Comment of the Network of Coordinating Centers for Clinical Trials (KKS-Network), Germany

on the

Consultation document "Ethical considerations for clinical trials on medicinal products conducted with minors" (01/06/2016)

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

General Comment:

We welcome the document which can serve as a good reminder on things to be considered in paediatric clinical trials for all persons involved in the planning, conduct and review of a clinical trial. The document provides definitions and reminds on differences in the European Member States regarding the legal framework.

For Rare Diseases there should be an exception made so that clinical development would not have to start in adults. In some of those diseases, primarily children with the disease are available. E. g. for congenital rare diseases adults may even not be available or treatment is considered to improve developmental processes which are not relevant for adults (e.g. growth).

The list of issues, recommended items and examples provided in Annex 1-3 can serve as check lists for all stakeholders. However, we would find a few adaptations in the assignment of some procedures to the different categories mentioned in annex 3 necessary:
As a standard, in our view the use of anaesthetic plasters to minimize local pain should be made mandatory for venipunctures. Furthermore, needles should not be used but "lines", i.e. if serial venipunctures have to be taken on one day. Lines are no more invasive than venipunctures but are less painful and therefore should belong to category 1. Sampling of skin cells for cell cultures are only minimally more painful as a venipuncture and should therefore also belong to category 1, maybe 2, but not to category 3. Psychological tests and IQ-measurements are judged as invasive and sometimes are as they might influence parents-patient relationship. We would therefore put those in category 2.

The Paper should include a statement that the IMP should be made available for further treatment of the minor if the treatment has shown to be effective and tolerable.

Specific comments:

Line 166-167: *"The neonate represents the most vulnerable of all paediatric age groups and requires even more careful review"*

We find this difficult. What is the measure for being most vulnerable? Some retarded children or children and adolescents with psychiatric disorders are also more vulnerable than others.

Line 195-197: *"Because of the special protection they deserve, minors should not be the subject of clinical trials when the research can be done in legally competent subjects (i.e. adults capable of informed consent)."*

It should be mentioned that some especially rare congenital diseases are detected in children and no adults will be available to test. So there should be a general exception that clinical development could start in children if there are no or very few adults available with the disease.

Line 494-498: *"It is important to realise that consent is a dynamic, continual process, and should therefore not only be obtained prior to enrolling a child in a trial but should be maintained during the trial on a continual basis. The child should be involved in this (cf. Section 7). This could be done, for example, by a brief discussion during each repeat visit. It is recommended to document this process in the medical records or equivalent."*

Is this meant as a requirement to discuss the consent for participation at each visit? Would it not be sufficient to document any objection against continued participation?

Line 615-627: *"The information material should have been tested in the relevant population..."*

How should this be done? What does tested mean?
Is this a legal requirement or a recommendation?

Line 621-627: *"Agreement, like consent, is a continual process and should be sought during the trial as well, e.g. during repeat trial visits. The processes for informing the child and seeking agreement should be clearly defined in advance of the research and documented for each child. While agreement may not be possible in all age groups (e.g., neonates), the information process provided to the child and the child's response should be documented. In any case, the investigator should report on the agreement procedure in writing, even if the agreement could not be given in writing."*

See comment above; it should not be necessary to obtain continued consent in writing, even if this would be possible.

Line 729 – 732: *"Paediatric expertise goes beyond having professionally worked with children and could be defined on the basis of a combination of education, training and experience on the various aspects of child development, ethics and psychosocial aspects. Paediatric expertise is preferably provided by a paediatrician with at least some years of experience in paediatric care, some years of direct experience of clinical trials with children in similar age groups, Ethical considerations for clinical trials on medicinal products conducted with minors expertise in clinical pharmacology and expertise in ethics."*

We agree this is important.

Line 770-771: *"Moreover, for paediatric trials, the following points should be examined:...The protocol has been designed with and reviewed by parents and patients (if applicable, based on age an level of understanding)".*

It might not be feasible to design and review the protocol together with parents and patients. We understand this is just a recommendation, but this seems to be in contrast to line 800-803.

Line 800 - 803: *"To ensure feasibility of trials to be performed, the investigator and protocol writer should ensure that there is involvement of children (suffering from the relevant condition) and of families in the development of information material, and where feasible also in the design, analysis and conduct of the trials. Exceptions to this recommendation should be justified".*

It might in most cases not be feasible to ensure the involvement asked for.

Line 849: *"In addition, they have more complex logistical issues, as participants are fewer and more dispersed (this is a higher burden to children and their families), and require often more trial sites."*

It should be added that for congenital rare diseases adults may even not be available or treatment is considered to improve developmental processes which are not relevant for adults (e.g. growth).

Line 988: *…,psychological,…"*

Should read "mental" oder "psychic"

Line 1080: *"…under topical anaesthesia if repeated blood sampling is necessary. Non-invasive procedures should be preferred, if validated. Population approaches…"*

The use of anaesthetic plasters to minimize local pain for venipunctures should be mandatory and then category one is reached for venipunctures and intravenous lines for repeated sampling.

Line 1255-1257: *"When there are multiple standard treatments, an ethics committee should assess the risks and burdens of the clinical trial in comparison to each of the different standard treatments that are common for the paediatric population under study."*

For very specific diseases or interventions (e.g. gene therapy) experts should be included if possible.

Annex 3, table on page 43

<u>Category 1</u>

Psychological testing
Psychological tests and IQ measurement can be invasive, because unexpected low results might influence parents-patient relationship. This should therefore be moved to category 2

Oral glucose tolerance test
Glucose Tolerance tests are regarded as invasive by patients because multiple blood samples are required and glucose solution tastes bad; Could stay in category 1 if anaesthetic plasters are used.

Category 2

Peripheral venous lines
Not more invasive than venipuncture; Peripheral venous lines should therefore be moved to category 1, i.e. if the use of anaesthetic plasters to minimize local pain for venipunctures would be made mandatory.

Spinal CSF tap
Only for trials in life threatening disorders

Bone marrow aspiration
Only for clinical trials in life threatening disorders

Category 3:

Biopsy:
Depends on site of biopsy: Skin biopsy could be moved to category 2 as it is an essential tool and can be carried out painless.

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