

Consultation on the revision of “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors”

A response from the Royal College of Paediatrics and Child Health (RCPCH)

Introduction

Whilst the RCPCH welcome the production of this guidance there are several issues we feel that need to be addressed to improve the report from a child centred perspective.

This guidance is likely to be read by a variety of audiences including researchers, clinicians, parents and patients; hence we suggest that the guidance is available in different formats to meet the differing needs of these audiences.

The RCPCH’s response to this guidance lists each section that needs to be addressed with reference to the relevant text’s line number(s) noted in brackets [].

Section 1: Introduction – rationale for the development of recommendations

We fully support this guidance and the need for clinical trials with children and young people [170-171] and their rights to be protected throughout the process [183-184]. The RCPCH’s Turning the Tide report⁽¹⁾ and the RCPCH’s Infants, Children’s and Young People’s Child Health Research Charter⁽²⁾ highlights the need for research, the importance of promoting and supporting clinical research to advance the evidence base and for children to be at the centre stage of efforts to increase and strengthen research to benefit their life long health.

Section 5: Definitions/glossary

For clarity dissent should be listed separately within the glossary. [362-364].

Section 5.5: Ethical review

We fully support the need for paediatric expertise in the ethical review of clinical trials [385-390]. This is a vital component in assessment to ensure high quality research. In July 2016 the RCPCH and Nuffield Council on Bioethics published a statement⁽³⁾ calling for NHS workforce planning bodies to acknowledge the importance of building capacity within the workforce to support more high quality research into child health. As well as asking for appropriate allocation of time for participation in research activities, this statement highlighted the importance for Research Ethics Committees to appoint member(s) with paediatric expertise and for their work to be recognised as a valuable contribution to the research agenda. This will help to ensure appropriate consideration of research proposals and provide access to timely advice on how best to involve children and young people throughout the research process.

Section 6: The process of informed consent

The section of the guidance addressing informed consent is thorough and includes involving children and young people in the process of decision making, along with their legal representatives [492-494]. We suggest further details on the need for researchers to be competent in communicating with children and young people, adapting information and providing children, young people and their legal representatives with the time and space to reach a decision. The infants’, children’s and young people’s child health research charter⁽²⁾ provides links to resources to support researchers in these areas.

Section 6.6: Consent, assent and agreement in emergency situations

We concur there are a variety of circumstances and situations where it would be possible to obtain prior informed consent from the children and young people and/or legal representatives prior to

emergency treatment, and researchers should make every effort to do this. There may, however, be circumstances where treatment needs to be delivered quickly, the child or young person does not have capacity to consent or the legal representative does not have capacity to provide consent or cannot be contacted⁽⁴⁾. By involving children and young people in the design of trials, researchers can ensure that all possible avenues for gaining prior informed consent are considered and protocols for when prior consent cannot be obtained are in place and take account of children and young people's perspectives and needs.

Section 7: Participation of minors in the informed consent process and agreement

For clarity the guidance should include the child's right to withdraw from the research [603-605] in a separate section or under the 6.5 *withdrawal of consent* [507]. Consent or dissent to take part in a trial or withdraw from the trial at any time is just as important to consider from the child or young person as that from the legal representative. This should be given more presence within the guidance.

Section [584-586] states that "If the child's agreement is not obtained, it is recommended that this be documented with justification in the consent form which is signed by the parents/legally designated representative and investigator". It is unclear if this sentence is confirming section [707-709] which states that in the case where "the child and parents/legal designated representative are not able to come to a consensus the dissent of either party is decisive". We fully support section [699-710], and feel this need to be reflected earlier within the guidance.

Section 7.2: Participation and agreement according to age groups and levels of maturity [635-639]

Decision making with regard to taking part in research is not just about a child's or young person's age, but their maturity, the complexity of the project and how the child or young person feels at the time. The Nuffield Council on Bioethics 2015 report⁽⁵⁾ proposes three different research situations, where the questions regarding how to treat children and young people in research will be different. Understanding the different situations and questions to be considered, along with adapted information and materials, will help to ensure children and young people are protected from harm and researchers are able to support and engage children and young people through the consent process⁽²⁾ [318-325].

Section 8.3: Opinion on the application dossier

We welcome the recognition that protocols should be designed and reviewed by parents and patients as appropriate [770-771]. It is important that children, young people and their legal representatives are involved in the assessment of research protocols and applications. The 2015 Nuffield Council on Bioethics⁽⁵⁾ states that Research Ethics Committees should require researchers to involve children and parents in the development of their studies, unless there are good reasons not to. This guidance should incorporate that this assessment is not only critical in ethics review, but at the early stage of shaping of protocols. This can help to prevent risks, burdens and vulnerabilities to children and young people [985-989], by ensuring researchers are working in partnership with children and young people to review study designs, processes and documentation for children, young people and families, prior to ethics committee procedures.

Section 9: Design of clinical trials conducted with the paediatric population

It is welcomed that the guidance highlights the importance of involving children, young people and families in the development of age specific information material, and where feasible the design analysis and conduct of the trial, with exceptions being justified [800-803].

It is important for children and young people to be appropriately involved throughout the research process, design and development of protocols and dissemination of result. Thus ensuring the trial is

grounded in the experiences of children and young people, and researchers remain mindful of children and young people's perspectives throughout. The RCPCH infants', children's and young child health research charter⁽²⁾ sets out how children, young people and their families want to be included in developing and delivering the research. Through a series of consultation workshops and survey responses carried out in 2015/16 children, young people, parents, carers and child health professionals told the RCPCH that they wanted to be given the opportunity to be involved in research design, help other children and young people and share experiences of child health research with others. They wanted professionals to speak to them positively about research and to choose words carefully that didn't have potential negative meanings such as "trial" or "investigate" – both made children and young people think about errors and mistakes.

Through involving children and young people in the early stages of clinical trial development the risk of burden to children and young people can be reduced, as children and young people are involved in assessing acceptability of harms and risks. Young person advisory groups can be one way to involve children, young people and families <http://ypag.grip-network.org/>.

We feel that this guidance needs to incorporate the need for researchers and professionals to ensure they have the time and support to meaningfully involve children and young people strategically and within the research; ensuring this is done in an evidence based, ethical, realistic and properly resourced way⁽³⁾. Professionals need to make time to explain information to children and young people, answer questions, and provide them with accessible information and communication support, as detailed in the NHS accessibility standard guidance⁽⁶⁾.

Section 11: Identifying, minimising and monitoring risks and burdens

The guidance addresses the issue of burden throughout. However it should be made clear that the child or young person and the family concerned should be involved in the process to assess risk, burden and benefit. Furthermore by ensuring the involvement of children and young people in the development and review of research protocols, the acceptable risk and burden for children and young people where they will not receive any direct benefit can be adequately assessed.

The balance between vulnerabilities, risks, and burdens along with the benefits for children and young people's needs to be carefully considered and is central to research involving children and young people. There are scientific grounds for expecting that participation in a clinical trial will produce a direct benefit to the child or some benefit to the population (Clinical Trials Regulations Article 32 1(g)), and in some circumstances a higher level of risk may be reasonable to the child, young person or their family.

The flow chart provided [1197-1244] should include a question as to whether the research has involved children, young people and families to determine if there is a benefit for the child, young person or family concerned.

Section 12.2: Assessing trials with prospect of some benefit for the population represented by minors

In reviewing Annex 3, we feel that Transcutaneous CO₂ and O₂ monitoring should be moved to category one and raised volume pulmonary function tests (infants) moved to category three.

Other comments: Extrapolation of adult data

Infants, children and young people have the right to the highest standard of healthcare. The biology of many diseases and the responses to treatments differ in children and adults, hence, conclusions extrapolated from studies in adults may have limited relevance. However, it is important that it is recognised that the extrapolation of adult data may be possible but this must be justified. A balance

needs to be struck, as there is a danger if appropriate adult experience is not used. Given the large amount of data that could guide care for children and young people there is a need for a more sophisticated discussion on when we and how we might extrapolate from adult research [157].

References

- (1) RCPCH. Turing the Tide: Harnessing the power of child health research. 2012. Accessed 01.08.2016: <http://www.rcpch.ac.uk/system/files/protected/page/Turning%20the%20Tide%20Full%20Report.pdf>
- (2) RCPCH. Infants', Children's and Young People's Child Health Research Charter. 2016. Accessed 01.08.2016: <http://www.rcpch.ac.uk/cyp-research-charter>
- (3) RCPCH and Nuffield Council on Bioethics. Statement on the protection of time for paediatricians to take part in Research Ethics Committees. 2016. Accessed 01.08.2016: (<http://www.rcpch.ac.uk/news/statement-protection-time-paediatricians-take-part-research-ethics-committees>)
- (4) Modi, N., Vohra, J., Preston, J, *et al.* Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees. *Archives of diseases in childhood*. 2014; 99, 887-891. Accessed on 01.08.2016: <http://adc.bmj.com/content/99/10/887.full>
- (5) Nuffield Council on Bioethics. Children and clinical research: ethical issues. 2015. Accessed 01.08.2016: <http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf>
- (6) NHS England. Accessible information: specification. 2015. Accessed on 01.08.2016: <https://www.england.nhs.uk/wp-content/uploads/2015/07/access-info-spec-fin.pdf>