

Response to Public consultation on Ethical considerations for clinical trials on medicinal products conducted with minors

August 2016

Introduction

- 1 This response draws on the conclusions of the Nuffield Council on Bioethics' report *Children and clinical research: ethical issues*, which was published in May 2015. The full report is available at <http://nuffieldbioethics.org/project/children-research/>. More information about the Council and about this report is annexed.

General comments

Research 'with' children, not 'in' them

- 2 Throughout the document there are references to research 'performed in' children. The Council's report takes the view that, in the context of research, just as in other spheres of life, children from a young age should be understood not as 'subjects' of research but as 'active participants': as people who take a proactive role in determining the direction of their lives, in the context of a life shared with others. Clearly the capacity of any individual child to act in this way at a particular time will vary, depending on any number of factors: their maturity, their state of health, and many other features of their family dynamics and upbringing. However, we make the general claim that, as soon as any child begins to have this capacity for engagement, it is crucial for researchers to understand their role as one of carrying out research 'with' children, and not 'on' or 'in' them.

Challenging vulnerability

- 3 The introduction of the consultation document states that,
"..children are a vulnerable population, relatively incapable of protecting their own interests, and therefore they deserve protection against the risks and burdens of research." (173-175)

The regulation of clinical research with children and young people is often based on this assumption that, by their nature, they constitute a 'vulnerable group', and that such vulnerability automatically demands a protective response. In our evidence gathering we heard concerns that this apparently protective response to perceived or actual vulnerability may not only exclude children and young people from opportunities to participate in activities that are inherently worthwhile, but could also harm the interests of many children in the future by preventing potentially valuable research from taking place. We would emphasise that the possibility of vulnerability rests in the *situation* that a person is placed in, not necessarily in the person himself or herself (as is recognised in the consultation document at 475-476). We suggest that the awareness that children may potentially be vulnerable in a research setting should be used positively, rather than negatively, as an 'alert' to help design better research. Researchers should ask themselves: 'Does this research with children and young people raise particular ethical challenges? If so, what are they, and what can I do about them?' We suggest that an appropriate response by professionals to concerns about children's potential vulnerability in research is to ensure that they work in partnership with children, young people and parents throughout the whole endeavour of research.

Comments on particular sections and themes

Design of clinical trials

- 4 We support the recommendation in 9.1 that the investigator and protocol writer should involve children and parents in the development of information material, but believe that the guidance could go further on the issue of involvement in trial design. We recommended that research ethics committees should routinely require researchers to have involved children, young people and parents, as appropriate, in the design of their studies. Researchers who have not sought input in this way should be required to justify to the research ethics committee why this was not appropriate or possible in their case (for example, because of the urgency of the research, insurmountable cost reasons for locally funded researchers in low-income settings, or because relevant guidance from children, young people and parents is already available), and be able to demonstrate an appropriate knowledge of relevant literature and guidance.

Age groups

- 5 We note that the consultation document acknowledges the importance of taking other factors such as maturity, and experience into account when assessing the capacity of a minor to participate in decision making (section 5.3: 375-377). Nevertheless, we would argue that the use of age categorisations in the document is problematic, bearing in mind not only the diversity of children's intellectual abilities, speed of development, and experience, including experience of illness, but also the *context* and nature of the particular research they are being asked to agree to. Asking a healthy child to take part in a questionnaire study is very different from asking a sick child to take part in research connected with their treatment.
- 6 We propose instead the use of three 'paradigm' or 'example' cases of childhood which raise distinct ethical issues with respect to decision-making in research, and which give rise to distinct concerns and responsibilities for parents and researchers. These draw not only on the capacities associated with particular stages of childhood development, but also on the complexity of the decision to be made, and on situational and temporal factors (such as emotional turmoil or ill-health) which may affect how children and young people experience, and are able to engage with, the research process.

Paradigm cases

Case One: children and young people who are not able at this time to contribute their own view as to whether they should take part in research. This case covers all babies and very young children, but may also apply on a temporary basis to older children or young people if they are unconscious, or very unwell. Children in Case One may, of course, express physical and emotional reactions to the procedures involved in research, but cannot actively participate in an initial decision as to whether they should undertake them.

Case Two: children and young people who are able at this time to form views and express wishes, but who are clearly not yet able to make their own decisions about research involvement without assistance. Many children will be able to express wishes and preferences in this way from a relatively young age. The sophistication of their views will vary significantly.

Case Three: children and young people who potentially have the intellectual capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered to be 'minors' in their domestic legal system. 'Capacity' to make a particular decision should be understood both in terms of the intellectual capacity to understand what is involved and the emotional maturity and experience to understand the wider picture – for example, the likely impact on their future life.

- 7 Although the developmental aspect of childhood means that most children, most of the time, will progress in a linear way through these three paradigm cases, it is nevertheless impossible to suggest meaningful age ranges for each case. This is because the case that is relevant to the situation of a particular child or young person will depend not only on their own maturity and development (combined with other factors such as temporary diminution of capacity), but also, critically, on the *nature* of the proposed research, and hence the nature of the decision to be taken. For example, Case One might potentially cover an unconscious 14-year-old whose parents are asked to consent to involvement in emergency research; or a frightened seven-year-old in severe pain whose parents need to make an immediate decision about commencing participation in cancer research on the day of diagnosis; as well as all babies. Case Two might cover a three-year-old who is a potential participant in a vaccine trial; a 12-year-old who is not used to being trusted with his own decisions in a study about his levels of physical activity; or a 15-year-old with a life-limiting condition faced with the prospect of participating in a phase 1 trial. Finally, Case Three might cover a confident and articulate eight-year-old invited to participate in research about her experiences of using a particular health service; a 13-year-old taking part in a study concerned with use of tobacco and alcohol; or a 14-year-old used to accepting responsibility to take part in a cognitive study including brain scans.

Assent / agreement / informed consent

- 8 We welcome the emphasis in the consultation document on consent and decision-making as a continuous process, rather than a one-off event, and on the importance of involving children in decisions in a way that matches his or her maturity. In particular, we support the stated aim of treating “children as persons who, in the context of their own family and social environments, have the potential from an early age to play an active role in determining their own lives and in engaging with others” (p570-2), as recommended in our report (paragraph 1.25). We further agree that children and young people who are unable to engage at the start of the process must be encouraged and enabled to do so as soon as they are able. This process of engagement is important not only because of the respect it confers on young research participants, but also because it provides the opportunity for them to understand the contribution they are making.
- 9 However, we find the distinctions between ‘assent’ and ‘agreement’ used in the consultation document confusing, particularly given existing and longstanding confusion over how ‘assent’ should be understood. It seems unnecessary to use two distinct terms. We suggest that users of this document would find it much more helpful to have guidance on how to create ethical ‘assent’ processes, alongside reference (as in current section 7.1 of the consultation document) that some Member states may have additional legal requirements, for example with respect to documentation, which must of course also be followed where applicable.
- 10 We welcome the fact that the guidance in the consultation document on assent/agreement is presented under the general heading of “Participation of minors in the informed consent process”, which helps reinforce the argument made in our report that the ethical significance of ‘assent’ is found in the appropriate involvement of children and young people in decisions that affect them. As noted above, we suggested that age categories are, however, problematic and that it is more meaningful to give guidance based on whether the situation in question falls in to Case 1, Case 2 or Case 3.
- 11 We would add to this that where a child or young person fall within case three (as set out above) - where children and young people have sufficient maturity and understanding, but are not yet treated as fully ‘adult’ by the law of their country - professionals have an *ethical obligation* to, wherever possible, seek consent both from the children or young people concerned, and from their parents.

- 12 In cases where the nature of the research is such that parental involvement is believed to be inappropriate, might undermine the research objective or even threaten a young person's well-being, we take the view that it may be ethically acceptable to approach children and young people in Case Three without parental knowledge or involvement. This might, for example, include research exploring young people's drug use or sexual activity. However, such approaches should be subject to specific review by a REC. In deciding whether to give approval, the REC would take into account both the likely value of the research (for example, with respect to informing health service provision within the area), and the sensitivity of planned recruitment processes. Depending on the circumstances, such an approach to research might need, or benefit from, wider community engagement at the design and development stage: openness towards the wider community at this early stage will do much to promote trust in the value of the proposed study, and in the robustness of the scrutiny to which it will be subject

Benefit, risks and burden

- 13 The consultation document describes a wide range of possible risks and burden (see 988-989 "*risks and burden may be physical psychological, or social, may be immediate or delayed, and may vary according to age groups*"). We would argue that a similarly broad definition is needed for the concept of benefit (currently it reads: 913-914 "*Benefit can be defined as progress in treatment, diagnosis, or prevention for the children. It is a tangible outcome that may be experienced by the child or the population*"). For example, at paragraph 2.23 of our report, we note that decisions about taking part in research may also be affected by non-health related motivations, such as an interest in science generally, the chance to learn something new, or because some research processes can be fun. It is also helpful to distinguish between benefits that participants may obtain (including the non-health benefits described above) from benefits that may accrue to the population.
- 14 In addition, the Nuffield Council's report suggests that the notion of children's longer term *welfare* must be understood in a more holistic way than is currently often the case, encompassing the concept that the possibility of contributing to wider social goods may be legitimately considered by parents as 'good' for their children. Such a contribution could take the form of participation in properly regulated clinical research in order to contribute to the knowledge base necessary to improve healthcare for all children in the future. Alongside this there must of course be concern for the physical and emotional well-being of every child participant. Parental consent to research should be based on their confidence that participation in the proposed research is *compatible* with their child's immediate and longer term interests.

Research in emergency situations

- 15 If research decisions can reasonably be delayed until a parent is present and able to make a decision, researchers should wait. However, this will not always be possible: particularly in the case of emergency research. In such cases, the role of the REC/IRB in scrutinising the risks, burdens and benefits of the research takes on added importance. They need to ask themselves whether the research is still a 'fair offer' (see *below under 'Assessment of research'*) in these special circumstances.
- 16 Children themselves should be as involved in the decision about research as they want to be, and are able to be, in a manner appropriate to the urgency of the situation (see *section 7.3*). In emergency research, children and young people are often in Case One at the time the research begins, because they are unconscious or in a lot of pain or distress. However, once they have recovered sufficiently, they should have the opportunity to find out about the research and take part in future decisions. Unless there are very strong welfare reasons to the contrary, any hesitancy on the part of children or young people to participate, in the absence of their parents, should be respected. If young people are in Case Three, then their own decision to consent or refuse should similarly be respected.
- 17 It is essential to inform and involve parents as soon as possible after the research begins. This process should not be understood as 'deferred' or 'retrospective' consent, since it is too late to

ask for consent once procedures have taken place. Instead, it should be seen, first, as the provision of information about what has happened. Then, second, researchers should invite parents to give their consent for any future procedures (where appropriate), and for the use of any data gathered as a result of the earlier procedures. Parents are clearly entitled to refuse such consent if they wish.

Assessment of research

- 18 In our report, we concluded that, in order for RECs to be well placed to make the sometimes very finely balanced decisions as to whether, in a particular case, the burdens and risks presented by a study protocol can ethically be justified, it is essential for them to have access to appropriate expertise: that of professionals with specialist knowledge of children's healthcare, and that of children and families. We suggest that Young Person's Advisory Groups¹ could help with this.
- 19 We take the view that the fundamental role of ethical review is to ensure that an invitation to participate in research would constitute a **'fair offer'** to children, young people and their parents, where the value of the research and its likely risks, burdens and benefits have been carefully weighed up.
- 20 We suggest the following prompts should assist in the assessment of any research involving children and young people (overleaf):

¹ More information about Young Person's Advisory Groups (YPAGs) in the UK and internationally is available at <http://www.icanresearch.org/>

Points to consider when carrying out clinical research with children and young people

- Have you involved children, young people and parents in the development of your study?
 - in the design of the study itself? (e.g. the number of appointments or interventions required)
 - in the development of easy-to-understand information about the study?
- Does your study represent a fair offer to prospective participants? Are you confident that the value of the study, and its likely risks, burdens and benefits, have been carefully weighed up from the perspective of potential participants? Have children, young people and parents been involved in identifying possible benefits, risks and burdens?
- Is expertise in a particular area of children's healthcare important in order for the REC to understand the approach taken in this study? Has this been communicated to the REC, so that it is well placed to obtain advice if necessary?
- Are you able to demonstrate how you will communicate, and discuss, information about the study appropriately and sensitively with potential participants and their parents, so that they are able to make free and informed choices about whether to take part? Does everyone in your team who will be interacting with children, young people and parents have the necessary communication skills?
- Good assent practice is about the process of involving children and young people meaningfully in decisions about research. Are the particular methods you have chosen for involving children and young people in decisions about taking part the most appropriate ones?
- Children and young people who have the capacity and maturity to make their own decision about your study should be invited to give consent (not assent), even if the law additionally requires parental consent. Does your consent process and documentation allow for this?
- Decisions about research participation should, wherever possible, represent a shared decision between parents and children/young people. How will you encourage shared decision-making?
- Is the subject matter of your research such that it may be appropriate or necessary to recruit children and young people without the involvement of their parents? If so, can you justify the approach you have chosen?
- What arrangements have you made to support children and young people who do not have a parent, or another adult exercising a parental role, so that they are not excluded from your study?
- Will clinicians be responsible for recruiting children and young people, for whom they are providing care, to take part in research? If so, is this the most appropriate approach? Have you considered alternative approaches?
- Does the information provided for children, young people and parents explain how and when they can find out about the outcomes of the research? Will those outcomes also be explained in accessible language?

Available online at <http://nuffieldbioethics.org/report/children-and-clinical-research-ethical-issues/12724-2/>

ANNEX

The Nuffield Council on Bioethics Working Party

The Nuffield Council on Bioethics is an independent UK body that examines and reports on ethical issues raised by developments in biology and medicine. It is funded by the Nuffield Foundation, the UK Medical Research Council, and the Wellcome Trust. For more information about the Council see: www.nuffieldbioethics.org.

The Nuffield Council on Bioethics Working Party on children and clinical research was set up in June 2013, and its report, *Children and clinical research: ethical issues* was published in May 2015. More information about the evidence gathering of the Working Party is available at <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>

Members (affiliations correct at May 2015)

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 at the KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

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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.