December 20, 2022

Dockets Management Staff (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852
Submitted at https://www.regulations.gov

Re: Docket No. FDA-2022-D-0738
Ethical Considerations for Clinical Investigations of Medical Products Involving Children
Guidance for Industry, Sponsors, and IRBs

To the Office of Pediatric Therapeutics, Dr. Snyder, and others,

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the request of the US Food and Drug Administration (FDA) for input on its proposed guidance, “Ethical Considerations for Clinical Investigations of Medical Products Involving Children Guidance for Industry, Sponsors, and IRBs,” published in the Federal Register. It is a timely and important guidance document. When finalized, this Guidance Document will be an important reference on ethical and other considerations for including children in clinical research. We offer these comments in support of the proposed guidance and offer suggestions to strengthen and extend it.

The MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. Over the last six years, the MRCT Center has been intimately involved in advancing diversity, equity, and inclusion (DEI) in clinical trials, and more generally, in clinical research. We consider that pediatric patients are also an underserved and underrepresented population in clinical research. We have worked to advance global pediatric clinical trials and to enhance the voice of young people in the planning, design, and conduct of pediatric clinical trials. We have worked with multiple international and national agencies, and in the US, that includes NIH, FDA, and OHRP, but please note that we have not discussed the comments provided herein with anyone at those agencies. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.¹

¹ Brigham and Women’s Hospital, Ropes and Gray LLP, Harvard Medical School, and Harvard University.
1. We suggest that this Guidance Document include a recommendation to engage young people directly as well as their parents, guardians, and caregivers in the planning stages of clinical research, including consulting with them on the study question, design, risks, potential benefits, conduct, endpoints, and reporting. What is important to young people and their parents or guardians is not often solicited directly and may differ from the opinion of clinical trial stakeholders (e.g., pharma, academia). What are acceptable risks given present alternatives should be a question best addressed to those with lived experience. These questions and others will depend on the specific condition, the study, and the age and maturity of the young person to participate in the discussion. We recommend further that the FDA require sponsors to discuss whether, when, and how patients and their parent(s) or legally authorized representative(s) were involved in the development of the study question, study design, conduct, outcomes, communications, and other aspect of the clinical trial development as a component of submission of the clinical trials application. There would be little added burden to these recommendations as they are already encouraged by the EU Clinical Trials Regulation, implemented in January 2022; FDA guidance on this practice would serve to further harmonize regulatory expectations.

2. Drug development for children lags significantly behind that for adults in diseases and conditions that impact both age groups. The MRCT Center recommends that the more routine practice of inclusion of adolescents in adult studies should be considered, and certainly addressed in phase 3 pivotal studies. Inclusion of adolescents may not be appropriate in all studies, and the age may vary (e.g., ≥16 or ≥12 years), but the sponsor should be asked to address how they determined eligibility by age. A multistakeholder group has already analyzed the impact of this approach (see: Bucci-Rechtweg C, et. al., Strategies to facilitate adolescent access to medicines: Improving regulatory guidance. Clinical Trials. 2022 Nov 5:17407745221132302.)

3. We agree with the emphasis on assent in this helpful guidance. We worry, however, that the FDA calls out the age of 7 as the appropriate age of assent, without adequate provision for the physiological, developmental, and emotional maturity of the child nor potential cultural considerations that might impact age-appropriate decision-making. The specific mention of a given age will potentially drive readers of the guidance to believe that the FDA is establishing the age of assent, rather than deferring to clinical judgement – which may then render the age either somewhat younger or older than age 7.

   a. We recommend removal of the specific language indicating “age 7” as the designated or implied of age of assent.
   b. We recommend that FDA clarify that if a child is unable to understand the assent process because of age, developmental or cognitive impairment, the need for assent may be waived.
   c. Similarly, we recommend that some mention of “assent” in the document be prefaced with “age-appropriate” [assent]. For instance, line 54 says “…adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians,” we recommend you replace with “…adequate
provisions are made for soliciting the *age-appropriate* assent of the children and the permission of their parents or guardians."

d. We recommend that FDA clarify that when a child is capable of providing assent, that expression of dissent to participate in a clinical trial be appropriately respected.

4. The MRCT Center recommends that the FDA emphasize that the principle of scientific necessity should be balanced by clinical necessity. Waiting for adult studies to complete, waiting for “effectiveness” determinations (rather than efficacy data), and waiting for adequate data to determine whether extrapolation will be appropriate or useful have too often led to delays in access to medicines for children, with particular reference to children with diseases for which there is no alternative or only a poorly tolerated or inadequate treatment. For instance, in these limited clinical settings, dose finding studies may be appropriate to begin in advance of completion and analysis of adult Phase 3 pivotal trials.

5. The distinction between minimal risk and minor increase over minimal risk remains an area of persistent disagreement and confusion among sponsors, investigators, and institutional review boards. It would be helpful for the FDA to clarify the distinction and give examples in each category.

6. The MRCT Center recommends that FDA provide further comment on the use of extrapolation, reliance on (and development of appropriate) biomarkers, and degree of similarity between the adult and the pediatric populations, including and beyond the draft ICH E11A Pediatric Extrapolation guidance. The current guidance relays a strong dictum to determine scientific necessity prior to commencing pediatric trials; we believe that the guidance should acknowledge the gaps in current knowledge to ensure that pediatric clinical trials are not inappropriately delayed. We suggest three further considerations on the use of extrapolation:

   a. The draft guidance addresses extrapolation in the context of effectiveness data. The extrapolation of adult safety data to children is often difficult. We recommend FDA provide examples of settings in which extrapolation may be used for both effectiveness and safety, and when it may not (e.g., certain oncology studies). We recommend FDA make specific mention of the need to collect pediatric safety data, and that safety data be stratified by age and developmental maturity (i.e., safety data on a neonate differs from a child and both differ from an adolescent). Whether and how safety data will be collected will depend on the specific conditions being treated, medicines themselves, alternatives to the investigational product and other factors.

   b. In addition to collection of safety data, the impact of investigational products on growth and development should be assessed.

   c. It would be helpful for FDA to acknowledge that some diseases in children may be phenotypically but not biologically similar to adults. Where differences are known, caution should be exercised in reliance on extrapolation.
7. It would be helpful for the FDA guidance to further describe when placebo-controlled trials are necessary or indicated, with specific reference to potential alternatives that may be considered to be of “direct benefit,” even when those alternatives are known to be inadequate. The comparison to an inadequate alternative, by the logic of the guidance, might give ethical cover to research-related procedures of uncertain or no direct benefit; however, such an approach will likely increase the enrollment number as the likelihood of a statistical difference between two arms of a trial may decrease or be harder to establish.

8. Age is a continuum, and the division between adult and child, and among pediatric subgroups is arbitrary. The guidance should acknowledge that many of the considerations will vary depending on the age of the child, the maturity of the child, the condition being studied, the treatment and study design, and the state of knowledge. The risks to a newborn generally differ from the same procedure or exposure to an adolescent, for example, and the utility of extrapolation from adult data is generally more reliable to adolescents and young adults than to neonates or infants. Relevant factors should include mention of developmental and intellectual maturity of the child; availability, efficacy, and access to alternative diagnostic, therapeutic or preventative approaches; and the perspectives of patients, parents/guardians, and caregivers. The guidance should reference these considerations, lest the regulated community interprets the guidance to the letter, rather than the spirit, as intended.

9. The MRCT Center recommends FDA include a strong statement about the need for the equitable selection of participants to include consideration of the diversity of participants for whom the intervention is intended. Inclusion and representation in terms of race, ethnicity, gender, disability, social determinants of health, linguistic preferences, and other considerations are necessary, and contextually important. We recommend that FDA recommend eligibility criteria be as permissive as possible and as restrictive as necessary and explained in the context of the protocol based on scientific and/or ethical justifications, that accommodations be provided, and that translation and interpreter services be available, as necessary. These considerations are important for children and for their parents, guardians and caregivers.

10. We recommend that FDA draw attention to emerging trends in research design and conduct, particularly as these may allow for greater inclusion of pediatric subgroups. For example, the mention of remote technologies and decentralized clinical trials would be helpful.

11. The MRCT Center recommends FDA include in the guidance recommendations for collection, storage, release, and use of biological specimens for future use, with particular attention to genetic information and unspecified future use. It would be important for FDA to emphasize that the collection of biospecimens for unspecified future use should be optional, and not a requisite tied to any clinical research that offers the prospect of direct benefit, unless such collection is required for the purposes of the research itself.
Unlike adults able to consent for themselves, children may not fully understand the potential use or impact, and with changing regulations and scientific knowledge, may unwittingly be subject to harms (e.g., employment, insurance) as a consequence of such donation. Participation in potentially beneficial clinical research should not be contingent on biospecimen or data donation collected for unspecified future use.

Thank you again for the opportunity to comment on these important issues. We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact the MRCT Center at bbierer@bwh.harvard.edu.

Respectfully submitted,

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