HEAL Response to the Nuffield Council on Bioethics' consultation on 'Children and Clinical Research: Ethical Issues'

This response is the product of discussion by members of the Centre for Health Ethics and Law, University of Southampton (HEAL UoS). This is an interdisciplinary group of academics and clinicians who are associated with the University of Southampton. It is not a formal response from the University as an institution, but reflects the views of members of the Centre. On a number of points the range of views is recorded rather than a single conclusion on the consultation questions. As one might expect, not every individual member is of the same view.

1. What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?

Difficulties can arise around conducting *any* form of research on children; and especially with treating children as 'objects' of the trial, rather than as subjects *per se*. The question suggests a presupposition that the focus is on the obstacles to recruiting individual children, rather than cohorts or populations; yet the challenges may vary depending on the context. Consider, for instance, cluster randomisation trials (CRTs) involving children with research conducted on groups of children in schools, clinics or communities. Considerations about recruitment – especially, what would make particular recruitment strategies ethically permissible – will differ in such contexts compared to traditional clinical research studies. With traditional research studies, either consent or some consent substitute (whether it be assent or substitute consent by parents/guardians) is often taken as an essential requirement for recruitment to be considered ethically permissible. When dealing with large populations or sub-populations of children, there may be good logistical, research design and/or moral reasons for not obtaining consent from each and every research participant without this rendering the research study ethically impermissible. While the focus of this consultation is primarily on clinical research, CRTs are increasingly being used within health services and public health research – as well as in research with direct clinical implications – and, as such, must be something kept in mind when thinking about the ethics of research participant recruitment and its obstacles.

With regard to recruiting individual children (as it were), researchers find it an obstacle to have different ages of consent in operation, dependent on the precise context, and a lack of clarity as to whether a *Gillick* standard of competence applies in different scenarios. This can, in turn, lead to difficulties for research ethics committees in advising on the appropriate approaches, reviews and guidance for individuals or teams of researchers, which can impact negatively on recruitment (or indeed on ethics approval). In short, the research frameworks can be difficult to navigate.

Further practical issues may arise regarding recruitment, i.e., how should children be recruited? Do medical professionals feel uncomfortable in asking families (children) to be involved in trials? Also, who should be involved in the decision-making process regarding involvement – the fact that more than one person may be involved in making the decision can create a further obstacle to recruitment. This is especially acute in cases

where it would be advantageous *not* to have the parents (or others) involved in the decision-making, e.g., research around domestic abuse, etc. For this research, it would be helpful to have more practical guidance on how researchers can better navigate such issues when encountered in the field.

For example, from the perspective of researchers (and also NRES committee members), another practical issue related to recruitment is that for studies involving children/adolescents across a broad age range, there will be the need to develop a number of different participant information sheets, consent forms, and (sometimes) assent forms - sometimes multiple versions are required. Researchers can often find this difficult to do and many of the drafts NRES committee members see are not 'age-appropriate', and either include too little information, or information that is not likely to be understood.

Wider issues include the difficulties that can arise when the 'general public' does not necessarily appreciate that the medicines in question have not been previously tested on children; and accordingly may be unaware of the need for further trials on child subjects. This can be linked to general observations regarding the lack of awareness of research methods, including, for example, the use of placebos and control groups, etc. This may lead to a lack of involvement *in toto*, or to difficulties for continued participation and/or subsequent research if the need for research and/or the methods used are not explained in a satisfactory or accessible way. Better efforts will need to be undertaken to make it clear to the public that safe and effective therapeutic and diagnostic interventions in children will, in many cases, require testing and evaluation on healthy children first. Without such research on healthy children, it is not possible to obtain the best evidence possible concerning what kinds of interventions ill children should receive.

2. Who should make the final decision as to whether a child participates, or continues to participate, in clinical research when parent and child disagree? What responsibilities do health professionals or researchers have in such cases?

This inevitably depends on the context. During our discussions support was expressed for the proposition that if either the child or adult/parent is against participation then the child should not participate. However, this view can be more difficult to sustain when the decisions in question are made by 'mature minors'. It is particularly problematic that the *Gillick* standard falls outside the ambit of the Clinical Trials Regulations, insofar as they pertain to trials of *new* medicines; and its application to other types of research remains unclear. Accordingly, we have concerns over the apparent lack of veto of children under the age of 16 regarding their involvement in clinical research, *per* the Clinical Trials Regulations. The lack of flexibility in these Regulations is problematic, not least in consideration of their (potential) interaction with the Children Act 1989 (including the welfare principle, and the statutory provision made for children with 'sufficient understanding to make an informed decision' to refuse medical, psychiatric of other assessments of the child, ordered by the court (see s.44(6)(b) and s.44(7) CA 1989)), and for challenges under the Human Rights Act 1998 or UN Convention on the Rights of the Child 1989. At the very least the Clinical Trials

Regulations seem to be 'out of kilter' with the broader approach to respecting the wishes of 'mature minors'.

There are also inherent difficulties in defining risk, i.e., if a policy based on low relative risk is used to justify a child's involvement in research. What is the threshold beyond which people should not be exposed to risk, ethically and legally? For example, a questionnaire given to a class of thirty children, which may raise sensitive or otherwise difficult issues, provides different kinds of risks to a clinical trial for medication developed for a specific condition. Ethics committees will weigh up different kinds of risk for each research project before them, but difficulties emerge if a singular approach to ethics is attempted or applied. That is, if something is deemed ethical in one context it can be read across into alternative scenarios, whereas a far more nuanced approach is required. It is not easy to say, then, that parents should decide in scenario X, but the child in scenario Y, as this is too blunt a tool to be useful in practice. In particular, clarity would be good on whether: the ethical approach is best achieved by reference to minimum thresholds of risk, below which research is *prima facie* permissible and above which it may or may not be; or whether it is always simply a matter of the relative weights of benefits and harms. The former lends itself to a more likely means of providing robust rights to children, whilst also not preventing the progress of research agendas.

Three further issues emerged in our discussions:

First, what about decisions concerning continuing to participate once the research is underway? Continued participation (consent/assent) should be a reiterative process, and no adult or child has a duty to participate in research – but the timing may prove essential with very small children (i.e., who say 'no' at one juncture but quickly shift, and vice versa).

Second, if researchers do not adhere to appropriate standards – e.g., in not meeting the research ethics approval protocol for the project in question or other relevant professional guidance - then there is a role for professional regulation to play in assessing, and if required addressing, 'breaches' of research ethics guidance. I.e., the responsibility for assessing which participants should be enrolled in a study does not simply fall on individual researchers, but must also be borne, in part, by the relevant associated professional or regulatory bodies.

Third, concerns may be raised in cases where there are children who want to participate in research, but researchers feel duty-bound to consult parents, which may be exacerbated in 'sensitive' research.

3. How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?

In the absence of a possibility of legal consent (i.e., in situations where the child is unable to give or refuse a meaningful consent), 'assent' can be a useful concept for 'pre-*Gillick*' children. However, acquiring or inferring assent or consent can be

complex in difficult/particular family circumstances, and what should be prioritised in such cases remains unclear.

For young people that meet the *Gillick* criteria, the question arises as to whether and why it cannot be used in the same way in the context of research decisions (putting aside the *dicta* of Lord Donaldson in *Re R/W*). With regard to medical treatment we expect this to be in the young person's best interests (i.e., overall, irrespective of the potential side effects that may/may not eventuate) - so why can they not consent to research too, where there may be similar risks and benefits?

4. A 'shared' or 'collaborative' decision-making model is often advocated for decisions about a child's research involvement, involving the child, relevant family members and professionals. Is this a helpful approach? How might any problems arising in this model be overcome?

As a general rule, or best practice model, 'shared' or 'collaborative' decision-making should be advocated; but there may be a number of valid exceptions which preclude its implementation in practice. For example, research into the use of drugs or sexual relationships, where involvement of the parents or other family members may be problematic; or in CRTs, where it may be inappropriate. In short, it should not be the only approach for research involving children as research participants.

5. Parents' views on whether (and how) children should be involved in decisions vary enormously both within and beyond the UK. How should the law and professionals take account of such different parenting approaches?

We considered how the this question could be interpreted, as there is a huge range of potential subtleties here, and issues were raised as to what should happen if two parents disagreed on the appropriate way forward. While - generally speaking - we would endorse the prioritisation of the child's perspective, the Clinical Trials Regulations currently favour parental viewpoints on enrolment decisions for children under the age of 16, irrespective of the 'style' of parenting or decision-making. One approach endorsed was that a consistently expressed 'no' from a child, of whatever age/development, should be respected (i.e., a persistent and endorsed refusal, as opposed to a single 'no', which might be given when the child is bored, tired or distracted, etc).

However, it is clear that not every parenting approach could be accommodated within the law or professional guidance, but - so far as is practicable to do so - provision could be made to accommodate parental views. It is, nevertheless, difficult to encapsulate this in law. How would it be possible to accommodate, for example, parental approaches that focused on virtue, altruism or solidarity, which provided the reason(s) for consenting to the child's involvement in clinical research? It would clearly be possible for considerations such as virtue and altruism to be explored in other ways, which may pose less risk to the child, e.g., voluntary work. Also, if it is possible to 'impose' virtue on children through the exercise of the law, then one argument raised was that we should do the same to adults too (i.e., both adults and children *might* have an obligation

to participate in research). We would prefer to respect diversity, and seek only to overrule parental views when good reasons for so doing could be shown.

6. Rewards (such as vouchers) for children participating in research may be welcomed as an appropriate way of saying 'thank you', or criticised as a form of undue incentive (to either child or parent). What forms of compensation/reward/expression of gratitude for research involvement do you think are acceptable, and why?

We had a range of responses to this question, and the framing of 'reward' or 'compensation' is significant. For example, we asked why shouldn't children be compensated a reasonable amount for the time (and burden?) of their involvement in research, i.e., as 'compensation' rather than 'reward'? What is wrong with giving children money, or other forms of rewards or expressions of gratitude, for their time? If the risks of the research are no more than minimal, then there shouldn't be an issue in giving rewards or compensation. However, 'rewards' need not be something of monetary value, but could be a certificate or plaque with their name and/or other commemoration of their participation.

The timing may also be key, i.e., would the child or parent know or expect that there would be a reward or some compensation prior to participating in the research? If so, would they know what it was, and if monetary, the amount? When would the reward/compensation be provided, and to which party? Examples were cited where researchers found that people refused to take the rewards offered, suggesting these were not critical to their decision to participate in the research. Other examples were provided of £50 being given directly to the child, at the conclusion of the research, but with parental knowledge. If questions do arise as to whether or not this is luring people into entering research, how can we measure the risk, and what is the harm we would be seeking to avoid?

What is essential in thinking about the potential impermissibility of using rewards or incentives for participating in research is to identify exactly what purports to be the source of wrongness in offering money, goods or services. Is it that such provisions would constitute exploitation, commodification, objectification, coercion, something else? Moreover, do such offers always constitute a wrongful act – and, if not, on what basis should we assess when and why particular levels of rewards/incentives would be impermissible? This is a concern that must be asked in clinical research involving both adults and children, so a further question must be asked as to whether, and why, the use of rewards or incentives in research involving children presents more of a moral problem. One potential source would be, presumably, the concern that children are more vulnerable than adults. Either that, as children, they are more susceptible to these concerns (e.g., exploitation, coercion, etc.) materialising or that when these concerns materialise in children that they are quantitatively or qualitatively worse than when they occur in adults. The key question is whether that comes down to a diminished capacity/competency issue – and in virtue of this diminished capacity/competence children are more likely to be exploited, coerced, etc. – or whether it is something else. Again, for all these possible claims, what matters are clear and reasoned arguments for the source and scope of wrongness that putatively exists when offering rewards or incentives for participation in research. This matters not only in terms of being clear

about what the potential moral issues are but also in terms of how we should approach practical solutions to such concerns.

7. How helpful is the notion of the best interests of the child participant? How would you define 'best interests'?

There are conceptual difficulties in defining 'best interests' in the context of clinical research, as it would operate in rather different circumstances than those usually found in Family Law decisions relating to the child's upbringing or property (and undoubtedly would be beset by the same benefits and burdens that the welfare principle currently 'enjoys' under the Children Act 1989).

8. How can the rights and interests of individual children (potential participants in research) be balanced against the rights and interests of all children (potential beneficiaries of the knowledge gained by the research?

No response.

9. Are there any situations in which you think it would be acceptable for a child to be invited to participate in clinical research when there will not be *any* personal benefit to them. If so, please give examples.

No response.

10. Are there any circumstances where it would be right for a research ethics committee to approve research involving risks they would usually regard as too high, if parents and young people had clearly expressed their willingness to accept these?

No response.

11. Do you think the current regulations strike the right balance between promoting clinical research in children, protecting child participants, and involving children in decisions about their own participation? What (if anything) would you like to change?

No response.

12. With limited resources, how would you decide which childhood conditions should be the priorities for research? Who should be involved in making these decisions?

No response.

13. What responsibilities do funders, researchers and stakeholder groups have to encourage the coordination of children's clinical research?

No response.

14. What responsibilities do researchers have towards child participants and parents when the study is over?

This is very much context driven, dependent on the nature of the study in question. Many research ethics committees would require feedback to be provided to the participants regarding the findings of the study; or, at the very least, this offer should be made. Participants might also be invited to be involved in future research, or assist with the design of future research, or otherwise be involved in the management of the project.

There are potential aftercare issues, including the need to provide information about appropriate support or resources, the researchers' contact information, and/or information about the broader project (if publicly available). Specific issues may arise from the nature of the study, e.g., should parents be given their school age children's test scores, when researchers are aware that these might be used as a basis for a possible (legal) challenge to the local education authority regarding educational provision and lack of appropriate support. Is 'withholding' these results an example of the lack of aftercare? Similar points can be made about the results of DNA testing regarding the future health of the person in question, and whether they should be informed, or be given the option of being informed of future risks. One should also certainly ask the question of whether there is an obligation, at all, to provide aftercare – up and above the mitigation of any potential burdens or risks that directly emanate from participation in research. Alternatively, if the participant has benefited from a medicine provided during a clinical trial, is there provision made for continued access after the study ends? Where there is a lag between the trial and marketing, is there an obligation to provide the drug in the interim period? Also, members of the control group in a study should be permitted access to the drug, just in case it is of benefit to them too. These are further considerations that should be attended to in the Council's deliberations.

Any other comments?

In terms of the provision of practical guidance in specific cases, where it is uncertain which principles should apply, perhaps something akin to the intervention ladder used in the NCOB (2009) *Public Health: ethical issues* report about how to approach public health interventions would be useful to researchers. One could foresee some framework that helps to guide researchers when encountering tough cases as to whether they should be, e.g., seeking assent, whether or not they should be asking parents for consent for sensitive research, etc.