ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

29 August 2016

Directorate General for Health and Food Safety DG SANTE
Unit B4 "Medical products – Quality, Safety and Innovation"
European Commission
F101 08/058
B-1049 Brussels

RE: Public consultation on "Ethical considerations for clinical trials on medicinal products conducted with minors"

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through pivotal studies assessing the safety and effectiveness of new products – as well as post-approval and pharmacovigilance research. With over 33,000 employees engaged in research activities in Europe, and more than 120,000 worldwide, ACRO member companies advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 pharmaceutical, biotech, and medical device sponsors of clinical trials each year.

ACRO's comments are organized into 3 sections:

- general comments and feedback on highlighted topics (Q1, Q2, F1, F2)
- suggested revisions to specific line numbers in the consultation document
- topics omitted from the consultation document and recommended for inclusion in the final document

I. General comments and feedback on highlighted topics (Q1, Q2, F1, and F2)

ACRO welcomes and strongly supports the draft recommendations on ethical considerations for clinical trials on medicinal products conducted with minors developed by the European Commission's expert group on clinical trials for the implementation of Regulation (EU) No 536/2014. ACRO congratulates the expert group on developing a very comprehensive and well-considered document that provides helpful, practical guidance to ensure that the complex ethical considerations associated with paediatric clinical trials will be understood by the target audience. ACRO especially welcomes the fact that the draft recommendations are intended to apply to all clinical trials in minors and do not distinguish between commercial and non-commercial research. ACRO is pleased to respond to the request for feedback on specific topics as follows:

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)?

ACRO Response to Q1 and Q2:

- Tanner staging involves undressing and examination of private parts, which is required in clinical medicine for children with particular conditions. This evaluation in children who do not have such conditions seems intrusive, and so should be in Category 2.

- Umbilical catheter placement is unlikely to be sensed by the neonate; it is unclear why this should be a Category 2 procedure.

- The reason for categorising pH-metry as Category 2 is unclear. If the measurement is performed on biological samples already taken, the burden is non-existent. If the measurement is conducted *in vivo*, e.g., by an endotracheal probe, then the discomfort relates to the probe rather than the measurement for which it is being used.

- Electrophysiological measurements using stimulation will commonly involve the use of sedation, the placement of electrodes in or near the heart, and the generation of symptoms in the patient which are probably new. The laboratory setting may also be intimidating. Based upon this, such measurements should be in Category 3, together with cardiac catheterisation.

- Spinal CSF tap will require the child to remain motionless during the procedure; given the risks to the child of moving during the placement of the tap, this should be a Category 3 procedure

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

ACRO Response to F1:

The consultation document does a good job of addressing the complexities associated with the absence of prior consent (deferred consent) in clinical trials in minors in emergency research. One point that is not covered, however, is that there may be cases where an emergency situation applies only to a subset of the trial population (i.e., the most severely ill patients who may die or suffer

long-term incapacity without immediate intervention) whereas for other patients it may be possible to obtain informed consent and assent/agreement in the usual way. Consequently, ACRO recommends the inclusion of a statement to the effect that the clinical trial protocol should prospectively define the parameters under which deferred consent will be permissible, as well as the process(es) to be followed for obtaining deferred consent (these may differ, with regard to sensitivity to the parents/legally designated representative, depending upon whether the intervention was successful in preventing the death/incapacity of the patient or not).
We also recommend inclusion in this section of the document of a clear statement that the minor's assent should be obtained as soon as he/she regains the ability to assent.

F2: If you are aware of any other relevant references you are invited to put them forward.

ACRO Response to F2:

There are no additional references that ACRO wishes to put forward at this time (however, please see comment on lines 642 – 656).

II. Suggested revisions to specific line numbers

Line Numbers	Current text	Issue/question	Suggested language
166	"…all paediatric age groups and requires even more careful review Finally, various other aspects…."	Minor typographical error (period at end of sentence)	"…all paediatric age groups and requires even more careful review. Finally, various other aspects…."
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	Minor re-wording might be useful for clarification	"Because of the special protection they deserve, minors should be the subject of clinical trials only when deemed necessary for the collection of data specific to the paediatric population."

	of informed consent)."		
199-201	"However, a 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended."	ACRO agrees with this position. However, the "staggered approach" has previously been recommended and is a common request from regulatory agencies outside the EU and from ethics committees (both within and outside the EU). ACRO recommends that references are included to support this statement, and that the finalization of the guideline is accompanied by outreach efforts from the European Commission, EMA and the national competent authorities to gain international acceptance and recognition of this view. Delays in the availability of paediatric data could well continue in the absence of an international consensus on this point.	References should be provided in relation to the evidence that this has not safeguarded younger children.
219-223	"The document is intended as recommendations for all persons involved in any stage of a clinical trial, including sponsors of clinical trials, assessors, regulatory authorities, pharmaceutical	Minor re-wording might be useful for clarification	"The intent of this document is to provide recommendations to all parties involved in any stage of clinical trials that involve children of all ages (minors, cf. section 5.8); these parties include clinical trial sponsors, assessors, regulatory authorities, pharmaceutical companies, insurance companies (regarding trial subjects), and investigators (including all trial-related staff), families, and participants."

	companies, insurance companies (regarding trial subjects), investigators (including all trial-related staff) of clinical trials performed in children of all ages (minors, cf. section 5.8), families, and participants."		
307	"5.1 Age groups"	As the text discusses the non-comparability between age groups and level of maturity, it would be helpful to indicate in the section heading that maturity is also addressed.	"5.1 Age groups and level of maturity"
320-325	"Maturity rather than age should be the starting point for the way a trial is discussed with children. Each individual child should be involved in a way that matches his or her maturity and ability to take part in the decision making process. Although this may be difficult, as 'maturity' is not a clear-cut criterion in contrast to age, such an approach will foster more	As noted, it may be difficult for the physician to determine maturity. ACRO therefore recommends adding a statement that the investigator should make this assessment on the basis of medical training/favoured approach to guide decisions on the most appropriate assent/agreement information to be used, and that this assessment should be documented. We also suggest adding a reference here to Section 6 (The Process of Informed Consent).	Add a reference to Section 6 (The Process of Informed Consent) and also the following sentence: "It is the responsibility of the investigator to make an assessment based on medical training/favoured approach on the most appropriate assent/agreement information to be used, based on the competency/maturity of child. The assessment should be documented in the study file accordingly."

	attention to differences between children and will support that they are properly involved in decisions that concern them."	Additionally, given that, in the past, ethics committees in some member states have insisted on use of specific materials with children of specific age ranges, which is not appropriate when a child has a maturity understanding that does not match their age, we recommend that the guideline should make clear that it is the responsibility of the investigator to determine the most appropriate materials to use.	
343 - 345	"The minor's assent is not sufficient to allow participation in research unless supplemented by informed consent of the parents/legally designated representative."	The concept of an emancipated minor, briefly discussed in the footnote to line 464, is also relevant to this statement.	"Except in the case of an emancipated minor, the minor's assent is not sufficient to allow participation in research unless supplemented by informed consent of the parents/legally designated representative."
421 - 422	"Of note, in the case of multinational trials the age of legal competence may differ across Member States."	No amendment to the text is proposed. However, ACRO recommends the addition of an Annex that describes the age of legal competence in each EU member state, in order to assist trial sponsors.	Addition of an Annex that describes the age of legal competence in each EU member state.
466 - 468	"As soon as a minor becomes legally competent to give informed consent during the course of	For the avoidance of doubt, we recommend that the guidance should also state explicitly that the consent of the	"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.

	the trial, no trial-related procedures may be performed until informed consent is provided."	parents/legally designated representative lapses upon attainment of legal competency by the former minor.	The consent of the parents/legally designated representative lapses upon attainment of legal competency by the former minor."
472 - 476	"Adolescents may still have some elements of vulnerability, even though they are legally allowed to provide their own consent. In practice, the adolescent with the legal capacity to consent may decide to involve his or her parents in the informed consent process. The information given to adolescents should therefore recognize the potential situation of vulnerability."	It is unclear how the vulnerability of an adolescent can be considered so far as the information provided is concerned; in this situation, the adolescent is entitled to the same information as an adult, and we recommend that this is clearly stated. The suggestion in the draft guidance raises the risk that information might be withheld from competent adolescents on a paternalistic basis whereas it is more likely that the vulnerability arises during the consent process rather than as a result of the information given.	"Adolescents who are legally allowed to give their own consent should be given the same consent information as an adult. However, such adolescents may still have some elements of vulnerability, even though they are legally allowed to provide their own consent. In practice, the adolescent with the legal capacity to consent may decide to involve his or her parents in the informed consent process. In this situation, the consent process should recognize and take account of the potential situation of vulnerability."
484-487	"Where appropriate, a translator and/or a cultural mediator, familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available	It is not clear who would be responsible for making arrangements for this person to be involved. The European Commission may also wish to consider including a statement as to whether or not the translator/cultural mediator should or should not be independent of the trial staff.	"Where appropriate, the investigator should arrange for a translator and/or a cultural mediator, familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent." Inclusion of a statement on the independence of the translator/cultural mediator should also be considered.

	in the process of obtaining informed consent."		
491	"6.4 Consent at the beginning of a trial and continued consent during trial"	This section also discusses assent and agreement, which are not referred to in the title.	"6.4 Consent, assent and agreement at the beginning of a trial and continued consent process during trial."
502 - 504	"During the progress of the trial, especially in long-term trials, the investigator should check the progressing maturity of the child and his or her ability for assent/agreement. This should be documented."	To help trial sponsors, ACRO suggests that it would be useful to include a recommendation to re-assess the child's maturity on at least an annual basis.	"During the progress of the trial, especially in long-term trials, the investigator should check on at least an annual basis the progressing maturity of the child and his or her ability for assent/agreement. This should be documented."
515 - 516	"The parents/legally designated representative need to be informed about the risks that premature termination of the trial would present to the subject's health, if applicable."	Also, the child/minor needs to be informed about risks of premature termination, if sufficiently mature to understand.	"The parents/legally designated representative and the minor (in case of appropriate maturity) need to be informed about the risks that premature termination of the trial would present to the subject's health, if applicable."
530 - 532	"It must be emphasised that after a child withdraws from a trial, the investigator is still responsible for reporting trial-related events. In addition, the	The nature and duration of follow-up in the event of withdrawal should be described in the clinical trial protocol. This statement should therefore refer to follow-up as described in the protocol.	"It must be emphasised that after a child withdraws from a trial, the investigator is still responsible for reporting trial-related events. In addition, the investigator needs to assure appropriate treatment and follow-up as described in the clinical trial protocol."

	investigator needs to assure appropriate treatment and follow-up."		
533	"6.6 Consent, assent and agreement in emergency situations"	This section regarding emergency situations lies between several sections of more general applicability. ACRO therefore recommends moving this section to after section 7.3 in order to aid clarity and understanding.	No change to text, but move the section to after section 7.3.
567 - 627	"7. Participation of minors in the informed consent process and agreement"	The section title refers to minors but the text refers to child or children. ACRO recommends use of consistent terminology throughout the section.	Use consistent terminology – minors or child/children.
615-618	"The information material should have been tested in the relevant population, and should include provision of information on all the relevant aspects of the trial, in terms that are honest, but not frightening, using visual such as drawings, cartoons etc."	ACRO recommends that this statement is expanded to explain more about testing requirements. In particular, while we recognize the need for conducting readability testing, this may not be necessary for each individual clinical trial. A sponsor may be able to put in place an overall process for readability testing that will not require testing for every clinical trial.	"The readability of the information material should have been tested in the relevant population, either for the specific clinical trial or by a more general process put in place by the sponsor. The information should include provision of information on all the relevant aspects of the trial, in terms that are honest, but not frightening, using visuals such as drawings, cartoons etc."
642 - 656	"7.2.2 Pre-schoolers (2-5 years of age)"	References demonstrating that children aged 3-4 can express altruism are needed here, as this section contradicts guidance from the	Add reference(s).

		American Academy of Pediatrics, which has long maintained that children below 7 years lack this ability (e.g., Katz, AL & Webb, SA . Informed consent in decision-making in pediatric practice. Pediatrics 2016;138(2): e20161485).	
685 - 687	"As in the younger age groups, the individual maturity and capacity to understand and agree is also linked to developing cognition and previous life/disease experiences"	ACRO recognizes the accuracy of this statement but is of the opinion that it is not needed in the context of this guideline and can therefore be deleted.	Delete the sentence.
707 - 708	"If the child and parents/legally designated representative are not able to come to a consensus, the dissent of either party is decisive."	Further explanation might provide more clarity here	"If, after reasonable efforts to reach consensus, the child and parents/legally designated representative are not able to come to a consensus on an issue requiring a "yes" or "no" answer of all parties, the dissent of either party is decisive, meaning that the parties will be considered to have agreed to answer "no"."
743	"Opinion on the application dossier"	ACRO recommends that the list presented in this section should include an item stating that the study protocol should include a consideration of a patient's weight (e.g., greater than a minimum weight [as defined in pharmacokinetic studies] as an inclusion criterion),	Add to the list of points that should be examined: "- whether the study protocol includes a consideration of a patient's weight (e.g., greater than a minimum weight [as defined in pharmacokinetic studies] as an inclusion criterion."

		as it relates to drug dose/exposure.	
770 - 771	"The protocol has been designed with and reviewed by parents and patients (if applicable, based on age and level of understanding)."	If this means that a non-medical parent/patient readability test should be performed, this should be clearly stated (and see above comment on lines 615 – 618). If this is not the case, lines 770 – 771 should be expanded to explain the intent, and to describe the evidence that regulators will require as confirmation that the review was performed.	Either state clearly that a non-medical parent/patient readability test should be performed, or expand lines 770 - 771 to explain the intent, and to describe the evidence that regulators will require as confirmation that the review was performed.
997 - 998	"Risk is defined as the probability and magnitude of harm or discomfort anticipated in the clinical trial."	ACRO recommends that this statement is better placed, and should be moved, as the first sentence in section 11.1 (Assessment of risk).	Move or repeat as first sentence of Section 11.1: ***"11.1 Assessment of risk*** Risk is defined as the probability and magnitude of harm or discomfort anticipated in the clinical trial."
999 - 1001	"Burden is defined as the subjective load that affects a participant, parents and family, due to elements of the trial that cause pain, discomfort, fear, disturbances of their lives and personal activities, or otherwise unpleasant experiences."	ACRO recommends that this statement is better placed, and should be moved, as the first sentence in section 11.2 (Assessment of burden).	Move or repeat as first sentence of Section 11.2: ***"11.2 Assessment of burden*** Burden is defined as the subjective load that affects a participant, parents and family, due to elements of the trial that cause pain, discomfort, fear, disturbances of their lives and personal activities, or otherwise unpleasant experiences."
1021 - 1022	"For both reasons, concurrent clinical trials using investigational medicinal products	ACRO supports this statement. However, for clarity, the document should make clear that this does not prevent the	"For both reasons, concurrent clinical trials using investigational medicinal products in an individual should be discouraged. However, this does not prevent the conduct of a single

	in an individual should be discouraged."	conduct of a single clinical trial using two or more novel investigational medicinal products that have already been shown to work in adults better in combination than singly, as may occur in some oncology trials.	clinical trial using two or more novel investigational medicinal products that have already been shown to work in adults better in combination than singly, as may occur in some oncology trials."
1081-1083	"Population approaches and sparse sampling for pharmacokinetic data should be applied to reduce the number of blood samples required to be taken for each child."	Additionally, the number of attempts to take a blood sample should also be limited by the protocol in order to reduce discomfort to the minor.	"Population approaches and sparse sampling for pharmacokinetic data should be applied to reduce the number of blood samples required to be taken for each child. Protocols should also limit the number of permissible attempts to take a blood sample."
1353 - 1359	"16. Trials with adolescent females"	Females may develop the capacity to become pregnant before adolescence; this section seems to equate the two things. ACRO therefore recommends changing the section heading.	"16. Trials in females of child-bearing capacity"
1374	"In addition, bridging PK data to the marketed pharmaceutical form may be required."	In the case of simple dosage forms, ACRO believes that there are situations where *in vitro* dissolution data rather than *in vivo* studies may provide suitable bridging data. ACRO therefore recommends that the sentence should be clarified.	"In addition, bridging PK data (from *in vitro* and/or *in vivo* studies, as necessary) to the marketed pharmaceutical form may be required."
1440	"As adult data are poorly predictive of safety in children"	ACRO recommends that this statement should be	Add a reference to support the statement.

		supported by an appropriate reference.	
1478 - 1480	"…in addition, the trial protocol should be submitted for ethical and scientific review in the EU Member State in which the sponsor or its legally designated representative resides."	ACRO is not aware of any legal basis for this requirement and recommends that the statement is replaced by the advisory language used in the current EMA Reflection Paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA (EMA/712397/2009). This language needs slight revision as the Clinical Trial Regulation (EU) No. 536/2014 does not allow for separate submission to an ethics committee (as currently written in the Reflection Paper). A revised form of the statement is therefore presented in the column to the right. Additionally, the Clinical Trial Regulation (EU) No. 536/2014 establishes an electronic portal for communication between applicants and member states and submission of applications in relation to clinical trials to be conducted in the EU. There is no mechanism described	"Where a clinical trial is to be conducted in countries that have limited frameworks for ethical review or regulatory oversight, the sponsor should consider submitting the study protocol for ethical and scientific review in a country with an established regulatory framework with ethical standards equivalent to those applying in the EU, in addition to doing so in the country concerned by the trial." Additionally, the European Commission should add text to describe the mechanism by which such submissions can be made to a member state in the EU.

		in the Regulation for communication between applicants and member states on clinical trials to be performed in third countries. Consequently, ACRO recommends that the final guideline should include a description of the mechanism for a sponsor to seek approval/advice from a member state for a trial to be conducted in a third country.	
Annex 2 Lines 2 and 3	"appropriate for the age of children"	For consistency with the statement earlier in the document that "Maturity rather than age should be the starting point for the way a trial is discussed with children", ACRO recommends rewording this statement.	"appropriate for the maturity of the target trial population(s)"
Annex 2	"Information for informed consent"	The list of items recommended could usefully be divided into information the parents/legally designated representative need to be given, and information the child needs to be given; the latter should be age- or competency- dependent.	Divide the list into information the parents/legally designated representative need to be given, and information the child needs to be given.

III. Omissions in consultation document recommended for inclusion in final document

<u>Tailoring scales and study questionnaires to paediatric populations</u>

Lines 1072 – 1074 refer to the importance of validated age-appropriate scales and measures of end-points. These are essential for studies in paediatric populations. We therefore recommend including a more detailed description of how scales, and also study questionnaires such as PROs, can be tailored to patient ages and level of understanding.

Balancing need for full birthdate with data protection requirements

There is no mention of the need, in some situations, to collect the full date of birth of patients in a paediatric trial, while this may be discouraged or not allowed by country-specific interpretations of data protection regulations. ACRO recommends including guidance on how to manage the situation where it is necessary to collect the patient's full date of birth in a paediatric clinical trial.

ACRO thanks the Commission for the opportunity to comment on this public consultation "Ethical considerations for clinical trials on medicinal products conducted with minors."

Please contact ACRO if we can provide additional information or answer any questions (knoonan@acrohealth.org).

Respectfully submitted,

Karen A. Noonan
Vice President, Global Regulatory Policy

EU Transparency Register information:
ACRO's public ID number in the Transparency Register is: **150920420956-26**