelines but this is problematic: each is designed to be read as a whole and it may not work if, for example, you take definitions of risk from one and benefit from the other.
- The Clinical Trials Directive requires that there should be “some direct benefit for the group of patients”. The Directive itself does not define ‘group’, but guidance issued by the EU recommends a broad definition encompassing children affected by the disease or like diseases. The Directive also requires an appropriate balance between risk and benefit.
- Both ‘group’ and ‘benefit’ are inconsistently defined throughout EU member states. Some countries adopt a wide definition in order to limit restrictions on paediatric research. Others, however, ‘gold plate’ the requirements in an effort to protect vulnerable minors. The Good Clinical Practice Directive allows states to increase protection over and above the requirements set in the Clinical Trials Directive. There are a number of ways of doing this, but the two most common are:
 - Using narrow definitions of ‘group’ or ‘benefit’. In England, for example, ‘group’ is narrowly defined as the group of trial participants rather than the group of children with the same disease. ‘Benefit’ also needs interpreting. For ‘benefit’ to be ‘direct’ it must be tangible, but the benefit might flow either from the trial itself (e.g. through access to a better alternative to existing treatment) or from the results (e.g. increased safety, dosing information, treatment duration etc).
 - Additionally incorporating the approach set out in the Additional Protocol to the Biomedicine (Oviedo) Convention, which takes a different approach from the Directive. In particular, the Additional Protocol to the Convention sets down special requirements if the research is of more than minimal risk, requiring that in such research there must be potential for direct health benefit to the individuals participating. In doing so, it distinguishes between two distinct ‘groups’: the group of trial participants for whom the research is of more than minimal risk (who should have the potential to benefit directly from the research); and the group of patients of the same age or with the same condition (who are not participating in the research and hence not subject to any risk but who may still benefit from the results).
- Where countries incorporate the Additional Protocol approach, the danger is that the wider definition of group recommended by the EU is only used when the research is of minimal risk and burden, rather than in *all* research as is envisaged in the EU guidance. The EU guidance does itself refer to the Additional Protocol, but in practice the amalgamation of the two approaches, with their inherently different definitions of group, can lead to inconsistencies and to a restrictive approach to paediatric research.

- Thus, the Directive (on a wide reading of ‘group’) permits research involving more than minimal risk in three sets of circumstances that would be forbidden by the Additional Protocol unless there was also potential individual health benefit:
 - i. where the *individual* will gain benefits from the research that are not ‘health’ benefits,
 - ii. where the *group of participants* will benefit from the results, or
 - iii. where the *group of children with the same illness* will benefit from the results.

- Is the Directive too liberal? – or is the Additional Protocol too restrictive? A review by Anna Westra of approved Dutch research projects criticised the use of the ‘minor increase over minimal risk’ criterion in the Netherlands because it was not accompanied by the same wide definition of ‘group’ as in the EU guidance: in Westra’s view this led both to too restrictive an approach, and to children at times being exposed to unacceptable risks.⁴

- Possible solutions include:
 - Abandoning the Additional Protocol and adopting the EU guidance in its current form, or
 - Adopting new guidance – paying more attention to defining relevant risks with respect to particular definitions of group

General discussion on risks and benefits

- Where no direct benefit is expected to a particular child (for example where pharmacokinetic testing of an antibiotic for the first time in this age-group), what is the rationale for testing in sick children rather than healthy ones? On the one hand there may be practical reasons why it is less burdensome (e.g. IV line already in place), and the research question may relate to how a child already suffering from an infection responds to the drug. On the other hand, is there a risk that such ‘opportunistic’ testing on sick children is an unfair burden on sick children? How compelling are the arguments that in such cases the appropriate sub-population of children is those already suffering from infections? How does this fit with the increasing focus on stratified medicine and subgroups of the population?
- Would it be permissible under the Directive for a new antibiotic to be tested on a child who is neither already ill nor at risk of a specific infection? How wide can the definition of ‘group’ be? Can it potentially include all children if the infection is one that may potentially affect any child? Refining our language around ‘group’ would be very helpful.

⁴ Westra AE, Sukhai RM, Wit JM, de Beaufort I and Cohen AF (2010) Acceptable risks and burdens for children in research without direct benefit: a systematic analysis of the decisions made by the Dutch Central Committee *Journal of Medical Ethics* **36**: 420–4.

- Our ability to understand the multiple nature of risk, set against different benefits, and different beneficiaries, has not really been looked at sufficiently. Regulatory transparency – for example around the assessment of risks and benefits– might help RECs and others when making their own decisions.
- Do RECs have the right composition at present? Clearly this varies: RECs may not always include the proper expertise but this may in practice be impossible: the important issue may be whether they obtain the advice they need. The involvement of representatives from patient groups may be problematic as they may not always understand the remit of a REC but instead seek to promote the view of a particular disease group.
- The standard form for REC approval specifically requests investigators to comment on how they are working with patients (in terms both of the design of the study as well as the appropriateness of the information to be provided to potential participants). This question is often the worst answered of all the questions. Some researchers regard simply it as another hurdle, while others are doing very interesting work in this area. Where it's taken seriously, the applications sail through the ethics committee as it's clear they're appropriate. Should it be made a requirement, given that at present there is no sanction?
- Children and parents should be better involved with RECs. NRES runs training programmes for RECs/investigators with the help of the Young People's Group from 'Involve' and there are ways of 'piggybacking' on the work of others in order to involve children appropriately. More publications in these areas would help.
- How do we best protect children? By improving the quality of ethical guidance? By 'tightening' the regulations/advice? And/or by improving the quality of expertise available to Ethics Committees?

Session 4: Is there a role for the Nuffield Council?

- What's new?
 - The change in EU regulation has resulted in a huge uplift of trials, and while the regulatory framework is much improved, it is also much more complex. Hence there is a significant change in the *context* in which trials take place. Some trials are really challenging around the minimal risk threshold.
 - Technological developments, especially in connection with genetics, bring new challenges.
 - Many children's diseases are rare and hence there is an increasing need to move to international collaboration – yet discrepancies in regulatory frameworks are hindering research in these areas.
 - Many of the issues discussed at the workshop are generic in nature and have long been the subject of discussion. On the other hand, the reason why these 'old' issues remain is because they have never been satisfactorily resolved!

- The RCPCH is currently revising its guidance on research involving children and is also working with bodies such as the GMC, NRES and RCN to streamline guidance to researchers (both due for publication in 2012). It would be important to avoid duplication with these initiatives.
 - It would also be important to be clear whether any project would consider all child health research, or be restricted to pharmaceutical research, or clinical trials.
- It was suggested that major issues in this area that could benefit from further discussion and analysis included:
 - Finding ways of putting children right at the heart of the process, and avoiding the trap that legal or ethical requirements become an end in themselves (cf the way US protocols don't allow pictures in information sheets).
 - Dealing with international disparities (regulatory/social/cultural) which hinder the progress of child health research – while recognising that countries are strongly influenced by their own legal frameworks and that harmonisation is hence exceedingly difficult.
 - Identifying the right level of protection for children, and ensuring that this is maintained despite the increasing emphasis on the promotion of research in children.
 - Challenging the way age is used as a guide or a bar: children vary so much and in so many different situations.
 - Considering how 'assent' should be defined and used.
 - Identifying the tools/expertise required if a family-based model of decision-making were to be developed – including taking account of the needs of particular groups (adolescents, children in care settings, children with incapacitated parents), ensuring safeguards against abuse are in place, ensuring that non-family significant others are included (e.g. patient support groups) and considering the role of good communication.
 - Considering whether the bar is set too high with respect to the understanding of research – parents and children don't need to understand everything.
 - Looking at the use of 'legally authorised representatives' where in fact there are parents who are competent.
 - Considering 'burn-out' in long trials, and how this is managed (cf the Optima group in Oxford which has very good retention rates because of high levels of input from research nurses building relationships)
 - Analysing the implications of the shift towards rights-based attitudes in research (especially in connection with rarer diseases where patient groups are becoming more powerful lobby groups), and related concerns that ethical scrutiny may act as an unreasonable bar preventing parents/ children/ researchers from going ahead with valuable research – distinguishing between the argument that people have a right that

research happens and the argument that individuals have a right to be in a particular research project.

- How we understand **risk** – its complexity, how it should be defined, how it should be affected by context (e.g. emergency care).

Attendees

Ms Sarah Barclay

Founder, Medical Mediation Foundation; Vice-Chair, Great Ormond Street Hospital Clinical Ethics Committee; former BBC Health and Social Affairs Senior Correspondent; author of Jaymee: The Story of Child B

Dr Joe Brierley

Consultant Paediatric Intensivist and Chair of Research Ethics Committee, Great Ormond Street Hospital; Honorary Senior Lecturer at the Institute of Child Health, University College London

Professor Steve Brown (Chair)

Director of the Medical Research Council Mammalian Genetics Unit, Harwell, Oxfordshire; Editor of Mammalian Genome; Council member

Dr Emma Cave

Senior Lecturer, School of Law, University of Leeds

Professor Imelda Coyne

Head of Children's Nursing/Research, School of Nursing & Midwifery, Trinity College Dublin

Ms Helen Haggart

Senior Policy Adviser (Public Policy), British Academy

Ms Lynn Hagger

Lecturer, School of Law, University of Sheffield; member, Sheffield Children's NHS Foundation Trust Clinical Ethics Forum

Dr Dan Hawcutt

Lecturer (Clinical) Paediatric Pharmacology, Division of Developmental and Reproductive Medicine, University of Liverpool

Dr Ralf Herold

Scientific Administrator, Paediatric Medicines, European Medicines Agency

Professor Ray Hill

Formerly Head of Licensing and External Research for Europe, Merck; Visiting Professor, Imperial College London; President-Elect of the British Pharmacological Society; Council member

Professor Søren Holm

Professor of Bioethics, University of Manchester; part-time Professor of Medical Ethics, University of Oslo; President of the European Society for Philosophy of Medicine and Health Care; joint Editor-in-Chief of the Journal of Medical Ethics; Council member

Dr Rhona Knight
*General Practitioner, Leicester; Senior Clinical Educator, University of Leicester;
Council member*

Professor Neena Modi
*Professor of Neonatal Medicine, Imperial College London; Chair, BMJ Ethics
Committee; Vice President (Science and Research), Royal College of Paediatrics and
Child Health.*

Dr Helen Sammons
*Associate Professor in Child Health, Academic Division of Child Health, University of
Nottingham*

Dr Agnès Saint Raymond
Head of the Sector, Human Medicines Special Areas, European Medicines Agency

Dr Ilina Singh
*Reader in Bioethics and Society, London School of Economics and Political Science;
Co-editor, BioSocieties*

Dr Fiona Ulph
Lecturer, School of Psychological Sciences, University of Manchester

Dr William van't Hoff
*Consultant Paediatrician and Head of Somers Clinical Research Facility, Great Ormond
Street Hospital*

Professor Jonathan Wolff
Professor of Philosophy, University College London; Council member

Dr Simon Woods
Co-director, Policy, Ethics & Life Sciences Research Centre

Dr Bridget Young
*Reader and Director of Communication Skills, School of Population, Community &
Behavioural Sciences, University of Liverpool*

Nuffield Council Secretariat

Hugh Whittall, Director
Katharine Wright, Assistant Director
Kate Harvey, Research Officer
Sarah Bougourd, Communications Officer
Carol Perkins, PA to the Director and Secretariat Administrator
Johanna White, Office and Communications Administrator