National Institute for Health Research

Public consultation on the revision of "Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors"

Response on behalf of the NIHR Clinical Research Network

NIHR Clinical Research Network
Date 31 August 2016

Delivering research to
make patients, and the NHS, better

1. Stakeholder details

This response is submitted on behalf of the National Institute for Health Research (NIHR) Clinical Research Network.

Our national network makes people and the NHS better by enabling and embedding high quality clinical research as an integral part of healthcare. As part of the NIHR, we improve the health and wealth of the nation through health research.

The NIHR Clinical Research Network aims to:

- Increase the opportunities for ALL people across England to participate in and contribute to research
- Provide researchers with the practical support they need to make clinical research studies happen in the NHS
- Work as a single network to improve the efficient and effective delivery of high quality clinical research
- Increase national and international clinical research investment to support the country's growth
- Provide a coordinated and innovative approach to national research priorities.

2. Response

The NIHR CRN welcomes this opportunity to comment on the guideline on ethical considerations for clinical trials on medicinal products conducted with minors. We believe that this is an important document to support understanding and interpretation of the new Regulation. We are supportive of the commitments in the document to involve minors and their parents/guardians in the design of trials and related trial information; and of the principle of supporting access to the benefits of research for this group, where the risks are appropriately balanced.

We have the following specific comments on the proposed text.

Line number(s)	Comment and rationale; proposed changes
149-152 180-184	We fully support the principle that minors should have opportunities to have access to the benefits of research, both from direct participation in clinical trials of new medicines and through benefiting from access to evidence-based medicines, ensuring an appropriate balancing of the risks of trial participation. We believe it is important to have more guidance and research on the balancing of these risks to ensure evidenced based care is available

	to our most vulnerable groups.
157-158	Whilst we support the principle that treatments targeted at minors should be based on research undertaken in minors, we would note that experience of similar products in adult populations should be considered when appropriate and it would be helpful to have further guidance when this would be appropriate.
219-223	Given the wide audience of this document, we believe more could be done to improve its accessibility, particularly for families and participants who will be less familiar with some of the concepts described within the guideline. In addition, it can be helpful throughout the document to make it clear when aspects are legally required by the Regulation, versus recommended best practice.
306	A definition of dissent should be included within the section on definitions/glossary.
329-380	The clarifications around ‘assent’ and ‘agreement’ are helpful. This could be strengthened further by the inclusion of examples where one rather than the other is applicable. The guidance currently reads such that all studies should be conducted with agreement of the child, which is not legally binding, and some also require the assent of the child, which is legally binding. Examples which illustrate this would further illustrate the point, and different requirements/approaches for children of varying ages in the same trial may be particularly helpful. It may support understanding if this could be presented in tabular form based on age range and the requirements for both the minor and their parent/guardian.
482-490	For families from a different cultural background (6.3) it is important for the translation of information sheets and consent forms to be checked to ensure an appropriate level of understanding and accuracy has been maintained through translation.
507	We are supportive of the guidance in this section, but would note that it should be made clear that both the minor (relative to their capacity) and their parent/guardian have understood the relevant aspects.
533-565	Emergency situations: We are supportive of the guidance and see no reason that research with minors in emergency situations should not be conducted on the same basis as with adults. Appropriate ethical

	review is essential in these cases, as is increasing the knowledge and understanding of ethical committees to ensure they are able to take a risk appropriate approach to the review.
542-547	We recommend an additional sentence in this section to ensure that the families have a clear understanding of the trial (given the potential severity of the situation).
553-558	We are supportive of statements relating to raising the research awareness of patients and the public, both in relation to known future risks for a particular patient group, but also as the example has highlighted through raising awareness in the community about ongoing clinical research activity. We believe this pre-awareness that an individual could be approached to take part in research is an important step to supporting the consent process in all circumstances. In our experience, simple measures such as hospitals highlighting on their routine paperwork that they are research active or using appropriate materials in patient waiting areas can be helpful. The NIHR CRN has also recently produced a Massive Open Online Course (MOOC), 'Improving Healthcare through Clinical Research' which is available freely to anyone wanting to learn more about clinical research.
711-794, 800-803	We believe that there should be more information relating to the expertise required for clinical trials relating to children. This should include the expertise required by both those involved in the assessment of the application and those supporting its conduct and delivery. Expertise in relation to the clinical trial should be relevant to the research carried out and should test the principle that the research methodology is robust and relevant and is appropriate for the age group involved. In consideration of the research trial, the appropriate setting should also be considered as a relevant aspect of the research in relation to children. We would also recommend the involvement of a clinical trials pharmacist with the appropriate expertise for clinical trials in children. We are fully supportive of the statements in the guidance regarding the involvement of patients and their families in both the design of the research and development of materials for research. We believe that this could be further strengthened by highlighting examples of existing good practice in this area, such as the use of Young Persons Advisory Groups when considering the design of trials. Apart from the clear benefits of involving children and young people in the design of

	research, the members of these groups are also trained and experienced.
1285-1300	The sampling section was particularly prescriptive (i.e. make one attempt and then move onto the next person). In reality this is not possible; clinicians often work on two attempts. In addition, our paediatric research staff have received feedback from older children that they would not mind extra samples being taken, even if this requires a repeat test. As such, it may be worth considering a more nuanced approach dependent on age and the individual preferences of the child. A more generic approach may be to suggest that in situations where sampling is challenging, researchers should consider the help of more senior colleagues or colleagues with expertise in sampling to minimise the distress to the patient, and should aim to limit the number of sampling attempts.
1301-1322	We believe it would be helpful to present guidance and recommendations on volume of blood for sample collection in tabular format.
1332-1352	The guidance relating to the involvement of healthy children is contentious and would benefit from qualification as it is too restrictive in its current form.
1353-1359	The section regarding the enrolment of young women is also lacking in detail. For example, there is no guidance or recommendations for pregnancy testing, particularly in relation to the use of new formulation of investigations, procedures or treatments using ionising radiation.
Annex 2	We have had feedback from families that information leaflets can often contain too much information. Therefore, we support the inclusion of precise and accurate information to allow the patient and families to give informed consent after having being 'well informed', but would advise ensuring that information leaflets are not over-burdening.
Annex 3	We are supportive of the approach and the classifications generally, though propose the following: Tanner staging: suggest moving to category 2. For some children,

	particularly those from religious backgrounds, this can be a deciding factor about whether or not to participate in the trial, suggesting there is more than minimal burden. Subcutaneous injections: add * as this could be a higher burden if required regularly, .e.g. every day. This can increase the burden both psychologically and physically, by the hardening of skin and formation of scarring making it more painful and difficult to inject overtime. Many children do not like to move injections to other areas such as the stomach, and this process can sometime cause distress and anxiety. Collection of tissue removed from body as part of medical treatment: suggest moving to category 2, as a procedure with no anaesthesia or local anaesthesia can cause great distress and anxiety. Arterial puncture: suggest adding * or moving to category 3 due to the nature of the procedure and the risks involved with the minor moving. Bone marrow aspiration: suggest adding * or moving to category 3 due to level of pain associated with this procedure. Topical analgesia: suggest removing * as negative experiences are not generally reported. Pulse oximetry: suggest removing * as negative experiences are not generally reported. The burden may be higher if needed overnight. MRI, DEXA and CT scans would all have an increased burden if the child needed sedation. As sedation is included in category 3 this may already be covered.