Children and clinical research international symposium

3 – 4 March 2016

Hosted at the Nuffield Council on Bioethics,
28 Bedford Square,
London, WC1B 3JS, UK

Report of the meeting

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Introduction

In May 2015, the Nuffield Council on Bioethics (a UK-based body, with a remit to explore ethical issues arising out of development in biology and medicine) published a report *Children and clinical research: ethical issues*. The key question that the report sought to address was how children and young people can ethically be involved in research concerned with their health, given the vital role played by research in developing evidence-based healthcare. In exploring these issues over two years, the Working Party established by the Council engaged with a large number of enthusiastic and committed children, young people, parents and researchers whose personal experience of research cast light on, and often challenged, some of the conceptual assumptions (particularly with respect to vulnerability) that have long underpinned research with children and young people.

The Working Party included members working in a major research centre in Kenya, who had further contact with a network of researchers working across Africa and South East Asia. This enabled the Working Party to draw in a wider range of input to its project, and to challenge the extent to which its analysis and findings were embedded in, or special to, the situation in the UK alone. Additional input was obtained from interested researchers in Latin America. Nevertheless, the Working Party was alert to the fact that its understanding of issues in low and middle income countries was inevitably much more limited than that of the situation in the UK. In the final report, therefore, the Council presented 'conceptual recommendations' with respect to children's ethical involvement in research that it hoped would resonate widely, while restricting its 'concrete' recommendations to the situation in the UK/European Union.

The aim of this symposium, drawing together delegates from a dozen middle and low income countries, with experience of working in many more, was to explore further how the conceptual recommendations might be understood or nuanced in very different settings from the UK, and what practical implementation in those settings might look like. Given the importance of using existing networks and centres of excellence to support further work in this field, the Nuffield Council was delighted that the Global Health Bioethics Network (coordinated from the Ethox Centre, University of Oxford), and the Wellcome Trust Brighton and Sussex Centre for Global Health Research were able to join with us in supporting this symposium.

Format of symposium and this report

The symposium examined five aspects of the report in turn, with short introductory prompts from three to four delegates with experience of working in different parts of the world or in relevant international organisations, followed by open discussion. This report summarises key themes under each of these headings. In a preliminary section it also highlights some of the cross-cutting themes that arose throughout the

symposium, many of them flagged in delegates' introductory remarks at the start of the first day. The final section then draws together the discussion of practical ways forward, including individual pledges for action put forward by delegates.

Cross-cutting themes

A number of important themes emerged early in the discussion, and are highlighted here, as their significance went beyond any of the individual 'ethical challenges' summarised later in this report.

- **The question of 'who is a researcher?'** The concerns addressed in the Nuffield report, and explored in this meeting, went far beyond those with the role of 'principal investigator' or those who would regard themselves as a professional researcher. Rather, they touch on *anyone* involved in a work capacity in research activity, including (and perhaps especially) field workers who are directly involved in data collection and personal contact with study participants. References to 'researcher' should thus be understood in this broader sense throughout this report.

- **The nature of the research and the place where it takes place**: interventional research raises very different questions from observational research or public health research, and research in the clinic is very different from research in the community.

- **The distinction between research conduct that is *ethically* required - and that which is *legally* required by a particular jurisdiction**. Examples were given both of conduct that could be ethically justified but might not be allowed for in law (such as the exceptional waiver of parental consent for research with young people, where the research is important, and parental involvement would put young people at risk, or undermine the research itself); and of lawful research conduct that might not meet ethical requirements (such as research participation authorised by parents but without input from a young person despite their capacity to contribute). Where the law is silent, ethical guidelines (whether international or national) can help to 'fill the gap'; but where the law actively prohibits certain kinds of research, as is currently the case in Peru for example, this is much more troubling. An innovative approach is found in South Africa, which explicitly allows its research ethics committees to authorise research that would otherwise not meet the requirements of the law, if satisfied that this is necessary for ethical reasons.

- **The concept of flourishing**: parents the world over want their children to flourish – and where action can be understood as enhancing children's ability to flourish, this is often a way in to exploring the possibilities of social change in the context of research practice.

- **The overlap between clinical care with children and clinical research with children**. Many of the concepts debated in this meeting, such as the importance of sensitivity to context and relating to children in the context of

their families (which will often extend well beyond parents and siblings) are common practice in the clinic. To a degree, the challenge is to encourage research ethics to 'catch up' with paediatric care ethics. At the same time, it should be remembered that practice in clinics is often busy, pressed and harassed – researchers in fact often have the luxury of more time.

- **The challenge of developing guidance that fills the gap between high level principle, and the 'granularity' of every day practice and experience**: avoiding prescriptive guidance which cannot take account of facts on the ground, while still being sufficiently generalised to be of common value. Possible approaches discussed in the final session of the symposium included the development of a series of case studies, in which the interaction between principles and facts in difficult situations could be explored.

- **The role of training and support**: for all those involved in conducting, and in reviewing, research. It was noted that a free online course based on the analysis in the Nuffield report is available on [The Global Health Training Centre](#) website.

- **The role of funders with respect to implementation**: funders are well-placed to support innovative work or research in particular areas that have been identified as important – whether in response to new grant proposals, or in connection with suggested additions / variations to existing proposals in order to explore such issues. More generally, funders do, of course, share responsibility with other actors in the research field with respect to the selection and development of research that meets ethical standards.

Ethical challenges 1: 'vulnerability', childhood and engagement

Background from the report

The understanding of children and young people as a 'vulnerable' research population is one of the main reasons why research with children and young people has long been seen as ethically fraught. The Nuffield report recognises that children and young people may indeed be vulnerable in research, but are not automatically so; and argues that there are many ways in which research may be designed so that the risks of children being placed in vulnerable situations are minimised or prevented altogether. Taking the view that children are able, from a young age, both to take an active part in decisions that affect their lives, and play a role in their wider community, the report recommends active partnerships between researchers and children, young people and parents throughout the research process. This approach enables families to contribute their *own* perspectives on how to prioritise, develop and conduct research studies in ways that meet children and young people's needs. (Clearly those providing early input in this manner are unlikely to be those taking part in the actual study further down the line: the proposal is that researchers should take on board the *perspective* of children, young people and parents in developing their design, so that, where possible, they avoid situations that children and families are likely to find particularly difficult.)

In developing this argument, the Nuffield Council drew on responses from children, young people and parents both in the UK and in Kenya, and from professionals from over a dozen countries, across four continents. However, we were well aware that attitudes to childhood, and the role of children within their communities, are deeply culturally embedded, and that attitudes prevailing locally will be very powerful in determining how children and young people can in practice be involved in meaningful partnerships. The aim of session 1 of the symposium was to explore delegates' views as to how, in practice, the Nuffield report's approach to childhood and vulnerability might be perceived in their own work settings, and how best to promote culturally acceptable forms of partnership.

Introduction

This session was prefaced by a showing of the Nuffield Council's film *Be a part of it: what young people think of clinical research*, produced as a result of a collaboration with three schools in Brighton, UK, whose students were filmed as they scrutinised a mock research proposal as a 'youth research ethics committee'. Introductory prompts were then given by Esme Lynch (an active member of the London Young People's Advisory Group), Maureen Kelley, Claudio Lanata and Calvin Ho.

Main themes

Practical impact of perceptions of vulnerability

- There are striking examples, for example at present in Latin America, where perceptions about the vulnerability of children and young people (and the assumptions these cannot be mitigated) *do* simply stop research taking place at all – with the consequence that the evidence base for how to treat children and young people safely and appropriately is not developing. The 'granularity' of the analysis in the Nuffield report, and the endorsement of the possibility of carrying out research ethically with children, has been very comforting to those in Latin American who are responsible for reviewing such research.

Vulnerability and context

- The focus on context in the Nuffield report, and the possibility of mitigating potential for vulnerability through sensitivity to that context and appropriate study design, ring true for those working, for example, with homeless orphans, or 'biologically vulnerable' children (such as those suffering from malnutrition). The real challenge is whether researchers have the skills, capacity and time to respond appropriately. What is required for practical implementation in other settings is not so much a 'translation' of the concepts in the report, as an 'accompaniment' in the form of practical guidance.

- The role of social support in mitigating the possibility of vulnerability is crucial (the central character in the Council's animation, is lucky – she has two parents supporting her, a comfortable home, and lots of friends and activities). Innovative approaches are needed for where this support is not available. Parents, too, may need social support – for example where taking a child to take part in research means missing a day's work on which the family depends. Where additional or related costs are not met by the study (including, for example, healthcare costs for siblings), researchers often end up meeting these out of their own pockets. The structural aspects of vulnerability, and in particular the role of poverty in dominating people's lives and life choices, should not be overlooked. Nor should researchers feel they have to solve everything on their own: collaboration (for example the role of local health services with respect to post-trial access or ancillary care) is critical.

- The emphasis on context is particularly challenging for RECs/IRBs: how can their review of a study protocol take account of contextual vulnerabilities of which they cannot be aware?

- Vulnerability arises when we extend ourselves into new 'spaces' outside the situation where we feel supported. It is the role of law, institutions and communities to provide 'shelter' for when we extend ourselves in these ways, responding to our need for recognition, and enabling us to flourish. Yet laws and communities, by their nature, find it difficult to respond to the singularity of individuals – and this can lead to what seem simplistic or over-protective responses, such as the exclusion of children from research. The involvement of children in research needs to be aligned with other aspects of their development, so that it is understood more broadly in the context of their flourishing. (See also the discussion on pages 13–14 of approaches to culturally challenging studies.)

Involvement in study development – family and community

- Consent is not the start of involvement in a study – researchers need to start with political leaders, communities and families – and when working with families, this should include not just parents and children themselves but also other 'key informants' such as mothers-in-law. Opportunities to visit the research facility and talk to other families is also important. Critically, this must be done at times that are convenient to families, even if this means researchers making themselves available late in the evening or at weekends. If children feel engaged and enthusiastic, then they will stay in the project – even if it involves multiple blood tests.

Engaging young people: role of Young People's Advisory Groups (YPAGs) and other means

- There are currently six of these groups in England under the banner of GenerationR (five general groups, and one specialist mental health group). These involve young people aged between eight and 19, and they are available to advise researchers at multiple points in the research process: for example, when they are first developing their research idea; when developing information materials to explain the study to future potential participants; and when seeking advice on how best to communicate with children and young people throughout the study, including disseminating final study outcomes. They have also produced multiple resources, available through their website, giving practical advice on involving children and young people in study design and development. One of GenerationR's key messages is that research should be *with* children, not *on* children - so that children are involved in creating research, and not just taking part in it.

- Increasingly, GenerationR is reaching out to other young people who are not involved in the groups - for example by raising awareness of research

concepts so that children have the confidence to ask questions and decide for themselves if they wish to take part, if the possibility arises.

- YPAGs are being set up in other countries, under the banner of the International Children's Advisory Network (iCAN). Currently the affiliated groups are all from developed countries, but the network might be interested in approaches from low and middle income countries.

- A YPAG has been set up, and had its first meeting, at Angkor Hospital in Cambodia, involving ten children between the ages of ten and 15. Parents (some of whom are staff at the hospital) were very keen for their children to be involved: participation is perceived as positive in terms of their education, which is highly valued.

- Questions remain as to how YPAGs should be funded (the UK groups are currently funded by public research money, although they are also accessed by industry researchers), how they should be structured, and how they should be made representative. Where families are not routinely involved in the clinical care of their children, the idea of children being involved in influencing research will be harder to convey: one way of starting would be to encourage greater involvement by families and children in their *own* care.

- In Singapore, a reflective theatrical play has been scripted for and with children, their communities and researchers, to explore vulnerability and encourage deliberation and engagement.

Risks of engagement

- There is a real risk that if the involvement of children and young people in the development of research studies, and in setting the research agenda more general, is *mandated* by RECs/IRBs, then this will become a bureaucratic burden that simply prevents research. Sensitivity to what is pragmatically possible at the time will be essential.

Ethical challenges 2: welfare, research and access to healthcare

Background from the report

A second key challenge that arises in the context of the ethical acceptability of clinical research with children and young people, is that of the **welfare** of the prospective participants. The Nuffield report analyses the concept of welfare in some depth, and suggests that parents (and by extension professionals such as researchers with duties of care towards the children whom they recruit into research studies) are entitled to take a broad view of welfare as encompassing what is 'good' for children in the widest sense. Thus, it is legitimate for parents to consider not only children's personal interests (eg in being protected from harm, and in having the opportunity to develop and experience new things), but also the value of contributing to the wider society in which they live.

However, such an opportunity to contribute to wider social goods should never be at the expense of children's personal interests: thus the report suggests that participation in a particular research study will only be ethically acceptable where the demands of the study are *compatible* with a particular child's personal interests. From a researcher's perspective, this wider approach to welfare provides reassurance that it is ethically acceptable to invite a child or young person to take part in a study that may not directly benefit them, as long as the study itself constitutes a 'fair offer' (see next section). Such an approach strongly challenges the view held by some that if research is not in a child's 'best' interests, then it cannot be ethically acceptable to invite him or her to participate.

Questions about children's and young people's welfare, and the extent to which research participation is compatible with their interests, become particularly difficult if research participation is the only way in which healthcare may be accessed. This situation may sometimes arise in countries with universal health coverage (e.g. where there is no approved treatment for a particular condition, but interventions believed to be promising may be accessed via participation in early stage trials) - but is particularly challenging in lower income environments where many people may have little or no access to healthcare. The aim of this session was to explore the extent to which the analysis of welfare in the report is helpful in contexts where access to healthcare will be an important influence in parents' and children's decisions about research participation.

Introduction

The session began with introductory prompts from Dorcas Kamuya, Abha Saxena and Arianne Shahvisi.

Main themes

Broad approach to welfare

- The broad approach to welfare suggested in the Nuffield report was largely endorsed, with emphasis placed on factors such as children's emotional needs and capacity for distress, as well as their physical welfare. It was noted that the concept of it being 'good' for children to contribute to society was a legitimate consideration for parents in their decision-making (or negotiation) with and on behalf of their children, but was not a reason for researchers to suggest that children *ought* to take part in research: such an approach would risk 'instrumentalising' children as a means to an end. The focus should be on cooperation and collaboration so that children are *part* of the decision to participate. While this argument cannot be applied in 'case 1' children (who cannot be involved in making the decision about research involvement and hence cannot collaborate), participation in such cases might be justified on the basis of solidarity, as long as that basis for solidarity can genuinely be demonstrated.

- The question of the social value of the research is also a key factor: if a study has little or no value, then it is hard to see how it can be 'good' for any child to take part.

Recognition of the massive challenges that health systems in low and middle income countries often face

- Even where local health services are available, they may be a long way away, or involve long waits, or provide only limited access to medicines. Parents of sick children will of course focus on their child's immediate welfare needs, and where research offers a means of accessing healthcare, this will be a prime motivator. This awareness puts particular pressure on researchers to be confident that their study constitutes a fair offer (see the [next section](#)) - if they can be confident that what they are inviting families to do is 'fair', then parental motivation becomes less troubling. Researchers may also have a role in *facilitating* access to existing services – for example, by assisting families who are entitled to register to access services provided through health insurance, but have not as yet done so.

- Although study information always says that a choice not to participate will not affect people's access to healthcare, this is just not true when research participation brings with it access that would otherwise not be available to people.

The risks of enabling children's voices to be heard

- Where children are in 'case 2' (children able to express a view about research participation) or 'case 3' (children intellectually and emotionally able

to make the decision for themselves), then a link between research participation and access to healthcare becomes particularly difficult. Researchers have a responsibility to ensure that these children's voices are heard – and yet are aware that children and young people's concerns will extend far wider than the question of healthcare access. By facilitating the involvement of children in decision-making, researchers run the risk that those children choose *not* to take part.

- Children may be more educated than their parents – but may also be culturally not encouraged to challenge them. Again, this puts pressure on the researcher who may be perceived to be encouraging children and young people inappropriately to challenge authority structures within the family or community. The role of schools and teachers should not be underestimated: note, for example, an MRC-funded project in China where children learned about the dangers of excessive salt intake and were found to have directly influenced the adults in their families.

Whose welfare – and challenging the cultural status quo

- There are real challenges in how researchers may encourage voices to be heard in culturally appropriate ways, especially where this may be seen as a fundamental challenge to the *status quo* (for example in relation to the role of women and girls).

- When considering the legitimacy of such challenge, it is important to see it as a two-way process and relationship: a conversation, arising out of the context. Where possible, the conversation will be locally-led: the example was cited of a research project in Uganda, where the initiative to enable adolescent girls to have decision-making space despite the tradition that a male member of the family would make decisions on her behalf was Ugandan-led (although highly contested in the community itself). Note too the pan-African approach to 'people's rights'. Researchers will often be local – this should not be framed as simple cultural imperialism. Where funders are requesting particular approaches, transparency is very important in conveying the rationale.

- Norms and principles set at a high level (such as the UN Convention on the Rights of the Child, or the CIOMS guidance) also provide a point of reference in challenging cultural norms with respect to factors such as women's and children's rights. There *is* a prescriptive or universal aspects of ethics – but the way in which ethical principles can be applied will always have a contextual element.

- Researchers do have this responsibility to 'make a difference' and 'be disruptive' where cultural norms threaten ethical research conduct – but this

responsibility cannot be borne by researchers alone, and collaboration with others is essential. Some degree of pragmatism is also important: what is possible for a major research centre, with a longstanding community engagement programme that has built up substantial trust, is very different from small-scale research studies that are not supported by such infrastructure.

- Examples of particularly difficult scenarios include research where pregnancy testing is indicated because of the potential risks to the foetus – and the cultural unacceptability of suggesting someone's adolescent daughter might be pregnant. In contrast, a positive example of how parents may agree to be excluded from information about their children's healthcare was cited from South Africa, where parents *did* agree to allow their children privacy with respect to their use of sexual health services because this was framed in terms of their children's welfare and access to high quality services.

- Do not underestimate the speed of change – and also the capacity of involvement in research to lead to change.

Role of training and practical guidance

- All these challenges highlight again the importance of both practical guidance, and also training, both for RECs and researchers themselves.

Ethical challenges 3: the idea of the 'fair offer'

Background from the report

One of the challenges in determining whether a study protocol is ethically acceptable is the fact that every child or young person is different, and will respond differently to the prospect of taking part in a particular study. What will be interesting and worthwhile for some may be frightening or tedious for others; and procedures that some children and young people will take in their stride will be distressing for others. However, those responsible for developing and reviewing research have to make decisions about the design of the study, the development of appropriate information materials, and the proposed recruitment processes, for the *generality* of children and young people in the target population – by definition they cannot know the individuals concerned.

The Nuffield report developed the idea of the 'fair offer' to encapsulate how researchers and reviewers might approach study design and review. While it is impossible to predict whether any particular child / young person and their parents might find it acceptable to take part in research, researchers and reviewers should be confident that what participants are being invited to do is 'fair' and reasonable. Fairness will, for example, be found:

- in the *design* of the study: e.g., is it fair to expect children to miss school if appointments could in fact be scheduled outside school hours, or to have multiple blood tests if these could potentially be combined?

- in the *appropriateness of the scrutiny process*: can potential participants and their families feel confident that the value of the study, its risks, burdens and potential benefits, and the appropriateness of its design, have been scrutinised in a manner in which they can place trust?

- in connection with *how children / young people and their parents are approached*: for example in the appropriateness of the information provided about the study, and in the communication skills of those extending the offer to participate. A key test with respect to the fairness with which the offer to take part is presented is whether children / young people and their parents genuinely feel able to say no, if they so wish.

Introduction

The session was introduced by Bobbie Farsides, who chaired the Working Party producing the report, with responses from Claudia Turner, Paulina Tindana and Reeta Rasaily, leading into open discussion.

Main themes

Moral basis for justifying children's involvement in research

- The notion of the fair offer was developed as a counter-balance to what has become almost a fetishising of consent, by shifting the emphasis away from the choices and motivations of children and parents to the responsibility of those developing, funding and reviewing studies.

- Where we know that participation may, for some, represent an 'offer that can't be refused' (for example because of the access to healthcare implicit in it), there is a particularly heavy moral responsibility for researchers and RECs / IRBs to be confident that the benefits and burdens of the research are fair and reasonable, and that the research itself has social value to the community where it is taking place. This emphasis on a fair offer stands in stark contrast to the idea that any study is acceptable if people are willing to take part in it.

- The *way* in which potential participants are then invited to take part in research constitutes a further element of the requirements of a fair offer.

Fair to whom?

- The 'offer' needs to be 'fair' to the children who may be taking part in it – with respect, for example, to the effect on their daily lives and relationships, as well as with respect to the physical risks and burdens entailed.

- It also needs to be fair to children's families: to their parent(s), with respect to what is required of them, such as the time away from home or work required to take their child to appointments; to siblings; and to wider family members who may be affected or who expect to have a say.

- Finally, it needs to be fair with respect to the wider community – for example with respect to any knock-on effect on existing health services.

Who decides what is fair?

- Depending on local context, decisions about what is fair may or may not be perceived as trustworthy. Something may be believed to be fair because someone in authority, such as a headman, has said it is, or because an organisation such as an NGO is looked upon positively because of services it provides. In contrast, figures in authority may sometimes be *dis*trusted because of a history of corruption.

- Funders can have a role in this too: for example with respect to their requirements that studies they are supporting include elements of public and patient involvement at appropriate points.

Process vs content

- In presenting the idea of the fair offer as an intuitive way of capturing what it is that researchers and RECs / IRBs should be seeking to find in an ethical study, the Nuffield report focused very much on *process*: the involvement of children / young people in study design, and the role of relevant expertise on the REC / IRB in providing an informed view, from a range of perspectives, as to what burdens, risks and benefits could be regarded as fair. One of the challenges for researchers and RECs is how they then respond to the input they receive from such engagement. The example was cited of a study involving a lumbar puncture that a REC thought unacceptable; but people living with the condition felt was a fair thing to ask them to do. The study was redesigned with patient input, and was then given REC approval.

- Further conceptual work with respect to contested areas such as useful definitions of 'minimal risk' would be very helpful, in order to give the notion of the fair offer more content. At present it provides an intuitive description of what RECs are already doing, with respect to consideration of risks, burdens, benefits and social value, but is not 'revolutionary'. Some felt that the notion added little to existing understandings of the role of the REC.

Language

- There were mixed feelings as to whether the language of the 'fair offer' was quite right: some felt that this wrongly implied a commercial contract, while others thought that it captured the right spirit, such as offering someone a glass of water (you are free to say 'yes' or 'no', but there is nothing wrong with what is being offered).

- In translating the term into other languages, it will be more important to convey the spirit (as in the glass of water analogy) than a literal use of terminology that might convey a very different impression.

'Fairness' as a dominant rhetoric of children ('it's not fair'; 'you're not being fair')

- In their appeals to fairness, children appeal to an idealised notion of what *should* happen; and one element of maturity is the recognition that fairness is an aspiration, and not necessarily always possible.

- The fair offer could be seen as a link between these ideal and 'real' worlds.

Ethical challenges 4: professional responsibility and ethical scrutiny – the role of RECs / IRBs

Background from the report

The responsibility for ensuring that research is conducted in an ethical manner is shared by all concerned in research: those designing and funding research protocols, those responsible for review, and those subsequently recruiting participants and conducting the study. Research Ethics Committees / Institutional Review Boards (RECs / IRBs) have a special role to play in scrutinising research proposals from an ethical standpoint, but this role does not relieve others of ethical responsibility.

The Nuffield report notes the risk that well-intentioned systems, devised to encourage and promote ethical research, may sometimes lead to unthinking adherence to a checklist of requirements, or alternatively may create such onerous hurdles that these, in practice, act as a barrier to research. It proposes that one way of minimising such risks is through the promotion of a reflexive approach to professional practice: one where ethical practice is not simply enforced 'top-down', but is promoted through emphasis on individual professional responsibility, mutual learning and experience, and sensitivity to context. Three professional 'virtues' (trustworthiness, openness, and courage) are identified as central to ethical, reflexive practice on the part of all those involved in research with children and young people.

This approach has important implications not only for researchers but also for those responsible for ethical review. It would require RECs/IRBs, when scrutinising research proposals, to recognise the role of professional judgment by the researcher, and the need at times to allow for professional discretion in the conduct of the research – for example through requirements describing guiding values and outcomes, rather than highly-specified processes from which no deviation is permitted. Such an approach requires RECs to be able to trust researchers – and in reverse researchers to demonstrate their capacity to be so trusted.

Introduction

Introductory prompts to start the discussion were provided by Carla Saenz, Vicki Marsh and Neema Mtunthama Toto.

Main themes

Not locating ethical responsibility solely within RECs

- There was strong support from delegates for the notion that everyone involved in research (from funding decisions, study design, and ethical review, to recruitment, conduct and dissemination of research) shares some degree of ethical responsibility: 'ethics' is not simply located in REC / IRB review. RECs / IRBs should be seen as part of a continuum in which ethical consideration takes place, and in which other organisations, such as states, funders and regulatory agencies, also have a role to play (as well as individual researchers - see below). This wide scope of responsibility for ethical conduct provides an additional challenge to those providing guidelines (for example, CIOMS, the Council for International Organizations of Medical Sciences): it is much harder to provide appropriately targeted guidelines when there are multiple addressees.

- Ethics should not be confused with compliance – but in countries with a history of dictatorship, for example, it is understandable that great weight is placed on the role of law, and this may lead to a very restrictive approach (for example preventing research that might be unethical in some contexts going ahead, even if it could ethically be carried out in others). Guidance and toolkits can help provide support and comfort to those confronted with difficult decisions.

- Questions about whether the current role of RECs / IRBs takes place either too early or too late in the process highlight the importance of understanding ethical consideration as a continuum. Should funders, as well as relying on REC / IRB review, also take an active role in promoting ethical consideration earlier in the process – for example by encouraging the establishment of an ethics group early in a project? This kind of model is more likely to be feasible in larger scale projects. There is also a real gap in ethical support *during* research: those on the ground, facing the many contextual challenges described earlier, need 'live action support' in responding to ethical dilemmas. One possible model is that of ethical consultations: access to others who have the expertise to help researchers think through the challenges and support their decision-making, but not just provide the 'ethical answer'.

Reflexivity and professional values

- There was similar broad support for the emphasis in the Nuffield report on professional virtues, and the need to trust researchers to exercise appropriate discretion. Examples were cited repeatedly throughout the meeting of the importance of well-founded trust (for example in building up relationships with communities), openness (for example with respect to the

rationale for REC / IRB decisions), and courage (for example in connection with the difficulties inherent in approving research perceived as sensitive, or indeed in some cases *any* research with children).

- However, some fundamental practical questions remain: first as to how to promote and support these professional virtues, especially in a context of squeezed resources; and second how to avoid overburdening researchers who are already highly alert to their responsibilities towards their participants, particularly where those participants are children. Examples were cited of researchers meeting participants' needs out of their own pockets, and of the assumption when working with orphans that researchers were there to adopt them, or to help with adoption.

- Most doctors, let alone others engaged in research, have little training in ethics, and are juggling multiple roles and time pressures. Training and mentorship are crucial, alongside guidelines that capture the granularity of ethics on the ground. Case studies that follow arguments through in real-life situations are very helpful. Practical communication skills and confidence in communicating with children and families are also essential.

- Research on research ethics could help to find a 'way in' to encouraging reflexivity. Such research should include both empirical and normative elements.

- The way in which the media report research can potentially have a significant effect on trust in the system. RECs / IRBs are well-placed to build trust by having a good story to tell about the robustness of research scrutiny.

Quality of ethical review

- Enhancing the capacity of REC / IRB members, both in general and with reference to paediatric research, will be crucial in supporting them in moving away from the comfort offered by checklist approaches. It was, however, noted that this is not just an issue for low and middle income countries. Good practice examples cited included RECs in Lima meeting together regularly to share best practice and discuss challenges; and online resources to facilitate such networking and mutual support on a remote basis too.

- Questions of transparency are very important, and it was noted that in some countries researchers are not allowed to attend REC / IRB meetings at which their proposals are debated. The model in the UK, in which lay summaries of REC decisions are published online, is a helpful means to opening up the 'black box' of REC / IRB decision-making.

- National bodies, that exercise a supervisory function with respect to the work of RECs / IRBs without attempting to control every detail of their work, have an important role to play. Where these exist, they are a good place to start in terms of disseminating good practice guidance.

- Multi-country ethical review can be particularly problematic, especially where research is primarily social and observational, rather than interventional. However, the delays caused by negotiating ethical review in multi-country research can also have positive outcomes if the process ensures 'buy-in' from relevant people or organisations.

- Training is important for everyone – but a key question is whether it results in researchers feeling *confident* in carrying out their role? And how can REC / IRB members be confident that any training promised for those carrying out data collection is appropriate?

Ethical challenges 5: the role of parents in decision making

Background from the report

The Nuffield report takes as its starting point the importance of thinking about children in the context of their families, and the importance of those family relationships in the making of decisions about research involvement. It puts forward three elements of parental decision-making (respect for children as individuals; support for children in developing as independent decision-makers; and concern for their welfare), and explores how these elements will be balanced in different ways, depending on the circumstances and capacities of particular children at the time research decisions need to be made. Three 'paradigm cases', or situations, are used to explore the different ethical challenges that may arise depending on whether children are, or are not, able to participate in a decision about research involvement, or indeed have the capacity to make decisions themselves but are not yet treated as legally adult by their national law.

Recommending that decisions about research should, ideally, be shared decisions between children / young people and their parents, the report also recognises circumstances in which this may not be possible: for example where there is significant disagreement between children and their parents, or between parents themselves; or where parents are absent. As discussed in the first session of the symposium on vulnerability, cultural attitudes to childhood, approaches to parenting, and the role of wider family and community will clearly be critical in influencing how such situations are, and can be, handled. This session will explore the respective role of parents and children / young people in research decision-making, and the extent to which it is feasible to develop universal approaches (for example through international guidance) to best practice in this area.

Introduction

The discussion was introduced with initial prompts from Phaik Yeong Cheah, Ann Strode and Annette Rid.

Main themes

Who is a parent?

- Many adults who bring children to research centres are not their biological parent, and may or may not have legal authority to consent on their behalf. Such proxies may have a very close relationship with the child, and be their primary caregiver, or they may have limited or no knowledge of the child.

- Some countries, such as South Africa and India, have clear definitions of who is legally authorised to consent on behalf of a child; many others do not. Definitions may be based on status (e.g. legal guardian or a particular biological relationship) and / or they may be based on the social relationship with the child (for example whether they have day-to-day care of the child, as specified in South Africa). Even where it is clear who is legally entitled to give consent, this may in practice be relevant only at the point of entry to research, and researchers will continue to interact with all those concerned with the child's welfare and upbringing, as they would in clinical practice.

- Requirements in some countries for both parents' consent can be highly problematic, especially where fathers are working away from home, or are simply absent. While these requirements may be seen as recognising the importance of broader family relationships (ideally researchers should want to involve fathers, and should be prepared to be flexible in their approach in order to do so), they may also simply exclude many children from research.

- 'Children of children' – those whose parents are themselves minors – are also often an excluded group: although minor mothers may be expected to take on many other responsibilities and make many other decisions, they will rarely be authorised to consent for their child's participation in research, and instead grandparental involvement will be required for participation.

Who is a child?

- Legal ages of majority vary significantly around the globe – and there may also be differences between formal legal majority and 'cultural' majority. In Cambodia, for example, the legal age of majority is 18 but culturally children are regarded as grown up at 15, while in Singapore the age of majority is 21 but young people often stay in their parents' homes and function as minors until they are 25 or older. In Thailand, the age of majority is 20, but those aged 18 and above in practice are permitted to give consent for themselves for participation in clinical trials. There may sometimes be genuine uncertainty as to the domestic legal situation. However, the UN Convention on the Rights of the Child, which uses the age of 18, offers a point of reference in cases of uncertainty.

- The concept of 'emancipated minors' – young people who are below the age of majority but recognised to be living independently – exists in some countries such as Kenya, but not in many others. These young people again can be inappropriately excluded from research, unless RECs / IRBs feel sufficiently confident to waive requirements for parental consent. However, this is clearly very difficult if it would involve going directly against the law (see below).

- There are also risks in treating children who are obliged to cope on their own as being fully adult: they can end up being over-burdened with decisions they do not wish, or feel able, to take. Social support is critical - as is a recognition that autonomy is not simply about self-governance, but is relational. Adults, too, make decisions in the context of their social relationships, and rarely entirely on their own.

The role of assent

- The focus on assent in many guidelines and regulations can be problematic in hierarchical societies where it could be perceived as encouraging children to challenge authority in an unacceptable manner (see also earlier discussions on pages 13–14 regarding the role of researchers in challenging cultural norms).

- Simple age cut-offs, such as the requirement for children aged seven and over to sign an assent form, do not reflect the diversity of children, their abilities, and their needs.

- In South Africa, the legal position is couched in terms of the rights of children to *participate* in decisions affecting them (reflecting the language of the UN Convention on the Rights of Child). This position is similar to the approach to assent set out in the Nuffield report, which interpreted the concept in terms of the importance of children being *involved*, to the degree they wish and are able to be, in decisions about research participation. (This involvement should be adequately documented for future reference, but need not necessarily involve a child being actively asked to sign a form, which can be inappropriate in many contexts).

Interaction of law, ethics and culture

- Law, ethical guidelines, and culture / practice play different and complementary / competing roles in shaping actions. Where law sets a baseline, ethical guidelines can set high standards / aspirations and also be more flexible and nuanced than law. Culture may shape actual behaviour far more than law – most people will not know precisely what the law requires.

- Problems arise where law and ethics clash: that is, where the law appears to prevent ethical action (and funders, for example, cannot simply ask researchers to ignore the law). However, there are examples of where law is couched with sufficient flexibility to avoid this conflict: for example, the way in which RECs in South Africa are explicitly authorised to waive parental consent requirements with respect to under 18 year olds, if there is good reason to do so. However, such approaches place great trust in RECs, highlighting again the importance of transparency as to how they come to their decisions.

- Projects such as H3Africa, which is carrying out genomic research across 25 African countries, demonstrate how early engagement and ethical deliberation (in this case through an ethics and regulatory issues working group that liaised with RECs from the start) can change attitudes and, in turn, influence the regulatory environment and practice. As a result of this project, attitudes to 'broad' consent for research, and to the acceptability of biological samples being stored out of country, have changed fundamentally in these countries.

The possibility of universal norms / guidance

- It was felt that it is possible, to a degree, to identify norms and standards that are universal, as long as scope is given to context in the way that they are operationalised. The CIOMS guidance, for example, is used as *de facto* law in many countries, including across SE Asia, where there is no specific national regulation on clinical research, or clinical research involving children.

- The CIOMS guidance is currently being revised, and the new guideline on children has many overlaps with the approach in the Nuffield report. These include the focus on respect for individual children; support for their involvement in decision-making; the broad approach to interests, including children's interests in living in a society that practises solidarity through research participation; the possibility of waiver of parental consent in particular situation; and the recognition of the importance of context. As discussed at several points during the meeting, however, there are of course tensions between being sensitive to context where that context does not necessarily respect children as individuals.

Next steps

The final session of the symposium focused on concrete steps that might be taken as a result of these discussions, whether at international, national, professional or institutional level. After initial thoughts from Bobbie Farsides, Katharine Wright and Kate Harvey, delegates debated in groups, and then fed back to the full group, their views on what needed to happen next, and who might be well placed to do it. The Nuffield Council cannot commit to substantive new work in this field at present, but as the purpose of the report was to inform policy and practice, there will be some limited capacity in terms of staff time to coordinate and facilitate action by others.

At the end of the meeting, delegates were invited to consider what they or their institutions might be able to do – and these 'pledges' are listed below.

What next?

Practical ways to 'fill the gap' between high level principles / law / guidance and the contextual challenges on the ground

- There was strong consensus on the need for such a resource, with a popular approach being the development of case studies that enable researchers to think through difficult situations in real-life contexts. A possible host for such case studies would be the *Children and clinical research* online course published through the Global Health Training Centre, and it would also be very valuable to work with the WHO. Case studies would also offer a way of exploring further some of the concepts in the Nuffield report, such as the fair offer, where it was felt more conceptual work needed to be done: for example by exploring in more detail what the 'fair offer' might mean in specific difficult cases such as where the format of a research study threatens to undermine local health service provision.

- A great deal can also be learned from how other countries have handled difficult situations: examples arising during the meeting included the legal concept of the 'emancipated minor' in Kenya, and the powers given to RECs in South Africa to authorise research that they are confident is ethical, even where it does not meet specific legal requirements.

- Many of the delegates had circulated accounts of the situation regarding children's participation in research in their country before the meeting. These accounts could be elaborated to support either or both of the above aims: of sharing approaches to difficult situations common to many low and middle income countries; and of developing case studies, drawing on the Nuffield report as appropriate, but also identifying areas where there may be a lack of fit. These accounts could then be published as a supplement to this symposium report.

- The frameworks established by H3 Africa through the work of its [ethics and regulatory issues working group](#) also provide a model for how to fill this gap between daily practice and high level principles in individual projects, particularly where they are relatively large-scale.

Sharing best practice in involving children and young people in the wider research agenda

- It would be very valuable to develop similar films to those produced as part of the Nuffield Council project but within low income country contexts, and it was suggested by funders present that they would be interested in receiving proposals for such a project.

- The [GenerationR](#) website of the English YPAG groups, and [iCAN](#) which brings together similar groups around the world, both provide networking opportunities and a platform for sharing good practice in children's and young people's engagement in the wider research agenda.

- Understanding the work of YPAGs as contributing to quality assurance within a research centre / hospital may be a helpful way of gaining acceptance of the potential value that the work of YPAGs can bring.

Supporting a reflexive approach

- Empirical research on research ethics: exploring the lived experience of researchers and participants, in order to inform normative guidance and training, would be a valuable tool in seeking to support a reflexive approach to research and research ethics.

Contributions to guideline development

- Delegates working in countries with no specific guidelines on children and research could use the framework in the Nuffield report, nuanced as necessary in response to context as discussed over these two days, as a basis for developing such guidelines – perhaps first at institutional level, and then with the prospect of encouraging them to be taken up nationally. The Nuffield report and the discussions at this symposium could similarly be used where existing guidelines are found to be problematic in some respects.

Working with others and embedding ethical concerns in funding proposals

- The Wellcome Trust, Medical Research Council, UK Department for International Development (DfID) and the Gates Foundation were all identified as key organisations from whom to seek support for developing these ideas further. One approach would be to ensure that new funding proposals include one or more of these elements as a package: for example

by seeking funding for establishing and evaluating a YPAG as part of new projects involving research with children and young people.

- A World Health Assembly declaration on the value of clinical research with children would send a powerful message to member countries where there remains considerable unease about involving children in any way in research. It was noted that this would require the initiative to come from a number of member states: it is they, not WHO, who can initiate such declarations.

Pledges

Engagement

- To explore the scope for setting up YPAGs in Kenya (SM, DK & VM) and Malawi (NMT).
- To work with relevant members of the Nuffield Council working party and others, to explore the possibility of developing some films around children in clinical research, focused on international settings, with the possibility of drawing on the budget of an existing Wellcome Trust Engagement Fellowship (BS).
- To think further what an 'ethically sensitive framework for engagement' looks like (BS).
- To develop a public engagement event in Bangkok, using a physical drama company to explore the theme of children and research, with the aim of performances by the end of 2016 (PYC).
- To prompt public engagement with parents and children / young people in Latin America, on the model of that carried out in Kenya as part of the Nuffield project, as part of post-graduate work in the region (CS).
- To put relevant contacts (such as Save the Children) in touch with the GenerationR website (GM).

Support for reflexive approaches to research ethics, and REC / IRB capacity

- To take forward discussions with colleagues in the International Strategy Team at MRC, to ascertain if there are any existing or future opportunities for funding research on research ethics (MF).
- To conduct empirical research to contribute to our understanding of the 'lived experience' of researchers and participants, understanding vulnerabilities and abilities of young people and their families in context, as part of a forthcoming Wellcome Trust collaborative award working in Thailand, South Africa and Kenya. This data will then inform normative guidance and training emerging out of the project (MK, MP, PYC, VM, SM, PK).
- To take these discussions back to the CIOMS group responsible for finalising the redrafted CIOMS guidelines (AR and HvD).
- To develop a more indepth analysis of the ethics and regulatory environment with respect to clinical trials with children in Ghana, based on some of the recommendations in the Nuffield report (PT).
- To coordinate the production of case studies working through difficult situations in real-life contexts (KW).
- To coordinate the revision and publication of the country analyses produced by many of the delegates in advance of the meeting (KW).

- To draw the attention of the European Research Council to the Nuffield report, with the aim of exploring further the challenges of obtaining ethical approval for multi-country non-intervention studies in study countries (GM).
- Happy to contribute to any work with DfID regarding ethics oversight of DfID projects (GM).

Dissemination and use in teaching

- Encouraging use of the report in teaching and training – for example by prompting presentations of different elements of the report in training seminars across Latin America (CS).
- Sharing these discussions and the concepts in the Nuffield report within professional networks in Peru with the aim of implementing a number of the recommendations and principles (CL).
- Drawing on the report in teaching rounds at the two paediatric hospitals in Singapore and highlighting its relevance to Singapore's human biomedical research governance framework (CH).
- Using the report in university teaching (AR).

Delegate list

- **Gabrielle Berman**, Research Ethics and Facilitation, UNICEF, Florence, Italy [apologies]

- **Phaik Yeong Cheah**, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand [second day]

- **Hans van Delden**, Professor of Medical Ethics, University of Utrecht, The Netherlands; President of CIOMS

- **Bobbie Farsides**, Professor of Clinical and Biomedical Ethics, Brighton and Sussex Medical School; Co-Director of the Wellcome Trust Brighton and Sussex Centre of Global Health Research, UK (chaired Nuffield Council working party)

- **Meriel Flint**, Programme Manager, Global Health Strategy, Medical Research Council, UK [second day]

- **Kate Harvey**, Senior Research Officer, Nuffield Council, UK

- **Calvin Ho**, Assistant Professor at the Centre for Biomedical Ethics in the Yong Loo Lin School of Medicine, National University of Singapore (NUS); Co-Head of the WHO Collaborating Centre for Bioethics, Singapore

- **Neha Issar-Brown**, Programme Manager, Population and Systems Medicine Board, Medical Research Council, UK [first day]

- **Dorcas Kamuya**, post-doctoral researcher in Ethics and Community Engagement at the Global Bioethics Network, Ethox Centre at the University of Oxford, based at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

- **Claudio Lanata**, Senior Researcher, Instituto de Investigacion Nutricional, Lima, Peru

- **Maureen Kelley**, Associate Professor of Bioethics at the Ethox Centre, University of Oxford, UK

- **Patricia Kingori**, Wellcome Trust Biomedical Society and Ethics Fellow at the Ethox Centre, University of Oxford, UK

- **Katherine Littler**, Senior Policy Advisor, Wellcome Trust, UK

- **Esme Lynch**, member of the London Young People's Advisory Group, UK [first day]

- **Vicki Marsh**, Senior Social Science and Public Health Researcher based at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya; Research Associate at the Ethox Centre, University of Oxford, UK (member of Nuffield Council working party)

- **Sassy Molyneux**, Senior Social Scientist based at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya; University Research Lecturer in the Nuffield Department of Medicine, and Research Associate at the Ethox Centre, Nuffield Department of Population Health, at the University of Oxford, UK (member of the Nuffield Council working party)

- **Virginia Morrow**, Senior Research Officer, 'Young Lives' project & Associate Professor, Oxford Department of International Development, UK

- **Neema Mtunthama Toto**, Clinical Trials Coordinator Malawi-Liverpool Wellcome Trust Clinical Research Programme at the University of Malawi, Malawi

- **Mike Parker**, Director of Ethox, University of Oxford, UK; coordinator of the Global Health Bioethics Network [apologies]

- **Reeta Rasaily**, Deputy Director General, Indian Council on Medical Research, Delhi, India

- **Annette Rid**, Senior Lecturer in Bioethics and Society, King's College London, UK; member of the working group responsible for revising the 2002 CIOMS guidance

- **Carla Saenz**, Bioethics Regional Advisor at Pan American Health Organization, US

- **Abha Saxena**, Coordinator, Global Health Ethics Unit, World Health Organization, Geneva, Switzerland

- **Arianne Shahvisi**, Lecturer in Medical Ethics and Humanities, Brighton and Sussex Medical School, UK

- **Bella Starling**, Wellcome Trust Engagement Fellow; Director of Public Programmes at Central Manchester NHS Trust, Manchester, UK

- **Ann Strode**, Senior Lecturer, School of Law, University of Kwazulu Natal, South Africa

- **Sebastian Taylor**, Head of Global Operations, Royal College of Paediatrics and Child Health, London, UK [first day]

- **Telahun Teka**, Professor of Paediatrics and Child Health, Addis Ababa University, Ethiopia; Chair of the Ethiopian National Research Ethics Review Committee, Ethiopia [apologies]

- **Paulina Tindana**, post-doctoral researcher, MRC Centre for Genomics and Global Health, at the Navrongo Health Research Centre, Ghana

- **Claudia Turner**, Research Paediatrician, Cambodia-Oxford Medical Research Unit at the Angkor Hospital for Children, Siem Reap, Cambodia

- **Sarah Walker-Robson**, Communications Manager, Nuffield Council, UK

- **Hugh Whittall**, Director of Nuffield Council, UK

- **Katharine Wright**, Assistant Director of Nuffield Council, UK

Membership of the working party responsible for the Nuffield Council report *Children and research: ethical issues*

- **Bobbie Farsides** (Chair), Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School

- **Joe Brierley**, Consultant in Paediatric and Neonatal Intensive Care at Great Ormond Street Hospital

- **Imelda Coyne**, Professor of Children's Nursing at Trinity College Dublin, Ireland

- **Elizabeth Davis**, Paediatric Nurse at the John Radcliffe Hospital, Oxford

- **Sara Fovargue**, Reader in Law at Lancaster University

- **Robin Gill**, Professor of Applied Theology at the University of Kent

- **Roland Jackson**, Executive Chair of Sciencewise

- **Vicki Marsh** ('job-share' with Sassy Molyneux), Senior social science and public health researcher based at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

- **Sassy Molyneux** ('job-share' with Vicki Marsh), Senior social scientist based at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

- **Helen Sammons**, General Paediatrician (Derbyshire Children's Hospital) and Associate Professor of Child Health at the University of Nottingham

- **Mark Sheehan**, Oxford NIHR Biomedical Research Centre Ethics Fellow at the Ethox Centre and a Research Fellow at the Uehiro Centre for Practical Ethics, University of Oxford

- **Susan Tansey**, Medical Director (Paediatrics) at Premier Research Group Limited and Associate Director for Industry for the NIHR-CRN: Children (formerly Medicines for Children Research Network)

- **Marc Taylor**, Chair of ISRCTN, a not-for-profit organisation that manages the unique identification of randomised controlled trials worldwide

- **Bridget Young**, Professor of Psychology at the University of Liverpool.