ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN

IN DER BUNDESREPUBLIK DEUTSCHLAND e. V.

- DER VORSTAND -

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Public Consultation on 'Ethical considerations for clinical trials on medicinal products with the pediatric population'

Comments

The Association of German Research Ethics Committees has been founded in 1983 and represents all Ethics Committees that are involved in the assessment of clinical trials with medicinal products and medical devices in Germany. We welcome that the 'Ethical considerations for clinical trials on medicinal products with the pediatric population' (Ethical Considerations) of 2008 get updated and that the EU has published the draft version for public consultation. The new version is in general well-balanced, covers relevant issues and is suited to promote high and uniform ethical standards in clinical trials with the pediatric population in the member states of the EU and beyond. Our comments are the result of intensive discussions with our members, in particular with pediatricians who are members of RECs themselves.

Points of major relevance

12.2. Assessing trials with prospect of some benefit for the population represented by the minor (lines 1159 – 1281, and Annex III)

Art. 32 para 1 g ii) of Regulation (EU) No. 536/2014 permits clinical trials with minors only if there is either the chance "of a direct benefit for the minor or some benefit for the population represented by the minor concerned and *such a trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition".* There is little doubt that this wording leaves room for various interpretations. All the more these Ethical Considerations should clarify the meaning as far as possible, having the well-being of the minors in mind. Appropriate examples should be provided to assist the correct understanding of this legal prerequisite. In our view the methodological approach of Annex 3 (Examples for levels of risks and burden) is inappropriate at least as far as category 2 is concerned. This catalogue had originally been

developed under the auspices of Directive 2001/20/EU which did not establish the *minimal* risk and burden criterion for minors, but merely the duty to *minimize* risks. Consequently, category 2 of Annex 4 of the 2008 Ethical Considerations has not been characterized as "minimal risk and burden" but – correctly – as "minor increase over minimal risk". In fact, the procedures mentioned in category 2 impose, as such, quite a considerable degree of risk and burden. *What has explicitly been more than minimal risk under Directive 2001/20/EU cannot be defined now, without any modifications, as minimal risk under the new Regulation.* Therefore it is inappropriate, simply to leave the catalogue as it is although the legal situation has changed by introducing the minimal risk-limit in Art. 32.

It would also be a misunderstanding of the wording *"minimal risk […] in comparison with the standard treatment of the minor's condition"* in Art. 32 para 1 g ii) of the new regulation. This means that it is not the total of the risks involved in the treatment which is relevant but the *increase* of risks and burdens in comparison to those which would also arise under the standard treatment of the minor's condition. This is probably meant when in the introductory text to Annex 3, category 2 is explained as being applicable only if standard treatment involves the same or comparable procedures anyway. However, this explanation is not quite precise. It is not sufficient that the standard treatment involves procedures of the same kind. It must also involve such procedures with the same frequency. In our view, the correct understanding of the minimal risk and burden requirement is that the *additional* risk and burden due to the clinical trial must be minimal, i.e.: the risk and burden coming on top of that of the standard treatment. Beyond this, there is no room for qualifying significant risks as being minimal simply because the standard treatment involves significant risks, too. This should be made unmistakably clear in the Ethical Considerations.

We missed some relevant topics completely: clinical trials involving still unborn human beings, institutionalized minors, and minors with legal carers. These three groups may be considered as particularly vulnerable.

The length (~ 50 pages) of the Ethical Considerations may discourage from reading and the use of this important document. Throughout the text are many repetitions, thus there are options to shorten the text, without waving important topics.

<u>Additional Points</u>

<u>199-203</u>

As far as we know there are few, if any studies on the effects of a staggered approach. Interestingly references are missing for the claim that a 'staggered approach' results in a prolonged off-label use for the younger age groups.

Thus we recommend to modify substantially the current wording which rejects a staggered approach without any limitations.

492-501

One wonders whether these frequent discussions and their documentation that are recommended here, provide relevant added value. All participants are well aware that they can withdraw the informed consent at any time.

599-603

We see no reason to be more strict than Art. 32 para 1 c) which says that "the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Art. 29 (2)……. is respected." Thus the statement : " The child's will should be respected……."(line 603-605) is too general and should be deleted.

614-615

Information material should not be approved by the Member State, but by the competent Ethics Committee in the MS concerned. The first part of the next sentence "The information material should have been tested" should be reconsidered given that this requirement will lead to a substantial delay of the trial start and additional costs.

621-627

This is a repetition of lines 492-501 and should be deleted.

650

References for this claim are missing

657 onwards

We recommend to discuss these issues considering whether the child shall participate in a trial with the chance for a direct benefit or not. We think the formulations used are too strict and do not consider special circumstances, e.g. when a clinical trial is the only option to receive a treatment for a life-threatening disease which is still untreatable outside of a trial.

692

We think it is inappropriate to use here the same wording : …. "should be respected" as is used for pre-schoolers (line 656). In our opinion the closer a child gets to the legal age of adulthood, the more it is obvious that he/she can only participate if informed assent has been provided.

755

We think that minors who do not yet use contraceptives should definitely not be included in a clinical trial that does provide some benefit for the group only. The same is true for trials for diseases where approved and evidence-based treatments are available.

770

The sentence “The protocol has been designed with and reviewed by parents and patients.” should be reconsidered re the implications. Does that mean, that a trial protocol that has been developed without pediatric patients and/or not reviewed by pediatric patients cannot be approved by the MS ?

803

One wonders how children and their? families shall get involved into the conduct and (statistical) analysis of a trial ?

804

It should be added here that for trials that provide for group benefit only, risks and burdens have to be minimal.

856-857

‘and for prophylactic vaccinations, when there are already effective vaccines" should be added to the first sentence.

934

The wording “equal chance to be allocated to either arm” neglects the option of unbalanced randomization, e.g. 1:2.

1020

A clarification is needed for the meaning of “over-studied population”

1123

It needs to be stressed that ‘high levels of burden’ are not permitted for trials that aim for group benefit only.

1171-1186

The exact meaning of these two paragraphs remains nebulous. Please clarify and provide examples.

1261

The sentence “For instance, when the minor no longer has a prospect for cure, standard treatment is palliative care.” is in our opinion not correct, as it disregards chronic diseases. Chronic diseases cannot be cured but the adverse

impacts can be relieved. Palliative care is very much associated with end of life care, particularly for patients with cancer.

1314

"In the rare case of simultaneous trials……".This should not happen with minors.

1353-1359

We think that minors who do not yet use contraceptives should definitely not be included in a clinical trial that does provide some benefit for the group only. The same is true for trials for diseases where approved and evidence-based treatments are available.

1417-1418

This sentence needs further specification. At present it requires that a summary is understandable even for neonates.

Annex I and II

Both annexes would benefit from a grouping.

Annex III

In addition to our comments re 12.2 we miss a statement that risks and in particular burdens are to a large degree depending to age, e.g. in the very young many imaging procedures require anesthesia, whereas older minors can do without. We consider oral glucose tolerance tests and digitally amplified chest or limb x-ray as more than 'no or minimal risk and burden'. Risks and burden can only be properly assessed by an Ethics Committee if the trial protocol with all the detailed provisions is available.

Question 1

The proposed categorization is partially not adequate, since risks and burden are often age dependent and the burden due to the clinical trial depends on the disease, its treatment intensity and the exact definition of medical procedures, necessary for evaluation of disease activity. Procedures in category 2, e.g. umbilical catheterization, MRI scan in infants, paracentesis, and skin punch biopsy require adequate sedation, but analgesia and sedation belong according to the categorization list in category 3. Repeated spinal CSF tap require analgesia and sedation as an adequate way of treatment in children. These considerations demonstrate that a simple categorization of procedures is not possible without knowing the exact circumstances and the age of the patients. The list as presented in Annex 3 is not helpful and somewhat misleading.

28.3 References

Please add: Imme Petersen, Claudia Spix, Peter Kaatsch, Norbert Graf, Gritta Janka, Regine Kollek: Parental informed consent in pediatric cancer trials: A population-based survey in Germany. Pediatr Blood Cancer (2013); 60(3), 446-450.