7 April 2017

Submission of comments on ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population, Step 2b (EMA/CPMP/ICH/2711/1999)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world, including 57,000 in Europe, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft ICH E11 Addendum on clinical investigation of medicinal products in the paediatric population. ACRO considers this to be a comprehensive and well-considered document that provides high level guidance on the implementation of important approaches in paediatric drug development. In particular, ACRO welcomes:	

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	• The acknowledgement that a common scientific approach, not common regional requirements, is at the cornerstone of efficient paediatric drug development and timely delivery of safe and effective medicines for children. • The recognition that extrapolation and modeling and simulation techniques have a role to play in minimising both the exposure of paediatric populations to clinical trials and the risks to individuals of trial participation, and guidance on the establishment of appropriate frameworks for the use of these techniques. • The acknowledgement that maturity, and not chronological age, serves better as an adequate categorical determinant to define developmental subgroups in paediatric studies. Additionally, ACRO recommends that, with regard to maturity, it would be useful for the guideline to make a clear distinction between physiological maturity as a determinant to define developmental subgroups (as noted in the draft guideline) and mental maturity/competency, again rather than chronological age, as a determinant of the appropriate materials to be used to obtain the assent of trial participants. ACRO recognizes, however, that the replacement of age groups with levels of maturity would be more difficult to	

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	determine and there would need to be a mechanism for consistent assessment of this across investigators in any individual clinical trial. Because the draft guideline issued for comment by the European Medicines Agency (EMA) was reformatted from the original ICH draft -- resulting in changes to the line numbers -- ACRO has included both the “ICH” (meaning the original ICH draft guideline) line numbers and the “EMA” (meaning the reformatted document published by the EMA) line numbers so that ACRO’s comments may be linked back to either draft document.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
ICH 10 – 13 EMA 51 - 53		Comment: The clarification of the interpretation of the word "should" is particularly useful. Proposed change (if any):	
ICH 27 – 64 EMA 66 - 100		Comment: ACRO recommends including a statement in the section on Ethical Considerations (section2) that paediatric trials with an "only placebo" arm are usually not accepted. All subjects participating in paediatric studies should be treated with active substance(s) (e.g. investigational product versus available standard of care, cross over studies, etc.). Proposed change (if any): Add the following statement: "Paediatric trials with an "only placebo" arm are usually not accepted. All subjects participating in paediatric studies should be treated with active substance(s) (e.g. investigational product versus available standard of care, cross over studies, etc.)."	
ICH 37 - 47 EMA 77 - 84		Comment: When the draft guideline refers to clinical benefit, it is not clear whether this means a potential clinical benefit for the target paediatric population in general or for the specific individual participating in the clinical trial. Also, use of the term "low" in relation to the risks to which a paediatric trial subject may be exposed is inadequate, especially in	

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		situations where the trial subject may not receive direct benefit and the risks should be minimal. ACRO therefore recommends that the guideline should include a statement to clarify that when a clinical trial does not offer the prospect of direct benefit to the minor, there should be the prospect of some benefit for the population represented by the minor, and that such a clinical 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. Additionally, ACRO recommends that the guideline should state explicitly that in the risk-benefit ratio the benefits should clearly predominate. Proposed change (if any): Add the following statement: “When a clinical trial does not offer the prospect of direct benefit to the minor, there should be the prospect of some benefit for the population represented by the minor, and that such a clinical 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. The benefit expected from the trial should be identified in the protocol.” Additionally, add the following statement: “The benefits should clearly predominate in the risk-benefit ratio.”	

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ICH 52 EMA 59		Comment: The statement indicates that information regarding the study is provided at time of enrolment. Therefore, it would be helpful also to provide clarity on the information that should be provided prior to enrolment to support the informed consent/assent process. Proposed change (if any): Add a statement to clarify the information that should be provided prior to enrolment to support the informed consent/assent process.	
ICH 53 – 55 EMA 90 - 92		Comment: For clarity, ACRO recommends adding to this text that it is the responsibility of the investigator to make an assessment based on medical training/favoured approach on the most appropriate assent information to be used, based on the competency/maturity of the minor. If this is accepted, then Investigators need to be made aware that they will need to justify the assessment to regulatory inspectors and in the event of litigation. Additionally, given the caution regarding interpretation of absence of objection as assent, ACRO recommends that the document should contain a clear position regarding dissent. Proposed change (if any): Add a statement to confirm that it is the responsibility of the investigator to make an assessment based on medical training/favoured approach on the most appropriate assent information to be used, based on the	

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		competency/maturity of the minor. The Investigator must be able to justify the assessment of maturity such that third parties, such as inspectors, can be satisfied that the information the child received was appropriate Additionally, add the following statement: “Dissent by a child must be respected to the extent required by relevant legislation.”	
ICH 58 – 59 EMA 93 - 95		Comment: It is ACRO’s view that the statement “During clinical studies there may be a requirement for obtaining adequate informed consent from paediatric participants once a child reaches the age of legal consent” is not sufficiently strong with regard to the legal requirement to obtain the trial participant’s informed consent when he/she reaches the age of legal consent, and suggests replacing the text as recommended below. ACRO also notes that most paediatric trials are conducted at specialist centres, which may entail a full day’s travel to reach, and it would be inappropriate to require the patient to make an additional visit on reaching the age of consent simply for the purpose of providing consent as an adult. Consequently, we recommend that the guideline should draw attention to situations in which obtaining consent in a conventional manner on the child’s birthday may be impracticable, and advise investigators to create provision for e-consent, remote	

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		consent, or conditional prospective consent, e.g., using wording to indicate that the child's consent will take effect upon a date in the future. Proposed change (if any): Replace the current text with "As soon as a minor becomes legally competent to give informed consent during the course of the trial, no trial-related procedures, including continued dosing of the investigational product, may be performed until informed consent is provided by the trial subject. The consent of the parents/legally designated representative lapses upon attainment of legal competency by the former minor." Additionally, the guideline should draw attention to situations in which obtaining consent in a conventional manner on the child's birthday may be impracticable, and advise investigators to create provision for e-consent, remote consent, or conditional prospective consent, e.g., using wording to indicate that the child's consent will take effect upon a date in the future.	
ICH 59 – 60 EMA 95 - 96		Comment: Data privacy legislation in various countries prohibits collection of date of birth by the sponsor, therefore responsibility for ensuring consent is taken at the appropriate time must reside with the investigator. ACRO recommends adding a statement to make this clear. Additionally, in view of the clarification of the meaning of "should" stated earlier in the guideline, ACRO suggests that here the word should be replaced by "must" as compliance	

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		with data privacy regulations is not optional. Proposed change (if any): Add a sentence as follows: "The Investigator is responsible for ensuring that consent is taken when required." Additionally, revise the sentence to read "Local regulations related to confidentiality and privacy of paediatric participants must be followed."	
ICH 74 – 75 EMA 110		Comment: The question "What is the medical need in one or more paediatric populations that the drug could address?" may result in a potential conflict between the planned guideline and current regulatory requirements in the USA and EU. According to the latter, all applications for marketing approval for new medicines have to include the results of studies as described in an agreed paediatric investigation or development plan, unless the medicine is exempt because of a deferral or waiver. In practice, this means there must be a paediatric investigation or development plan for all drugs approved for adult use if the condition occurs in children. However, if, for example, three drugs of the same class are already approved for paediatric use, can a medical need for a fourth drug of the same class be justified? Proposed change (if any): Align the text with current US and EU regulatory requirements.	
ICH 88 – 90 EMA 122 - 123		Comment: ACRO recommends including in this section of text a statement similar to that proposed by the European	

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		Commission's expert group on clinical trials in their proposed recommendations on Ethical Considerations for Clinical Trials on Medicinal Products Conducted With Minors: "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." Proposed change: Add the statement "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."	
ICH 118 – 150 EMA 149 - 160		Comment: ACRO recommends including in section 5 (Approaches to Optimize Paediatric Drug Development) the need to highlight the deviation from the normal standard of care for a patient with a specific diagnosis if a paediatric patient is to be exposed to a very different treatment pathway or regime from the standard clinical care. This is a frequent discussion point in a wide range of Industry and governing body meetings. Proposed change (if any): Add a statement on the need to highlight the deviation from the normal standard of care for a patient with a specific diagnosis if a paediatric patient is to be exposed to a very different treatment pathway or regime from the standard clinical care.	

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ICH 135 – 137 EMA 164 - 166		Comment: Existing knowledge includes also retrospective clinical data and existing data from off-label use (if available), which should be included in the statement. Proposed change (if any): Revise the sentence to read "Existing knowledge also integrates nonclinical data, retrospective clinical data and existing data from off-label use (if available), data about related compounds, disease pathophysiology, as well as consideration of the developmental physiology of the paediatric population or subgroup."	
ICH 151 – 199 EMA 179 - 224		Comment: ACRO recommends that the process of extrapolation should be explained in additional detail, including the development of an extrapolation plan, including the systematic synthesis of available data and agreed with the relevant regulatory authorities prior to implementation, details of the calculation of the paediatric dosage regimen resulting from the extrapolation, and adaptation of the extrapolation plan and any follow-ups considered necessary. Proposed change: Include further explanation of the extrapolation process as recommended above.	
ICH 214 – 216 EMA 238 - 240		Comment: The M&S approach is to be welcomed. However, ACRO recommends that the guideline should make clear that the strategic M&S plan needs to be discussed with, and agreed by, regulatory authorities prior to commencement, otherwise the risk exists that the M&S plan will be conducted but subsequently held to be unacceptable, which will delay the	

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		availability of a potentially valuable new treatment. Additionally, ACRO considers that the phrase “several criteria” is insufficient to describe the requirement for model building and should be replaced by “as many criteria as possible”. Proposed change (if any): Revise the sentence to read “The incorporation of M&S into paediatric drug development should be based on a strategic plan established through multidisciplinary discussions, including relevant regulatory authorities, outlining objectives, methods, assumptions, deliverables and timelines.” Additionally, revise the sentence to read “When building a model, as many as possible relevant criteria should be considered…”	
ICH 228 – 229 EMA 251 - 252		Comment: ACRO recommends that the impact of “influencing parameters” to the M&S process should be added here. Proposed change (if any): Add the following statement: “As many as possible influencing parameters and co-variates, as well as their impact, should be considered in the M&S process. These parameters and/or co-variates might be known from already existing data and include but are not limited to age of subject, maturation of organs, disease types, disease severity, etc.”	
ICH 263 – 267 EMA 284 - 287		Comment: ACRO concurs that relevant end-points and outcome measures may indeed be different for children. §3011 of the 21st Century Cures Act, just approved,	

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		allows the FDA up to 5 years to issue a report on the acceptability of drug development tools, including endpoints. The current wording in this document should be amended to indicate the extended timeframe. Proposed change (if any): addition of a clause (in bold) to the last sentence of the paragraph as follows, "**Given that establishing the acceptability of an endpoint may take many years,** where relevant, it may be…..."	
ICH 268 – 281 EMA 289 - 301		Comment: ACRO recommends adding guidance about relevant aspects of adaptive trial designs in section 6.3 (Long-term Clinical Aspects, Including Safety), as indicated below. Proposed change (if any): Add the following statement: "Adaptive trial designs could also be considered as an appropriate method to react on new safety aspects resulting from clinical trial data. For this, interim data analyses are to be planned and to be performed to allow modification/adaptation of further study conduct (within pre-defined measures) based on new safety data."	
ICH 301 – 314 EMA 319 - 330		Comment: ACRO recommends that, in section 7.1 (Dosage and Administration), a statement should be added to explain that pharmacodynamic and pharmacokinetic data should be considered when establishing the dosing regimen (dependent on age /maturity). Proposed change (if any): Add the following statement: "Pharmacodynamic and pharmacokinetic data should be considered when establishing the dosing regimen (dependent	

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		on age /maturity)."	
ICH 318 EMA 334		Comment: Given the comments earlier in the guideline about the importance of maturity rather than age, ACRO recommends that the phrase "paediatric age group" should be replaced by "maturity". Proposed change (if any): Replace "paediatric age group" with "maturity".	
		ACRO thanks the Agency for this opportunity to comment on **ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population, Step 2b (EMA/CPMP/ICH/2711/1999).** Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.	

Please add more rows if needed.