This response was submitted to the evidence call issued by the Nuffield Council on Bioethics' Working Party on *Children and clinical research: ethical issues*. Responses were gathered from 7 August to 31 October 2013. The views expressed are solely those of the respondent(s) and not those of the Council.

NHS
Health Research Authority

Health Research Authority Response to the Nuffield Council on Bioethics Call for Evidence - Children and Clinical Research: Ethical Issues

1. Introduction

1.1 The Health Research Authority (HRA) was established in December 2011 in England to promote and protect the interests of patients and the public in health research. We strive, with partners, to make sure the UK is a great place for health research. Recognising that many members of the public want the opportunity to participate in research, we aim to ensure that health research involving them is ethically reviewed and approved, that they are provided with the information that they need to help them decide whether they wish to take part, and that their opportunity to do so is maximised by simplifying the processes by which high quality research is assessed. In doing this, we will help to build both public confidence and participation in health research, and so improve the nation's health.

1.2 To provide some context for our response during the period August 2012 to September 2013 HRA Research Ethics Committees (RECs) reviewed 854 applications involving children. These involved research in the following categories:

Research Category	No. of Applications
Other Research	703
Clinical Trials of an Investigational Medicinal Product (CTIMP)	113
Research Database	23
Research Tissue Bank	15

1.3 In preparing this response the HRA has sought comments and advice from the Chairs of Research Ethics Committees flagged for the review of research involving children and the National Research Ethics Advisors' Panel (NREAP). The panel is comprised of 7 members including individuals with expertise in moral philosophy, research ethics committees, patient and public involvement and clinical research. The panel is independent but hosted within the HRA and is a resource available to all RECs, funded by the UK Health Departments, within England and the devolved nations. The panel's primary role is to help research ethics committees deliver robust, consistent and fair decisions through consultation with all stakeholders, including RECs.

2. HRA RESPONSE:

How should children be recruited to clinical research?

1. What do you consider to be the main obstacles to recruiting children to research?

1.1 Fear of conflict between children and their parents on the possible outcome of raising the issue.
1.2 Lack of time and training among those who would have to broach the subject with children and families.
1.3 Assumption that children are incapable of making decisions, or may not have the altruistic approach that some adults have.
1.4 Parents may worry about making decisions on behalf of their children. They need to be given careful explanations and a full details of what is involved, and the risks and potential benefits – to their child or others.

1.5 Paternalistic attitudes towards children by clinicians who don't want to burden parents/children with research and don't ask.
1.6 The public's perception that research should only be undertaken with healthy adults. The HRA's recent report "Patient and Public Engagement Project: Patient and Public Dialogue Workshops" found that members of the public were surprised that children took part in clinical trials and thought that such involvement was limited to healthy adults[1].

How might these be overcome?

1.7 The HRA believe that the provision of high quality professional education for all those involved in research involving children will be an important element in any approach to overcoming obstacles to undertaking research with children. The HRA are committed to furthering our training programme, and increasing collaboration with other organisations, enabling development and delivery of joint training and the provision of a forum to facilitate sharing of expertise in this area[2].
1.8 Encouraging engagement and involvement of children, parents/carers and patient groups in the design and conduct of research will ensure that such research is more closely aligned to their needs of children and thus facilitate recruitment.
1.9 the HRA have recently set out its Patient Public Involvement (PPI) strategy and as part of this strategy will exert its influence on those who conduct, fund and manage health research to understand the benefits of public involvement for health research and support the involvement of patients and the public more in their work. The HRA aims to promote and support the spread of public involvement in health research with a view to this becoming the rule and not the exception.[3]
1.10 Raising public awareness about health research in general and clinical trials in particular.

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? (You may wish to distinguish between children at different stages of development and/or the different ways in which disagreement may arise or be expressed.)

2.1 The HRA are in agreement with the UN Convention on the Rights of the Child which "*affirms that children are full-fledged persons who have the right to express their views in all matters affecting them and requires that those views be heard and given due weight in accordance with the child's age and maturity*". Thus, increasing weight will be given to the views of the child shifting the balance of decision making from parents/carers to the child until the point at which the child attains sufficient maturity and understanding ("Gillick competence"[4]) to give valid consent for themselves.

[1] http://www.hra.nhs.uk/documents/2013/08/patient-and-public-workshops-dialogue-report.pdf
[2] Health Research Authority Business Plan 2013 – 2014. http://www.hra.nhs.uk/documents/2013/09/hra-business-plan-2013-2014.pdf
[3] HRA Strategy for Public Involvement. Version No. 1.1. http://www.hra.nhs.uk/documents/2013/08/hra-draft-strategy-for-public-involvement.pdf
[4] The term used to describe a young person's ability to make a decision regarding consent. Although statute (in England, Wales and Northern Ireland) does not govern the rights of those under the age of 16 to give consent for medical treatment or research, case law provides the example of the Gillick case with respect to treatment. This case determined that where a young person has sufficient understanding and intelligence to understand fully what is proposed, and use and weigh this information in reaching a decision, he or she can consent to treatment themselves and consent from parents is not legally necessary – although parental involvement should always be encouraged.

2.2 Where there is disagreement the opinion expressed by a “Gillick competent” child should always be respected. (N.B. The Medicines for Human Use (Clinical Trials) Regulations prohibit children under the age of 16 from giving consent to take part in a clinical trial of an investigational medicinal product (CTIMP))

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

3.1 The concept of assent is considered to be useful. It provides the child with information, and includes them in the research process, before the research begins. It also identifies questions the child may have about the research which may not be obvious to the researcher/parents, and provides an opportunity to address these at an early stage. It ensures that the important voice of the child is heard alongside the consent required from the parent/carer.

3.2 Whilst acknowledging the lack of legal clarity in the use of the two terms the HRA currently provide the following guidance to help differentiate between the two terms:

> “"Consent" - this represents agreement by someone who has been given reasonable information about the request, can understand this, is free of undue influence and has the capacity to make a decision whereas
>
> "Assent/Dissent" - this represents agreement/disagreement by someone who has been given information about as much of the request as they might understand, is free of undue influence and can make a decision on this basis. Seeking assent is not sufficient to authorise participation in research. However, by seeking assent from a child or young person it demonstrates respect for them as potential participants and is important as it includes them in the process even though they cannot make decision to consent to participate. As with seeking consent, assent must be voluntary”[5]

3.3 The HRA have recently updated their current information sheet and consent form guidance which has been published as a “consultation-in-use version”. The following guidance is provided with regards assent:

> “Children’s/young person’s wishes and assent
>
> Even when a child or young person is deemed not competent to make a decision for themselves and in situations where legally they are not empowered to do so (e.g. in a clinical trial of an investigational medicinal product (CTIMP)), it is important that:
>
> - You should give the child/young person information about your study, which is understandable to them and which explains what is involved and the potential risks and benefits.
> - Staff with experience of working with children / young people should provide this information.
> - You must consider the explicit wishes expressed by any child or young person who is capable of assessing the information and forming an opinion. This includes their refusal to take part, or to withdraw from the trial.
>
> Whenever practical and appropriate, a child's assent should be sought before including them in your research.

[5] Information Sheets & Consent Forms Guidance for Researchers & Reviewers (March 2011)

When is it appropriate to seek assent from a child? You have to make an informed judgment to determine when seeking assent is appropriate; the age of a child can only be taken as a guide.

Consider also the child's developmental stage, knowledge of illness and experience of health care.

How are decisions usually made in the family? How much autonomy does the child normally exercise? From observation does the child wish to be involved in the discussions?
What are the parents' views and can they help with this decision? They know the child best.
Although there is a danger that children can be asked to exercise greater autonomy than normal, this must be balanced with the potential loss of trust associated with denying their assent.

Such judgment needs a framework of considerations for analysis, a record of observations and discussions and a documented decision.

In circumstances where seeking assent at the outset is not appropriate, you could provide the child with information as and when required (i.e. 'drip feeding')."[6]

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?

4.1 The HRA believe this to be a helpful approach. However, it may require quite intensive work from the professionals involved. They should be properly trained in communicating with children and young people, using a range of techniques. It may not be helpful to try to achieve a decision in a single meeting. Care should be taken to explore the assumptions that are being made by all parties, with plenty of opportunities for questions. As with all research, it is essential that no-one feels that the child's care or treatment will be jeopardised through non-participation in research.

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?

5.1 Parents should always act in their child's best interests and we believe that these interests, in most circumstances, are best served by the child being given appropriate information and seeking the child's assent to their involvement in research in accordance with their capacity and maturity to understand what is being proposed. By seeking *assent* from a child or young person it demonstrates respect for them as potential participants and is important as it includes them in the process even though they cannot give their *consent* to participate.

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

[6] Consent and Participant Information Sheet Preparation Guidance: consultation-in-use version. http://www.hra-decisiontools.org.uk/consent/principles-children-EngWalesNI.html#four

compensation/reward/expression of gratitude for research involvement do you think acceptable, and why?

6.1 It should be noted that The Medicines for Human Use (Clinical Trials) Regulations (2004) explicitly prohibit financial incentives or inducements being given to children or their parents/carers to take part in clinical trials:

> "8. No incentives or financial inducements are given—
> (a) to the minor; or
> (b) to a person with parental responsibility for that minor or, as the case may be, the minor's
> legal representative,
> except provision for compensation in the event of injury or loss."

6.2 Notwithstanding this legal prohibition in the case of clinical trials we do not believe such an absolute prohibition should be applied in the case of non-CTIMP research.

6.3 It is acceptable to reimburse parents for loss of earnings in facilitating the child's involvement. For older children, near adulthood, small rewards/incentives may be no different in principle from rewarding or incentivising adults. Younger children, however, may be excessively swayed by incentives, or may feel hurt if their participating peers are rewarded when they are not (if they or their parents decide against participation).

6.4 Where rewards to children are deemed acceptable they should go to the child directly not to the carer/parent. Cash payments to children would rarely be acceptable but vouchers may be. In all cases, the reward should benefit the child rather than the parents.

6.5 Compensation (for non-financial losses such as inconvenience, discomfort and time) may be appropriate for children participating in research which may involve longer/more hospital visits/interventions.

What research proposals should be regarded as ethically acceptable?

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

7.1 'Best interests' in the research context are difficult to define given that the inherent nature of research, and the rationale for undertaking it, will inherently mean that outcomes are difficult to predict. However, given the legal requirement for those with parental responsibility to always act in the best interest of the child the concept will continue to play a central part in the decision to allow a child to become a participant in research.

7.2 The current HRA information sheet guidance quotes the Department of Health (DH) on this issue:

> "21.2.2 Legal consideration
> Department of Health, London, Consent: why should we seek it?
>
> The lawfulness of medical research on adults or children who lack capacity has never been considered by an English court and therefore no definitive statement of the law can be made. Where children lack capacity to consent for themselves, parents may give consent for their child to be entered into a trial where the evidence is that the trial therapy may be at least as beneficial to the patient as the standard therapy. It may also be compatible with the welfare principle for a person with parental responsibility to give consent to a research intervention which is not strictly in the

best interests of the child, but is not against the interests of the child. Such an intervention must involve only minimal risk."[7]

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)?

8.1 The balancing and protection of the rights and interests of participants and the rights of those who may stand to benefit from the knowledge gained in the research is central to the review carried out by research ethics committees. Whilst we recognise that the Declaration of Helsinki requires that the well-being of the individual research subject must take precedence over all other interests, it should not be assumed that children may not be altruistic and wish to help other children. Children with life threatening and life limiting conditions may well wish to help others through their own participation in research. In such circumstances, it is extremely important that researchers are completely honest and open about who may be helped, the likelihood of possible benefit and the degree of risk/discomfort etc.

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.

9.1 Yes. As noted in our response to question 8 children may hold altruistic views and wish to participate in research that, whilst it may not benefit them directly, will provide knowledge that may benefit others.

9.2 Research solely involving additional scans or other non-invasive procedures involving minimal risk and minimal burden which is not against the interests of the child is acceptable.

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?

10.1 Not in normal circumstances. One of the roles of research ethics committees in protecting participants is to provide an objective, independent assessment of the risk/benefit ratio involved in the research and to take a view of its ethical acceptability. In doing so RECs take into account the likely prognosis of the potential participants. Clearly, where the patients being asked to take part in the research have a poor prognosis and the research may represent a possible therapeutic opportunity for them, albeit with an associated risk, the REC may find that they will assess a relatively high risk/benefit ratio to be ethically acceptable in such cases.

10.2 However, whilst the "willingness" of the potential participants will be taken into account by RECs in such circumstances it will not be determinative. Other factors will always be in play and the 'strength of feeling' or 'desire' to take part exhibited by the potential participants will rarely outweigh other more objective factors considered by RECs.

10.3 Where researchers and patients wish to challenge the unfavourable decision of a REC in the face of such "willingness" the onus will be on the applicant to provide evidence that the REC has misunderstood the nature of the disease or the burdens that would be imposed by the research which has resulted in an error regarding the

[7] Information Sheets & Consent Forms Guidance for Researchers & Reviewers (March 2011)

weighing of the risks and possible benefits. However, willingness of patients in and of itself will not be persuasive in reaching such decisions.

10.4 The HRA's current Information Sheets & Consent Forms Guidance for Researchers & Reviewers (March 2011) states the following with regards acceptable risk in research with children:

> "19.0 Annex 11: Children's research - what are acceptable risks?
>
> 19.1 Summary
>
> Risk in children's research is a difficult area; guidance to answer the question "What constitutes an acceptable risk for a child participating in a research study?" is limited and guarded. It may be this can only be decided "case by case", using the guidance below. This is another situation where consultation with child and parent groups may help define acceptable risk."

How should research in children be encouraged?

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?

11.1 The HRA fully support, facilitate and promote clinical research in children through their work with stakeholders and through the provision of RECs tasked with both protecting the rights, safety, dignity and well-being of research participants and facilitating and promoting ethical research that is of potential benefit to participants, science and society.

11.2 During our recent public dialogue work, children and young people suggested to us that knowing that patient and public involvement had taken place would encourage them to take part in a study. In particular it was important for them to know that the children and young people had been consulted. Consequently the HRA have amended the latest draft of the patient information to show what patient and public involvement has taken place.

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?

12.1 The priorities would need similar assessment to those made by NICE. The HRA would support the identification and prioritisation of research into diseases that could offer improvements to the majority of children. However, at the same time we believe the benefits of ethical research should be available to all children and would not wish to exclude the targeting of rare diseases where significant benefits can be achieved through research.

12.2 The balancing of such competing priorities in the face of limited resources is a complex and difficult task and would benefit from careful consideration of how to achieve greater and more meaningful patient and public involvement in the priority setting process.

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

13.1 There is an imperative to ensure better coordination of research in this area partly to ensure the same research is not being done repeatedly, particularly if producing unfavourable results.

13.2 Funders have a responsibility to encourage, where applicable, appropriate patient and public involvement with children of the relevant age and to require this as a condition of the funding.

What should happen when the research is over?

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

14.1 Researchers should provide participants with information on the research results at the end of the study. RECs do take into consideration proposals for doing so when reviewing research applications. The HRA have produced guidance relating to the issue of the provision of care after research setting out the issues involved and providing a framework of questions to help NHS RECs and their applicants address this issue. See http://www.hra.nhs.uk/resources/during-and-after-your-study/care-after-research/.

14.2 The HRA have also published "The HRA interest in good research conduct - Transparent research (May 2013)"[8] which acknowledges that there is work for the HRA to do in encouraging researchers to inform participants of the results of the research they have participated in:

> "The HRA public engagement work has identified that further work is required to look how we most effectively provide information to participants and to look at the barriers to getting information to potential, current and past research participants. A high level summary of relevant findings is provided in Appendix 8, a full report will be published shortly. The HRA is currently developing guidance on the provision of information specific to an individual, e.g. what happens to them when the study ends, what arm of a randomised trial they were in, as well as general access to study findings. The emerging view from the work so far is that participants want summary findings to be made available so that they can access them as they wish. The HRA will work with others to set standards and provide guidance on how information should be provided to participants. Consideration of these plans against agreed standards will continue to be an issue for the REC to review at approval. This work will continue through the HRA involvement work stream.

[8] http://www.hra.nhs.uk/documents/2013/08/transparent-research-report.pdf