General Directorate for Health and Food Safety. DG SANTE.

Contribution regarding Public consultation on the revision of "Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors "which has been developed in preparation for the implementation for the Clinical Trials Regulation (EU) No 536/2014.

This contribution letter represents:

- Medicines Committee of the Spanish Pediatrician Association (CM-AEP).

- Translational Research Network in Pediatric Infectious Diseases (RITIP)

- La Paz Central Research and Clinical Trials Unit (HULP-UCICEC).

- Investigational Ethic Committee of University Hospital 12 de Octubre.

- Clinical Trials Unit -Hospital Clinico Universitario de Santiago – Instituto de Investigación Sanitaria de Santiago

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General considerations

The document is drawn up following the provisions of the EU Regulation, and we have not found disagreements regarding the new Royal Decree (RD1090/2015) regulating clinical trials in Spain. Nevertheless, some details would have to adapt to our legislation. In general, it seems that it covers all relevant information to be used as a guide for action in pediatric clinical trials.

Specific considerations

Q1: The table of Annex 3 (previously Annex 4) has not been changed. Is the proposed categorisation of these procedures still adequate?
Q2: Which insights may lead to changes in categorisations (in particular those indicated in yellow)?

Classification of risk and burden table

We recognize that a classification and categorization is necessary and the proposal (in ANNEX 3) remains adequate, however we have some doubts if a standard categorization is valid for all age groups, above all for extreme groups.

In any case, we would like to point out that the level of risk should be compared with the risk in routine clinical practice, more than with a determined technique or procedure. Additionally, it should be highlight there are some procedures that are at the boundary between one group and another; if in doubt, we would choose the next higher level of risk. For example, in category 2, if there are invasive procedures that are not part of routine clinical practice in these children, you could be considered Category 3.

Following, we detailed some comments about the procedures.

Items in category 1:

- Tanner staging. Correct
- Collection of tissue removed from body as part of medical treatment*. It seems low risk, but it is not very common as technique.
- Lung function tests (peak flow, exhaled NO, spirometry). Correct.
- Oral glucose tolerance test. Only in healthy children could be considered of minor risk in other cases, should be included in category 2.

Items in category 2:

- Umbilical catheter. Correct
- Transcutaneous oxygen or carbondioxide tension monitoring. Correct. Involves greater risk than a pulse oximeter because sensor could produce burns in a preterm baby.
- Peripheral venous lines. Correct
- MRI: only category 2 if sedation is necessary. In any case could be in category 1.

- Airways or skin hyper-reactivity challenge test. Correct.
- X-ray DEXA bone density measurement. Correct, but it could be value as high risk because the radiation.
- Airways or skin hyper-reactivity challenge test. Correct

Items in category 3:

- Biopsy. Correct. But depending the localization or if it is part of the clinical practice could be considered as category 2.
- Sedation. Correct
- Hypoglycaemia test. Correct
- PET scanning. Probably could have similar risk than other test that need contrast media (category 2).

F1: General feedback on clinical trials in minors in emergency situations (within the meaning of article 35 of the clinical trials Regulation) is welcome.

The text contains properly all that should be done ethically in emergency situations. We would like to highlight that the consent of the parent / guardian (assent of minor if applicable) or ratification must be requested (as applicable) as soon as possible.

Regarding the possibility of inclusion of a third party in the consent of participation in clinical trials, this is not contemplated in the Spanish regulation, but also we are not in favor of this option. This responsibility should be limited only to the parent/guardian.

Other considerations

- Informed consent of families with different cultural backgrounds. Pag.13. In Spain, informed consent must be always in in the local language, Spanish in general and in other languages spoken in Spain like Galician, Catalonian or Basque. Obviously any strategy in order to facilitate the informed consent understanding, should be implemented, including to translate it into other languages when appropriate.
- Consent at the beginning of a trial and continued consent during trial. Pag. 13. We especially agree with this part of the document.
- Withdrawal of the consent. Pag. 14. In trials where anesthesia is involved, the informed consent must include the information about withdrawal.

- Agreement of minors. Pag. 15. Agreement is not mandatory by law. It is not considered in the Spanish regulation. We do not consider for the moment necessary to ask for it. In this regard we consider difficult to assess whether the child can give agreement and to know who and how he can value it.

- Assent. Pag. 16. Spanish law RD1090/2015 provides the age for assent between 12 and 17 years old.

- Opinion about the dossier. Pag.19. Usually in Spain, the protocol is not reviewed by parents and patients.

- Other consideration that we understand that can be covered by legal (national) regulations are those related with the consent by divorced or separated parents.

- Relative to point 15.-Trials with healthy minors, and point 21.-Inducement versus compensation for children, we find a lack of information/discussion about the possibility of compensation (with gifts or money) to mature children participating in clinical trials (or substudies) without direct benefit for them (for example pharmacokinetic studies in hemophilic adolescents with new antihemophilic factors).