30 August 2016

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

Comments from:

Name of organisation or individual
[redacted]

1. General comments

[redacted] welcomes and strongly supports the **revision of "Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors"** document and the emphasis on child maturity, on classification of age groups, on new term of agreement vs. assent, on continuous consent process and consenting in emergency cases.
However, we consider that the use of a medical product without MA as reference in controlled trials would need more explanation, as well as the procedure for consenting in emergency cases.
Moreover, we would also consider important if this guideline would set basic requirements for allowed advertising in clinical trials in minors (especially in rare diseases, but not only).
Considering that this guideline makes reference to the national legislation on many aspects, it would be very helpful to the industry to have attached to this guideline a list on per EU MS basis with consolidated requirements for assent and agreement depending on age of legal competence (similar to ICF and Assent Tool Kit), as it may happen that the EU regulation will come in force, but not the national legislation to set these requirements.

2. Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes
170 202	"Off label use" term should be defined.
216-218	Is this guideline also applicable for non-interventional CTs in minors? If so, it should be added.
221	It should be specified that this guideline is also intended for the use of CROs among the rest of stakeholders.
282	EMEA/CHMP/EWP/147013/2004/Corr guideline "Role of pharmacokinetics in the development of medicinal products in the paediatric population" is not listed among relevant guidelines. Also, the revised GCP guideline version should replace the current one, when finalized.
466-468	"As soon as a minor becomes legally competent to give informed consent during the course of the trial, no trial-related procedures may be performed until informed consent is provided." If the patient is already participating in a CT, but in an outpatient setting, would it be ethical to stop treatment until his/her consent is obtained?
553-554	For obtaining consent in emergency situation, we believe that since it may happen that the national legislation is not in place, a minimum set of requirements or restriction should be included in the document as a general guidance.
603	On one hand, it is the right of minor to be able to withdraw from a CT without providing any reason, but on the other hand the investigator should be able in case of resistance

Line number(s) of the relevant text	Comment and rationale; proposed changes
	to understand and appropriately respond to child's worries. Practically, how can a PI respond if no reasons are provided?
615	The information material should be tested in relevant population prior to use. More details on the actual requirements should be provided. Also time needed to have the information document tested should be taken into account when setting up a study in minors. It is expected that this will delay the start-up of research in paediatric population.
770-771	It is expected that the protocols for CTs with paediatric population are to be reviewed and designed by patients and parents. How is it considered that this can be achieved and documented at the practical level? Moreover, it is expected that this will delay the start-up of research in paediatric population.
781-783	Continuous access to newly developed drugs until the products are readily available on the market or through national programs is more than welcomed (when clinical benefit has been proved, of course); however, the national legislation in different MS may be in contradiction with this honourable principle, thus, probably it should be emphasized that the national legislation should be harmonized to encourage this continuous access.
895-902	It should be clarified what type of reference, not registered, medicinal products would be acceptable in children: products not registered in the respective country but registered in another European MS or in an ICH country? Or products registered in another region/country? Or products not registered anywhere?
1273	Typo "minorsn" to be corrected
1468-1476	"According to Directive 2001/83/EC, clinical trials submitted in a marketing authorisation application in the EU, which were performed in third countries (non-EU countries), should be conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of Clinical Trials Directive (to be repealed by the Clinical Trials Regulation) and should comply with equivalent good manufacturing practices of EU countries." The Directive 2001/83/EC only refers to GCP compliance of CTs conducted outside EU and not to GMP compliance equivalent to the EU("A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC."). This is a misunderstanding and should be corrected/rephrased.
1485-1488	This document recommends actions to be taken by Investigators and Sponsors carrying out trials in third countries that may not be practically achieved without the involvement of local CAs. How is this foreseen to be done at this stage?
1496-1498	GCP noncompliance in CT on minors are not to be reported via EU portal?
1513	"Non-GCP compliant trial" syntagm should be defined, as currently is vague.
Page 43	Table with classification of risk and burden contains items accompanied by "* "symbol that is not explained in the text.