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December 23, 2022

Lauren K. Roth, JD
Associate Commissioner for Policy
Office of the Commissioner
Food and Drug Administration
19903 New Hampshire Avenue
Building 32, Room 4239
Silver Spring, MD 20993-0002

RE: Docket No. FDA–2022–D–0738 for "Ethical Considerations for Clinical Investigations of Medical Products Involving Children; Draft Guidance for Industry, Sponsors, and Institutional Review Boards."

Dear Ms. Roth,

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s Draft Guidance for Industry, Sponsors, and Institutional Review Boards on "Ethical Considerations for Clinical Investigations of Medical Products Involving Children," published in the *Federal Register* on September 26, 2022.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

PRIM&R believes the FDA's draft guidance is well thought out and will be extremely useful to the regulated community. Below are additional recommendations that we believe will not only enhance the utility of the guidance but also bolster public trust and confidence in biomedical research with children.

III (A) Principle of Scientific Necessity

Lines 100-104: IRBs should consider the scientific necessity of conducting a clinical investigation in children. It may be more efficient to consider scientific necessity before assessing risk and benefit under 21 CFR 50, subpart D. Children should not be enrolled into a clinical investigation unless their participation is necessary to answer important scientific and/or public health questions directly relevant to the health and welfare of children.

PRIM&R agrees that it is imperative that IRBs assess the scientific necessity of the proposed trial before conducting a risk-benefit analysis. We also applaud the fact that the guidance exhorts IRBs to base determinations regarding benefit not on intuitions, but on assessments of whether there is sufficient evidence outlined in the application to support both the level of risk and the prospect of direct benefit.

Lines 111-114: Regarding minimization of risk, research procedures should be consistent with sound research design and should not expose subjects to risk unnecessarily. When appropriate, procedures already being performed as part of clinical care should be used to meet research needs.

In addition to the recommendation that procedures performed as part of clinical care be used to meet research needs, PRIM&R recommends that the FDA provide additional details and examples of procedures that can be implemented to minimize risks of harm to children involved in clinical investigations.

Lines 116-122: When it is considered scientifically necessary to conduct a clinical investigation in children, it is imperative that the clinical investigation be well-designed to collect interpretable data. Key elements of well-designed clinical investigations include the selection of appropriate control groups and study endpoints relevant in the pediatric population. Studies that are not well-designed expose children to unnecessary risks, are unlikely to yield informative study results and as a result may be considered unethical. In pediatric drug development, randomized, placebo-controlled trials may be necessary to establish safety and effectiveness.

PRIM&R strongly endorses this general statement, which clearly articulates the relationship between good science and ethics. Based on the language in the preamble to the revised Common Rule, which implicitly equates "ethics" with risk of harms (*i.e.,* studies with little risk of harm do not need ethical oversight), IRBs often provide little scrutiny for minimal risk studies. The FDA guidance, on the other hand, explicitly directs the IRB to first evaluate the scientific integrity of the proposed study, before conducting a risk-benefit analysis.

III (B) Risk Categories for Interventions or Procedures without Prospect of Direct Benefit

Lines 152-156: Minor increase over minimal risk should be understood to mean a slight increase over minimal risk that poses no significant threat to the child's overall health or well-being. Any potential harms with the intervention or procedure should be expected to be transient and reversible and the probability for severe pain, discomfort, or harm should be extremely small or nonexistent.

PRIM&R recommends that FDA provide further guidance on when a reversible harm would meet the criteria for minimal risk and when it would qualify as minor increase over minimal risk.

III (E) Component Analysis

PRIM&R applauds FDA for the extremely clear and helpful discussion of component analysis. It will provide IRBs with the tools necessary to take a more systematic approach to the review of pediatric research. PRIM&R recommends that FDA consider enhancing this guidance by providing a tool, (for example, an interactive template or a flowchart that provides a step-by-step guide to the various factors that should be taken into consideration) that could be used by IRBs both a) to explain to investigators what they need to provide in

IRB applications for pediatric research and b) to help the IRB itself understand what it needs to systematically assess and steps for doing so.

III (F) Potential for Review per 21 CFR 50.54

Lines 279-296: The Commissioner, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following opportunity for public review and comment, determines …. set forth in 21 CFR 50.55

PRIM&R strongly supports this recommendation and notes that HHS's Secretary's Advisory Committee for Human Research Protections (SACHRP) had in fact addressed this issue. PRIM&R also recommends that FDA provide additional information on criteria for identifying and selecting experts, details about the public review process, etc.

PRIM&R also strongly endorses the following recommendations to the FDA from The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard:

- 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.

- 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.

- 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,

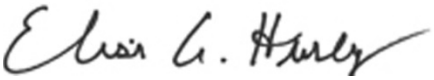
might give ethical cover to research-related procedures of uncertain or no direct benefit; however, such an approach will likely increase the enrollment number as the likelihood of a statistical difference between two arms of a trial may decrease or be harder to establish.

- 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.

- 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 the draft guidance. We hope our comments will be useful to the FDA in its ongoing deliberations on this important issue. PRIM&R stands ready to provide any further assistance or input that might be of use. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Sincerely,



Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors