14 November 2019

Submission of comments on *Preparedness of medicines’ clinical trials in paediatrics –* Recommendations by Enpr-EMA working group on trial preparedness – EMA/56009/2019 Corr. 1

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA |

*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).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | EFPIA welcome the opportunity to provide comments to an important recommendation document that is aimed at improving paediatric CT preparedness and successful delivery of those trials.  The concepts highlighted in the Enpr-EMA’s recommendations are logical and reflect considerations that should be thought through when sponsors design and prepare their paediatric studies. Considering how sites perceive the study, which other studies are conducted in the same indication, and the patients’ feedback is important for Sponsors. However, there are situations where there are guidance on what study designs should be considered for a particular condition. Sponsors who deviate from such guidance because of the practical and ethical feasibility of the “guidance design” may face challenging discussions with PDCO during the PIP reviews despite academia experts and patients’ feedback. As such, these CT preparedness recommendations should be considered by all concerned including regulators.  **General comment on the format of the document:** to improve document readability, we suggest to include a simplified checklist presented in a tabular format; this could be included as an appendix.  **Section 3:** The sub-title of the document and the scope section mention that these are recommendations of the Enpr-EMA working group. This is not always clear for the items listed in section 3, i.e., for some it is stated “consider” or “ideally”. Given that these are recommendations, in the introductory paragraph of section 3 it should be stated that “the following aspects should be considered if applicable and/or relevant”, also in relation to the fact that it is mentioned in the scope section that the document relates to a global assessment, so not all recommendations might always apply.  Moreover, it is not clear if this section presents concepts in order of prioritisation. If not, this should be stated upfront. It appears, for example, that #3.1.1 #11 “*Take account of the regulatory environment and requirements for drug development*” is given equal weight and placed below (suggesting lower priority) #3.1.1 #1 “*Develop an understanding of the context for planning of the study [how many sites (with facilities required by the trial), how many participants at each site, costs of the study] and implementation of the study that is a combination of qualitative and quantitative information derived from multi-method assessments (questionnaires, site visits, broader discussion)*.”  Please also add at the start of the section the importance of defining the study objectives before defining the study design and start assessing clinical preparedness.  Finally, the section ‘*Trial Preparedness’* includes sections on both trial/study preparation as well as development plans. Since these are two different areas with different challenges, it is suggested to organise content into 2 different sections.  **Timing**—some of the steps are performed during the planning phase (PIP deign) and some are done at a protocol launch phase. These phases can have a significant time separation. To move all steps to a design (planning) phase would be challenging as the specific study details are not always available (or stable) until closer to actual study start.  **Additional considerations:**  It is suggested to add considerations on age groups. Although the ICH E11(R1) age groups are indicative – they do help with looking at the different issues for different age groups. There are different considerations depending on age of the population. For example, a disease can present differently for certain age groups, for whom a different formulation or a different endpoint may be needed:   * First 2 years of life: paediatrics ontogeny needs to be considered, ie body composition, renal and liver function, growth, CNS maturation. * Later in life: growth, CNS maturation, sex hormones.   Consider also trials impact on families related to study feasibility – consider planning around school commitments, family schedule and potential impact on siblings.    **Share learnings:** the possibility to share the findings from a preparedness exercise could be useful. Performing a thorough review exercise will take some resources from Sponsors and the multiple stakeholders involved (sites, research networks, patient groups etc.). A mechanism for sharing findings, e.g. an online database, categorized by condition, may help avoid duplication of efforts and would maximize use of resources.  In addition to these general comments EFPIA has detailed comments on the text, as shown below. |  |

1. 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)* |
| --- | --- | --- | --- |
| Glossary |  | **Comment:**  ‘Drug development plans’: A generic term to mean Paediatric Investigation Plans (PIP), Pediatric Study Plans (PSP) and similar documents.  **Proposed change (if any):**  ~~Drug~~ ***Pediatric*** development plans: A generic term to mean ***EU*** Paediatric Investigation Plans (PIP), ***US*** Pediatric Study Plans (PSP) and similar documents.  **Comment:**  ‘*Sponsor readiness*’:  Recommend revising this to reflect the fact that sponsor readiness is much more than “respecting governance norms and promoting efficiency.” Sponsors conduct paediatric trials in the context of society generally, and specifically in the context of laws (which are complied with, not merely respected), and the medical and scientific community (which requires that studies be scientifically sound and valid, and conducted based on widely accepted ethical principles).  **Proposed change:**  A collection of measures taken by a sponsor to allow them to open and conduct a study ~~while respecting governance norms and promoting~~ ***in a manner that complies with applicable laws and regulations, is scientifically rigorous, endeavours to provide usable data for regulatory decision making, is consistent with internationally accepted ethical principles, and promotes*** efficiency.  **Comment:**  Study design - For both adult and paediatric studies, it is generally universally accepted in bioethics that “minimizing the burden on study participants” is not enough for most studies – that only addresses the principle of non-maleficence, it does not address the ethical principle of beneficence (or the joint principle of beneficence as described in the Belmont Report). For clinical trials generally, the goal should be to minimize risks and to maximize the potential for benefit to the extent possible. In paediatrics, the beneficence principle goes even further, for studies that involve more than low risk/burden there must be a prospect of direct benefit to the individual paediatric research participants that is commensurate with other treatments available to the child.  **Proposed change:**  ***Paediatric*** study design - The selection of methods to answer a research question reliably (or set of research questions) in a manner that minimizes the ***risks and*** burden***s*** ~~on~~ ***to*** study participants ***and, when the risks and benefits are not low, that maximizes the potential for direct benefits to the individual paediatric research participants so that they are comparable to other treatments available to them.***  **Comment:**  *‘Trial preparedness’*: This would seem to be trial feasibility rather than preparedness. Please clarify.  **Comment:**  Knowing the scope of the document, it would be useful to add the term ‘feasibility’ and its definition to the glossary. |  |
| Section 1 |  | **Comment:**  *Aim and scope of the document*: We recommend revising the section to have it more simplistic and in line with the scope of the document as clearly detailed in the first paragraph which outlines recommendations for trial preparedness.  Study and trial are used interchangeably throughout the document however the term “Trial Preparedness” as defined in this section appears to be a broader term that could be related to a larger program of studies to support a particular investigational product. We recommend to clearly use trial or study and be consistent in what is meant by this term.  **Comment:**  It is suggested to include neonates in the following sentence, as neonates have additional specificities to address above that of infants.  **Proposed change:**  Design needs to take account of the specificities of ***neonates,*** infants, children and young people while maximising the use of extant data… |  |
| Section 2 |  | **Comment:**  ‘*The survey specifically mentioned the often limited number of eligible paediatric patients…’*  Obviously the survey here refers to was used to develop this document and is used further in section 5. Since the survey was not mentioned in previous sections, we suggest either to include a short paragraph explaining the survey or a link to appendix.  **Comment:**  *‘There is often no resource allocated to support trial preparation.’*  Our experience is that there may be resources available, however the site may underestimate the required resources to adequately support the trial preparation. For example, there may be additional steps/review/assessments required by the site prior to submission to a HA/EC. Other factors may include gathering information and/or onboarding of supporting facilities and or investigators such as ECG centres, pulmonologist, epidemiologist, etc.  Also, it should be clarified whether the resources considerations are referring to the study centre or to the sponsor. |  |
| Section 3.1.1 |  | **Comment:**  The process for collecting relevant information is time sensitive as this usually occurs after the protocols are finalized and usually causes time delay. The importance of “time-sensitivity” at this step should clearly be articulated. |  |
| Section 3.1.1 #1 |  | **Comment:**  Please clarify what is meant with “*with facilities required by the trial”.* Develop an understanding of the context for planning of the study [how many sites (with facilities required by the trial), how many participants at each site, costs of the study] and implementation of the study that is a combination of qualitative and quantitative information derived from multi-method assessments (questionnaires, site visits, broader discussion). |  |
| Section 3.1.1 #2 |  | **Comment:**  In the sentence, “*Justifications of judgements or opinions need to be explicit*”, it is unclear what is meant by “opinions”.  Please clarify. |  |
| Section 3.1.1 #3 |  | **Proposed change:**  Suggest adding a new bullet **“*preclinical data*”** under sources of data. Preclinical data is important prior information in addition to all the bullet points provided. |  |
| Section 3.1.1 #3 |  | **Proposed change:**  Suggest adding a new bullet **“*paediatric research networks or initiatives (e.g. C4C, I-ACT, COG, PRINTO, etc)*”** as another source of data. |  |
| Section 3.1.1 #8 |  | **Comment:**  Clinical reality should also take in account the setting in which paediatric patients receive care. Consider adding the following sub-bullet.  **Proposed change:**  ***iv. setting where paediatrics receive care e.g. adolescent centre.*** |  |
| Section 3.1.1 #10 |  | **Comment:**  Consider listing some of the ethical issues here (similar to burdens list below) e.g.: direct benefit, risk minimization, child assent, confidentiality, incentives to participants |  |
| Section 3.1.1 #11 |  | **Proposed change:**  Please rephrase to reflect better the complexity of the regulatory environment:  “Take account of the ***global*** regulatory environment and **the *different*** requirements for drug development across regions” |  |
| Section 3.1.1 #13iii |  | **Proposed change:**  Please revise as proposed:  Parent burdens of a child’s participation in a trial including effects on work ~~including~~ ***and*** the possibility to reimburse costs. |  |
| Section 3.1.1 #15 |  | **Comment:**  The draft framework calls out that sponsors should consider the "need to gather data that supports HTA assessment and reimbursement decision" in this section. To this end, we recommend adding to consider seeking early HTA advice (or joint regulatory/HTA advice) in section 3.1.2 as another means of involving relevant contributors. |  |
| Section 3.1.2 |  | **Comment:**  This section refers to involvement of relevant contributors and should thus include some comments and recommendations regarding confidentiality agreements and data protection, especially important for industry. |  |
| Section 3.1.2 #17 |  | **Comment:**  This bullet should be expanded to refer to soliciting feedback from applicable regulatory agencies where the study is intended to be run, so as to align as much as possible on the acceptability of the trial design and evidence generated for all subsequent regulatory submissions.  However, early regulatory input may not be appropriate in all cases as often the final design of a study may depend on earlier studies and the information collected from them. Would recommend instead to seek regulatory input when the sponsor has gathered the necessary data to maximise regulatory input.  **Proposed change:**  Seek regulatory input ***as*** early ***as possible and when the necessary data have been gathered to maximise the input from health authorities where the study is intended to be run (***for example on ***the******acceptability of* *the*** study design***, evidence generated,*** or regulatory requirements***).*** |  |
| Section 3.1.2 #18 |  | **Comment:**  Suggest adding additional bullet ‘e’ to identify mechanisms to retain children in the study if a decision is made to stop treatment, so essential data is continued to be collected to derive primary outcome(s) being used to address the study objectives and minimise missing outcome data’  **Proposed addition:**  **“*Identify mechanisms to retain children in the study to ensure continuation of essential data collection to derive primary outcome(s) and minimize missing data, if treatment is stopped*”** |  |
| Section 3.1.3 #22 |  | **Comment:**  Please clarify what is meant by futile trial. It is not clear whether “futile trial” means designing a trial that is not realistic and fails to recruit enough patients to address the trial objectives. Also, how to demonstrate that due care has been taken to avoid a futile trial.  Providing an example of a futile trial would be useful. |  |
| Section 3.1.3 #23 |  | **Comment:**  Consider adding the following additional sub-bullets:  **Proposed Change:**  ***d) study assumptions which are key influence on preparedness***  ***e) length of regulatory interactions*** |  |
| Section 3.1.3 #24 |  | **Comment:**  In constructing the flow diagram, it is important to make any assumptions explicit.  **Proposed Change:**  “Construct flow diagram from epidemiology to eligibility (see Figure 1 Components of a flow diagram about participant availability during preparation of a medicines development plan) and from eligibility to contents for locked database, ***ensuring all assumptions are explicit***.” |  |
| Section 3.1.3 #25 |  | **Comment:**  Suggest including simulations that consider extrapolating data. Also, consider using Modelling and Simulation as part of the design to support/integrate with the data collected during the trial. This could include assessing different levels of extrapolated data compared to the amount of data collected in the trial. |  |
| Section 3.1.3 #25 & #26 |  | **Comment:**  Timing of clinical trial simulation is very important. Pediatric development plan such as PIP may be submitted and discussed years before initiating the actual trial and many of the trial readiness information may have changed over time and become obsolete. Recommend planning proper level of simulation relevant to the development stage (PIP or study protocol).  **Proposed addition:**  Suggest adding a new bullet point **“*Appropriately plan and time clinical trial simulations relevant to the development stage (e.g., PIP or study protocol)*”** |  |
| Section 3.1.3 #27 |  | **Comment:**  As highlighted in the document, innovative design should be considered to protect children from unnecessary exposure of clinical trial experiments. In addition, as per comments above, the timing element is important.  We recommend discussing feasibility of extrapolation concept (e.g., similarities between adults and children in the disease and its natural history) rather than detailed extrapolation method during initial PIP. Extrapolation methods can be proposed and evaluated at a later stage with the help from modelling and simulation when paediatric PK/PD data and adult clinical data become available.  We also suggest to consider including use of historical data as another option, particularly where there is low availability of potential participants and high need for information (per Table 2).  In addition, please consider adding the following statement.  **Proposed addition:**  ***Include a futility analysis to assess the likelihood of a null treatment effect (or lack of a targeted treatment effect), and* determine corresponding futility stopping rule to prevent children being exposed unnecessarily to an ineffective treatment.** |  |
| Section 3.1.4, last paragraph |  | **Comment:**  We recommend deleting the last paragraph as considerations on the “remuneration” of sites are not in the scope of the document.  **Proposed change:**  ~~It is noted that from a clinician’s perspective, remuneration for well-conducted preparedness activities facilitates, from an operational perspective, the high-quality conduct of studies in terms of recruitment figures and produce complete data, thereby avoiding expenditure for poorly prepared plans and studies.~~ |  |
| Section 3.2.1 |  | **Comment:**  Two similar terms are used in the document: trial preparedness and preparedness concept. These terms overlap with the term “trial feasibility” which is widely understood. Please highlight the factors that would be considered trial preparedness and not trial feasibility to help readers understand the differences. Please provide examples as appropriate.  A preparedness concept is introduced but its relevance is unclear in relation to the recommendations in the other sections of the document (i.e. which steps to undertake and what to consider when evaluating preparedness). Perhaps this proposal is a step too far and too high-level for the purpose of this document. Also, it is unclear what is intended with “Proposals to handle points of difference between Sponsors and regulators could be evaluated according to explicit criteria during the preparation or conduct of development plan/studies”. These evaluations can then prompt iterative changes to the preparedness concept, but it is unclear which explicit criteria to use. |  |
| Section 3.2.1 Figure 1 |  | **Comment:**  While the concept of “fortuity” is defined it is not clearly indicated how that could be quantified or what adjustment would be acceptable to come to the next step in the flow diagram “Total available for a clinical development plan”. Please explain how one may quantify its effect and reach agreement with health authorities, and provide an example of how that step might be used in this Figure 1. |  |
| Section 3.2.1  P. 10 |  | **Comment:**  In considering the availability of participants it is important to be explicit on any assumptions being made.  **Proposed addition:**  In the paragraph starting with *‘The number ‘available for recruitment’’, please add the sentence:*  *‘****Make explicit any assumptions on the number of children available for recruitment.’*** |  |
| Table 1 |  | **Comment:**  Please add to Table 1 as first point: to define the study objectives that the study is built around and to also address ethical considerations. |  |
| P. 11 #1  Table 1 |  | *“Subsequent steps are needed for all studies; for plans each study should be considered and a synthesis presented.”*  **Comment:**  Not clear what is meant with “synthesis” and whether it refers to synopsis; please clarify. |  |
| P. 11 #4  Table 1 |  | **Comment:**  A key consideration is the ability to keep patients in a study after stopping treatment rather than having patients lost to follow up leading to missing data.  **Proposed change:**  At the end of bullet 4) (a), please add **‘*including what the expected retention is anticipated to be*’.** |  |
| P. 11 #5  Table 1 |  | **Comment:**  It is important to consider uncertainties in any assumptions that are being made.  **Proposed change:**  Please add to the end of bullet b), **‘*uncertainties in assumptions being made*’.** |  |
| Table 2 |  | **Comment:**  This is in contrast to all regulatory (and scientific) documents on paediatric extrapolation - feasibility itself is never the only reason for extrapolating and also if there are children potentially available to be included into a clinical study, the number of participants should always be determined by scientific rationale, sound statistical methods; and a paediatric study should (as all clinical study) only be conducted if there is a question which can be answered by the trial. Extrapolation should be used to reduce unnecessary trials in children however without lowering the standards for determining efficacy and safety.  We would recommend removing this table completely.  Otherwise, please consider the following comments:  **Comment:**  It is not clear how the arrows in the table are supposed to be interpreted: stepwise approaches? For example, a low availability of patients usually does not evolve into a high availability. Please clarify. |  |
| Table 2 High-High category |  | **Comment:**  A traditional design might not lead to high confidence about efficacy/safety.  **Proposed change:**  Consider traditional development design ***versus innovative approaches and select approach that leads to highest confidence to recruit planned number of patients to assess*** ~~as necessary, with appropriate numbers of recruits leading to high confidence about~~ efficacy/safety |  |
| Table 2 Low-Low category |  | **Comment:**  It is unclear what the key message is in the low-low’ category description provided in this box and how is it different from the ‘high-low’ category description right above. Please provide additional description for clarity. |  |
| Table 2 Unclear availability of participants |  | **Comment:**  The “unclear” category does not differ by “need for information.” Please explain why and provide examples, as appropriate. |  |
| Text below  Table 2 |  | **Proposed change:**  Please consider rephrasing as proposed:  “… but neither academic community nor sponsor ***have sufficient information available*** ~~has done the work~~ to support the preparation of a development plan” |  |
| Section 3.2.2 |  | **Comment:**  In the bullet starting ‘Use best judgement...’ also refer to declaring any assumptions being made.  **Proposed change:**  “Use best judgment to provide estimates of recruitment ***and provide explicit assumptions*”** |  |
| Section 3.2.3 |  | ‘It is highly important to learn from patients  and caregivers which elements of the trial proposal are acceptable to them and which are not and which might therefore hamper the conduct of a study. Protocols should then be made flexible enough to reflect this input if possible.’  **Comment:**  The approach should preferably be to ask for patient input **prior** to protocol and regulatory input and not after protocol approval. |  |
| Section 3.2.4 |  | **Proposed change**:  After first sentence consider adding a sentence in this section that addresses Think ahead:  ***Design adult programs and trials to inform paediatric programs and trials and consider the inclusion of adolescents and or children in adult program as appropriate***. |  |
| Section 3.2.4 |  | ‘*Risks and hurdles identified by sites should not be under-estimated at risk otherwise of re-appear at a later stage of study conduct, likely to be then a major constraint in the conduct of the study*.’  **Comment:**  Please clarify as the sentence doesn’t read well |  |
| Section 4 #1d |  | **Comment:**  Please consider creating more sites and recruiting more investigators who are willing to participate in clinical trials. The document does not address clinical trials preparation.  **Proposed change:**  Suggest adding a new bullet under 1: **“*Creation of sites and recruitment of investigators to******participate in Paediatric clinical trials*”** |  |
| Section 4 #3 |  | ‘*Tackle critical trial practicalities such as location of sites and traveling costs for participants as a way of minimizing the burden of research*.’  **Comment:**  Suggest including wording to explore home visits/home nursing and use of digital technologies here as an option too. It would be good to increase awareness and acceptance for these.  **Proposed change:**  Please consider adding the following sentence:  ***Explore the option of virtual or home clinical trial visits and the use of continuous data collection and wearable digital technology to provide more comprehensive view of what is happening with the clinical trial participant.*** |  |
| Section 4 #5a |  | **Comment:**  Mentions communication programmes devoted to patients and parents. Since this is about paediatrics and the patients are often minors, this section should note that there needs to be sensitivity to privacy, parental consent, etc. that may be needed with such communication efforts. Also, the topics addressed should include bioethics – iCAN has made bioethics education a part of their program for two years now at the request of the youth involved. Kids are interested in this and want to know about it. |  |
| Section 4 #5b |  | **Comment:**  These programmes should be made available to industry sponsors not just HCPs as it is valuable information for both.  **Proposed change:**  Educational programmes that support the involvement of Health Care Professionals (HCP) ***and Industry Sponsors*** in research………… to meet the needs of different groups of HCP ***and Industry Sponsors.***  ***Education on Bayesian statistical methods and novel trial designs is needed for stakeholders e.g. investigators, regulators and clinicians.*** |  |
| Section 4 #7 |  | ‘*Consider efficient, patient focused study designs and identify how regulatory requirements have implications for preparation*.’  **Comment:**  Please refer also here to 1) the use of extrapolation and Modelling and Simulation to support/complement/replace patients required to be assessed in a clinical trial; and 2) to the fact that the paediatric community should also further push for global convergence regarding regulatory requirements.  An additional bullet is suggested  **Proposed change:**  ***d) Use where appropriate extrapolation and Modelling and Simulation, or other innovative approaches to support, complement, or replace patients required to be assessed in a clinical trial, and ensure the minimal number of paediatric patients are exposed to clinical trials especially placebo and / or control arm.*** |  |
| Section 4 #8 |  | **Comment:**  It is unclear if the sentences “There is still a need to improve understanding ……… regulatory networks and ethics committees” and “These issues …… from multiple stakeholders” represent a separate bullet or a closing statement. If so bullet # 9 should be created. Also, the fact if a trial addresses a relevant unmet paediatric need should be included early in the assessment i.e. in section 3.1.1. |  |
| Section 4 (end of P. 15) |  | *‘There is still a need to improve understanding of paediatric study requirements across the regulatory network and ethics committees’*  **Comment:**  We believe there is also a need to improve researchers’ understanding of regulatory requirements and processes and ethics considerations.  It is suggested modifying the statement to reflect the need for improved, mutual understanding by researchers, regulators and ethics committees etc of the many challenges and requirements involved in paediatric clinical trials. |  |
| Literature |  | **Comment:**  Consider adding this publication to the literature section:   Nuffield Council on Bioethics 2015. "Children and Clinical Research: Ethical Issues". Available at: http://nuffieldbioethics.org/project/children-research |  |

Please add more rows if needed.