Health Research Authority

Ethical considerations for clinical trials on medicinal products conducted with minors Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Consultation Response from the Health Research Authority[1]

v1.0 3108/2016

Introduction:

1. The Health Research Authority (HRA) was established to promote and protect the interests of patients in health and social care research and to streamline the regulation of such research. We aim, with partners, to make the UK a great place to do health and social care research, to build confidence and participation in health and social care research, and so improve the nation's health. Our responsibilities include the appointment and operation of statutory research ethics committees.

2. The Health Research Authority welcomes this revised guidance regarding the ethical considerations for clinical trials on medicinal products conducted with minors and the changes made to align the document with the regulation and with the latest (scientific) insights on research with children.

Our Comments

3. Much of the current content is applicable to any clinical trial and it is difficult to identify the issues that are either specific to, or have particular relevance for, trials conducted with minors (e.g. section 9.1 "Design and analysis"). A shorter document which focused on the specific issues related to conducting clinical trials with minors would be more helpful to those involved in conducting such research. In addition, a summary sheet with the key points would be particularly useful.

4. **Line 389/712:** reference is made in this document and the Clinical Trials Regulation (CTR) itself to "*paediatric expertise*". This guidance could set out more clearly why paediatric expertise is required and what purpose it serves. Being clear about this will inform exactly what sort of expertise is required for a particular study. In many cases the specific expertise required may not be best provided by a paediatrician and it should be made clearer that in some cases parents (with expertise gained from raising a child with the condition under study) as well as "*nurses, health practitioners, paediatric clinical pharmacologists, and bio-statistical experts*" will be best placed to provide relevant 'expertise' (e.g. around family interactions, consent/assent etc.) rather than a paediatrician.

5. **Line 468:** It would be helpful to clarify that when an adolescent is no longer a minor that data that has been collected previously may be kept and analysed up until such time that further consent, or otherwise, is given by the participant. It would also be helpful to provide guidance on what would happen with regards the retention and use of data previously collected if the participant refuses further to continue taking part in the trial.

[1] This response includes comments received by the Welsh Government's Division for Social Care and Health Research.

6. **Line 715:** In some cases the paediatric expertise may have been provided as part of peer review and consideration may need to be given as to whether further expertise, sought by the ethics committee, is also required.

7. **Line 74/1408**: it needs to be acknowledged that replication is an integral part of the scientific process and, under certain circumstances, may be necessary for some paediatric trials.

8. **Line 832:** Unblinded trials may be permissible in pragmatic paediatric trials where there is no placebo arm and no reason to believe that the participants/parents would have a preference.

9. **Line 836:** Some low intervention, pragmatic trials use medicines that have been provided as part of normal prescribing practice rather than blinded treatments. Whilst it may be desirable to blind it will not always be possible or necessary where hard outcomes are being measured.

10. **Line 862:** It might be helpful to include discussion of cross-over trials in this section (9.2.1 Use of placebo).

11. **Line 900:** Unfortunately many medicines used routinely in children have little evidence to support their use. It might be preferable to acknowledge this and allow for the use of controls that represent 'standard of care'. In addition, medicinal products without a marketing licence can sometimes be the main treatment under investigation.

12. **Line 904:** Radioisotopes are also used for *diagnostic,* as well as *therapeutic,* purposes and this should be acknowledged here.

13. **Line 1207:** An additional question with regards 'subsidiarity' should be added regarding the necessity to conduct the trial in children i.e. "Could this trial be carried out in adults alone and still address the key question?"

14. **Line 1354:** The inclusion of young females who might become pregnant would need to be assessed against the known risk of teratogenicity of the drugs involved. In addition, there are ethical issues to consider where an adolescent girl (under the age of consent for the relevant Member State) screens positive for pregnancy but does not wish this information to be disclosed to her parent(s)/guardian(s). These issues would need to be addressed in the protocol.

15. **Line 1418:** The statement that "*In case of paediatric trials, the summary should be understandable by the children that have participated in the trial*" would benefit from further qualification given that, as currently drafted, this would logically apply to trials involving neonates etc. Furthermore, this statement is not reflected in the "*Summary of Clinical Trial Results for Laypersons Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use*". There would be no requirement for sponsors to upload multiple versions of lay summaries to meet the needs of different ages of children in addition to their parents. If lay summaries are expected to be specifically aimed at child participants, then this should reflect the ages targeted in the information sheets used in that study. There may be studies with poor outcomes or particularly high mortality where the parent/guardian does not wish to disclose the full findings to their child; it should not be assumed that full disclosure of the results to the child is always desirable.

16. **Line 616/ANNEX 2: Information for informed consent:** In Line 616 it states that the information material "should include provision of information on all the relevant aspects of the trial… See also Annex 2 for recommended contents." Annex 2 (which it is implied

by the title relates only to informed consent and *not* assent or agreement) then lists a large number of items that are recommended to be covered in the information sheets but it is unclear whether these items are also recommended for information aimed at minors in order to seek their assent/agreement (as opposed to informed consent). In the absence of further detail it might be assumed that all the recommended items should be included in information sheets for young children. This would not be appropriate and may encourage sponsors/researchers to include all of the items listed in their information sheets for minors – which would be counterproductive and not in the spirit of this guidance. Indeed, the HRA's own guidance (which the expert group kindly reference) points out that:

> *"When seeking assent, an information sheet for children and young people should be much shorter and simpler than a PIS [participant information sheet] designed for obtaining consent. When seeking assent, it is perhaps more important that the child / young person understands what is involved in general terms rather than attempting to ensure that they fully understand every detail of what is being proposed."*

It would be preferable to emphasise that investigators take a proportionate approach and only include those items that are relevant to the study. Some items will be redundant in some studies. For example, in a simple pragmatic trial of existing licensed treatments where all options represent standard care, several of the items on the list will not be required.

17. **Page 39. Points 26 & 27:** It should include the recommendation that sponsors should consider testing the proposed information sheet for readability and understanding with parents and children where applicable.

18. Whilst we recognise that the CTR requires that "*no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial*" it may be helpful to clarify whether age-appropriate, small gifts given in recognition of the child's participation are generally permissible (i.e. which are not presented as inducements at the beginning of their participation but provided following their participation in the trial). We would suggest that, with the agreement of an ethics committee, such tokens of appreciation should be permissible.

For further information, please contact Clive Collett, HRA Ethics Guidance & Strategy Manager, Health Research Authority (clive.collett@nhs.net).

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