ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

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Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration, Dockets Management Staff
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: ACRO comment submission on Food and Drug Administration [Docket No. FDA–2022–D–0738]
Ethical Considerations for Clinical Investigations of Medical Products Involving Children; Draft Guidance for Industry, Sponsors, and Institutional Review Boards

Dear Ms. Roth,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all FDA-regulated clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

ACRO thanks the Agency for this draft guidance, which offers clear and helpful information to enhance the ethical conduct of clinical research in pediatric populations. We do have some general and specific recommendations, which we outline here.

General Comments
The draft guidance emphasizes the extrapolation of effectiveness data. Because this concept is developed without a parallel emphasis on the extrapolation of safety data, the reader could infer a need to generate actual *clinical* data in pediatric populations, in order to specifically assess safety in these populations. That is, the draft guidance could be misconstrued as open to the conduct of "toxicology" studies in pediatrics, which must be avoided at all costs. We therefore urge the FDA to ensure that the final guidance addresses extrapolation of safety data in detail. Moreover, we also recommend that the final guidance should state explicitly the need to investigate any effect on growth and development of the child if such data are not yet available. In this respect, it would be helpful if the final guidance provided examples (for extrapolation of both effectiveness and safety data) of situations where extrapolation would be appropriate without the need for additional clinical data in the target population.

The section of the draft guidance concerning use of placebo (lines 234-265) gives us some concern. If an approved medication for a condition exists, placebo-controlled trials may not be acceptable in certain circumstances. In such circumstances, data are often lacking to justify withdrawing or withholding approved treatments for a period of time that will not result in detriment to the child.

The use of placebo in pediatric trials is a challenge not only due to ethical concerns but also because of caregivers' and patients' (especially if adolescent) acceptance. Sponsors may include appropriate mitigation strategies in the study design as well as informative measures in order to clarify for families the potential risks of being randomly in a placebo arm study, as this is one of the most important barriers for a pediatric patient´s recruitment and caregiver's permission for their child's participation in a trial. Design of the trial, therapeutic indication vs baseline condition, and duration of the study are important factors when considering an active study arm and a placebo-controlled clinical investigation.

Other than mentioning the competence to assent of children aged 7 and above, the draft guidance seems to make no distinction between 7 year-olds and 17 year-olds, which seems unrealistic. This also seems at odds with the move to include adolescents in adult trials. We recommend that the implications of the development of the child should be addressed at relevant points throughout the final guidance. We also recommend that the final guidance more strongly emphasize that – where a child that is capable of providing assent chooses to dissent from participation in a clinical trial – the dissent of the child should be respected.

Line-specific comments
Line 104-107:
This section currently states *" . . . if effectiveness in adults can be extrapolated to children, then effectiveness studies in adults should be conducted to minimize the need to collect effectiveness data in children."*

The current draft of ICH E11A on Pediatric Extrapolation – which is referenced in this draft FDA guidance – considers factors that can contribute to the extrapolation of both effectiveness and safety data. We therefore recommend that the text of this final FDA guidance reflects this. Additionally, the pediatric extrapolation plan is such an important element in the development of any successful pediatric clinical strategy approved by the FDA that we recommend the guidance should encourage sponsors to consult the relevant FDA review division before finalizing the pediatric extrapolation plan. Further, we recommend an explicit statement that the number and size of studies required for extrapolation should be minimized and discussed with the FDA review division.

In addition, we ask the Agency to consider the unique considerations in oncology studies. The draft guidance states that, if a product is developed for adults and children, then adult data should be extrapolated to children to minimize the amount of data that is needed from children. In cancer, although a diagnosis might be the same, the biology of the disease is often different in children and adults, and so it may actually be important that the effect of an intervention be adequately studied in children. Cancer therapies that have worked in adults often do not translate into the same efficacy in children.

> *. . . if effectiveness and/or safety in adults can be extrapolated to children, then effectiveness and/or safety studies in adults should be conducted to minimize the need to collect such data in children. The number and size of studies involving children required for extrapolation should be minimized. However, various factors impact whether the extrapolation of adult data is appropriate. For example, in oncology, cancer therapies that have worked in adults often do not translate into the same efficacy in children. Therefore, given the challenges unique to certain therapeutic areas, sponsors are encouraged to consult the relevant FDA review division before finalizing the pediatric extrapolation plan.*

Finally, ACRO asks the Agency to consider including a reference to the Research to Accelerate Cures and Equity (RACE) for Children Act, which was approved by the U.S. Congress in 2017 and took effect on August 18, 2020. The act requires all new adult oncology therapeutics under consideration for approval by the FDA to be evaluated for safety and efficacy in pediatric cancers if the treatment is directed at a molecular target relevant to pediatric cancer, including therapeutics with an orphan drug designation. RACE Act increased the number of cancer drugs with required studies for use in pediatric patients.

Line 108:
We recommend the insertion of additional, new text here.
We ask the Agency to consider incorporating an additional paragraph between the paragraph ending on line 107 and that starting on line 109 to reiterate the advice in ICH E11(R1) that the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of pediatric medicines.

> *The arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study. Depending on factors such as the condition, the treatment and the study design, it may be justifiable to include pediatric subpopulations in adult studies or adult subpopulations in pediatric studies.*

Lines 111 – 113:
The draft guidance reads: *"Regarding minimization of risk, research procedures should be consistent with sound research design and should not expose subjects to risk unnecessarily."* We recommend adding that – in addition to not exposing children to risk unnecessarily – all efforts should be taken to minimize burden for children (e.g., if different procedures yielding comparable data, the procedure involving less risk and less burden should be selected). The final guidance should read:

> *Regarding minimization of risk, research procedures should be consistent with sound research design and should not expose subjects to risk unnecessarily. Further, all efforts should be taken to minimize burden for the children (e.g., if there are different procedures yielding comparable data, the procedure involving less risk and less burden should be selected).*

Lines 113 – 114:
The current text states: *"When appropriate, procedures already being performed as part of clinical care should be used to meet research needs."* We recommend adding that – if possible – the frequency of performing the procedures during the study should be adjusted to the frequency clinical care would require so that the final guidance reads:

> *When appropriate, procedures already being performed as part of clinical care should be used to meet research needs, And, if possible, the frequency of these procedures should be analogous to the frequency they are performed in clinical care.*

Lines 120 – 121:
The draft guidance states: *"In pediatric drug development, randomized, placebo- controlled trials may be necessary to establish safety and effectiveness."*

We recommend adding the use of a comparator if effective treatment is available so that the final guidance reads: *In pediatric drug development, randomized, placebo- controlled (or comparator controlled trials if effective treatment is available) trials may be necessary to establish safety and effectiveness.*

Lines 151-160 – and their alignment with Lines 268-297 and Lines 320-325:
The guidance notes that if an intervention in a pediatric protocol exceeds minor increase over minimal risk without the prospect of direct benefit, the protocol is not approvable by an IRB but may proceed if the IRB and the FDA Commissioner conclude that three criteria are satisfied. One of these criteria is the assent of the child. We recommend that the final guidance should include an additional sentence noting that – where a pediatric patient is unable to give assent due to age or mental impairment – the need for assent may be waived. This would be consistent with the statement in lines 320-325. As currently written, the statements in lines 151-160 and 320-325 appear contradictory. We suggest that the final guidance read: *If a child is unable to understand the assent process because of their young age or mental impairment, the need for assent may be waived.*

Line 218:
We recommend the insertion of additional, new text here.
We ask the Agency to consider incorporating a line referencing the mechanism of action to be considered for assessment of safety.

Lines 223-231:
We recommend the insertion of additional, new text here.
We ask the Agency to consider explicitly stating that the potential effect on growth and development of the child (including behavioral and psychosocial effects) should be considered in the assessment of the risk level of the study. And, we ask the Agency to consider adding text at the end of this paragraph to make clear that appropriate mitigation measures may be included in the study design in order to reduce any risk identified to no more than a minor increase over minimal risk, and that IRBs should consider the appropriateness of such measures for use in the trial population.

> *Sponsors may include appropriate mitigation measures in the study design in order to reduce any risk identified to no more than a minor increase over minimal risk, and IRBs should consider the appropriateness of such mitigation measures for use in the trial population.*

Line 238:
The draft guidance currently states *"For children in the placebo arm, however, there is no prospect of direct benefit from the placebo intervention or procedure."*

ACRO asks the Agency to consider the following additional language:

> *Therefore, randomly assigning children to placebo could be deemed unethical, not only because it goes against standard practice but also because it could result in target-organ damage or deterioration of the underlying condition that might be improved by treatment with active drug. Appropriate and tailored study design is essential when considering a pediatric trial.*

Lines 241-247:
In addition to the current bullets in the draft guidance, ACRO recommends inclusion of two additional bullets:

- Baseline condition and grade or severity of the disease (for instance, placebo may be not only ethical but actually necessary in pediatric antihypertensive efficacy trials because of the placebo effect. However, severity of the disease is also crucial when considering the use of a placebo arm in a study. If we have a mild to moderate uncomplicated HTN where the usual first approach is nonpharmacological treatment before starting drug therapy, the use for a brief period of a placebo is acceptable and may even have ethical justification, since it would not vary from accepted standards of care, comparing to a higher grade of hypertension. On the other hand, the use of placebo in oncology patients is not feasible or ethical)

- Close monitoring has to be performed for prevention of clinical deterioration (and characterization of what would constitute deterioration during a trial should be specified).

Lines 253-254:
The draft guidance reads: *"Oral administration of a placebo for a short time period should generally be considered minimal risk."* We recommend insertion of an additional sentence to define "short" in this context and recommend the final guidance states:

> *Oral administration of a placebo for a short time period should generally be considered minimal risk. "Short" in this context means the minimum period necessary to assess the efficacy of the investigational product or, in a pharmacokinetic study, the time required to reach steady state.*

Lines 263-266:
This section currently states: *"In some cases, placebo-controlled drug trials requiring injections or infusions administered over the course of one or two years have been justified as a minor increase over minimal risk depending on whether appropriate risk mitigation strategies are included as part of the protocol."*

ACRO recommends incorporating a discussion here of the impact of repeated placebo-controlled drug trials requiring injections of infusions over a long period of time, especially for pediatric patients with a *chronic condition*, where a visit to see the doctor and the need of regular treatments, blood analysis or other type of complementary exams are very often cause of high burden, anxiety, and socioemotional detriment.

Line 330:
We recommend the insertion of additional, new text here.
We ask the Agency to consider incorporating text at the end of this paragraph to note that, in long-term clinical studies, it may be necessary to re-assess the assent of pediatric patients and/or to obtain informed consent when the patient reaches the age of legal consent.

> *Over the course of a long-term clinical study, it may be necessary to reassess the assent of a child in recognition of their advancing age, evolving maturity and competency. Informed consent for continued participation in a clinical study will be required when a pediatric participant reaches the age of legal consent.*

Line 360 – 371:
In addition to the bullets currently listed in the draft guidance, ACRO recommends inclusion of an additional bullet in the final guidance:

- Chronic conditions under treatment with regular follow-up exams for a long period of time and their impact on burden, anxiety, and socioemotional well-being. Especially in this this subgroup of patients, the study requirements should be -- as much as possible -- aligned with the standard of care for the study indication.

Lines 370-371:
We recommend the insertion of two additional bullets to the list here. Pediatric Medical Traumatic Stress (PMTS) can result from serious illness, medical procedures, and invasive experiences. Participation in a clinical trial can cause or exacerbate PMTS for the participants and caregivers in a clinical trial. Consideration of the potential impact of procedures and interventions should be part of the study design, including strategies to minimize and mitigate.

> *Protocol design, and the impact of invasive and repeated procedures on the risk of causing or exacerbating Pediatric Medical Traumatic Stress (PMTS) for participants and their caregivers, along with measures to mitigate and alleviate this.*

In addition, we recommend adding to the list of factors to consider when designing a clinical investigation and assessing potential risks to children involved in the study to ensure appropriate follow up. We ask the Agency to consider including the following additional bullet:

> *Duration of observation required following discontinuation of the drug or device to ensure potential investigational related events are identified, reported and treated appropriately*

Line 410-416:
The draft guidance currently reads: *Multiple-dose studies intended to collect PK data may offer prospect of direct benefit, but the dose and duration of exposure to the study intervention should be sufficient to have the potential to result in a clinical benefit or to effect some change in a surrogate of clinical benefit. To provide studies of adequate duration to offer prospect of direct benefit, adaptive study designs should be considered when additional dose finding is required within the context of the clinical investigation.*

MAD studies may require exploration of lower doses to establish safety prior to escalation to the anticipated efficacious dose(s). We recommend acknowledging this as a minor increase over minimal risk similar to a single-dose study. We agree with the recommendation to consider adaptive design to facilitate appropriate escalation to a potentially more efficacious dose when feasible. Therefore, we recommend insertion of the following additional language in the final guidance:

> *In multiple ascending dose studies, initial lower doses may not offer the prospect of direct benefit similar to single-dose studies; therefore, these studies may be also considered under 21 CFR 50.53 as a minor increase over minimal risk where study intervention does not offer benefit but may contribute to generalizable knowledge about the child's disorder or condition.*

In addition, ACRO recommends incorporating additional language regarding the type used for PK and impact on burden and willingness to participate in these studies. For example:

Population modelling using non-linear mixed effect modelling is an excellent tool since this approach allows for the analysis of sparse and unbalanced datasets. Additionally, it permits the exploration of the influence of different covariates such as body weight and age to explain the variability in drug response. Where appropriate, this methodology will improve the efficacy/safety balance of dosing guidelines, which will be of benefit to the individual child. PopPK modelling (rather than multiple-dose PK collections) may also have a positive impact on patient´s burden, anxiety and willingness to participate in trials.

Lines 444-445:
We recommend expanding the existing text by the following additional text.
Further expansion upon what represents harm to include psychosocial and behavioral impacts, as well as what efforts can and should be made to mitigate these should be considered.

The potential for harm and the invasiveness and frequency of the planned procedures should be considered when assessing the risk, inclusive of behavioral and psychosocial effects such as anticipatory anxiety and Pediatric Medical Traumatic Stress. Recommended mitigation strategies such as Trauma Informed Care and tools to alleviate PMTS should be considered when assessing the risks.

Omission and recommended solution:
We believe that it would be helpful to expand the language regarding behavioral and psychosocial effects of the clinical trial on participants using patient and/or caregiver reported outcomes (please refer also to the comment above to lines 370-371).
It would be helpful:

- to include recommendation and guidance for the increased use of pediatric patient and caregiver reported outcome measures (ex. Simple pediatric ePRO) to assess and improve overall patient experience in pediatric clinical trials.
- to emphasize need to collect data on child's wellbeing, to validate and inform questions of pain, discomfort, and/or disruption to lifestyle caused by participation in clinical studies, having in mind sensitivity to understand how discomfort and trauma can vary with age, development, and disease
- to include further recommendation for mitigations which can be included in the trial design (strategies and tools) would be helpful.

Omission and recommended solution:
We believe it would be helpful if the final guidance provides clearer guidance regarding the number of PK draws that would be deemed a 'minor increase over minimal risk'. Most single-dose studies intended to collect PK data in children do not offer prospect of direct benefit because the study duration is too short to offer a clinical benefit.

A study intended to collect single-dose PK data might be considered under 21 CFR 50.53 as a minor increase over minimal risk if there is adequate safety information to characterize the risk from exposure to the investigational drug and any additional study procedures as no more than a minor increase over minimal risk. In this case, the study intervention does not offer benefit but may contribute to generalizable knowledge about the child's disorder or condition.

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Omission and recommended solution:
As with clinical investigations in general, we believe peer review of documents and materials to be shown to potential participants is important. This has become a requirement in Europe and – given the recurring concerns over the length and complexity of information sheets – we believe this would be wise approach for clinical investigations involving children.

Omission and recommended solution:
We ask the Agency to consider the inclusion of patients and patient organizations in the study design of clinical investigations involving children.

Thank you for this opportunity to provide feedback. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.

Respectfully submitted,

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