The Ethics of Clinical Studies in Children – FDA Draft Guidance

11-01-22 • alert • katherine leibowitz

As FDA explains, historically, children were not included in clinical trials due to a misperception that excluding them was in fact protecting them. As a result, doctors often had to use products on children that had not been reviewed by FDA for safety and effectiveness in children. To this end, FDA recently published draft guidance on Ethical Considerations for Clinical Investigations of Medical Products Involving Children (September 2022). In the news release, FDA explains, "Children need access to safe and effective medical products and health care professionals need data to make evidence-based decisions when treating children." Because children are a vulnerable population who cannot consent for themselves, they receive extra safeguards when participating in clinical investigations.

This Update lays out the regulatory background for studies in children and then delves into the ethical considerations of the draft guidance, including examples provided by FDA.

I. REGULATORY BACKGROUND

For FDA-regulated clinical investigations, the ethical principles for human subject protection are set forth in 21 CFR Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards (IRBs)). When reviewing and approving clinical investigations enrolling children, IRBs must follow these regulations, including the additional safeguards for children in Subpart D of 21 CFR 50. All FDA-regulated clinical investigations of medical products must comply with these regulations even if an investigational device exemption (IDE) or an investigational new drug application (IND) is not required.

A. Three Main Avenues for IRB Approval

Under 21 CFR 50.50, IRBs must review clinical investigations involving children as subjects and may grant approval only if the clinical investigation satisfies the criteria in Part 50.51, 50.52, or 50.53, as well as any other applicable sections of Subpart D. For all three avenues, adequate provisions must be made for soliciting the assent of the children and the permission of their parents or guardians under Part 50.55. The regulations are:

21 CFR 50.51: Clinical investigations not involving greater than minimal risk. Requires the IRB to find that the clinical investigation presents no greater than minimal risk to children.

21 CFR 50.52: Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. Requires the IRB to find that:

– The risk is justified by anticipated benefit to the subjects, and

– The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

21 CFR 50.53: Clinical investigations involving greater than minimal risk but no prospect of direct benefit to individual subject, but likely to yield generalizable knowledge about the subjects' disorder or condition. Requires the IRB to find that:

– The risk is a minor increase over minimal risk;

– The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual medical, dental, physiological, social, or educational situations; and

– The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition.

– In the draft guidance, FDA notes that children in studies of this risk level should either have or be at risk for the disorder or condition being studied.

Fourth Avenue: As further discussed below, if the IRB is not able to approve a protocol under any of the above three avenues, a fourth option involving the FDA Commissioner exists under Part 50.54.

II. DRAFT GUIDANCE: THE ETHICAL FRAMEWORK

Section III of the draft guidance lays out the fundamental ethical concepts underlying the requirements of 21 CFR Parts 50 and 56.

A. The Principle of Scientific Necessity

The draft guidance highlights the fundamental concept of "scientific necessity," which is encompassed in the regulatory requirements for "equitable selection of subjects" under 21 CFR 56.111(a)(3) and "minimization of risk" under 21 CFR 56.111(a)(1). This principle is also grounded in the Belmont Report. Of note in the draft guidance:

– It may be more efficient to address scientific necessity before performing the risk/benefit analysis under 21 CFR 50 Subpart D.

– Children should not be enrolled in a clinical investigation unless their participation is necessary to answer an important scientific and/or public health question directly relevant to the health and welfare of children.

– If a product is being developed for both adults and children, and effectiveness data can be extrapolated from adults to children, FDA advises that effectiveness studies should be conducted in adults first in order to minimize the need to collect data in children.

– "Procedures already being performed as part of clinical care should be used to meet research needs."

B. Two Risk Categories for Interventions or Procedures without the Prospect of Direct Benefit

21 CFR 50 Subpart D includes two categories of risk for when there is no prospect of direct benefit:

Minimal risk: Minimal risk is defined in 21 CFR 56.102(i). In a nutshell, it means that the risk of the research is not greater

than what the child would normally encounter in daily life in during the performance of routine physical or psychological exams. Among other things, the draft guidance recommends that the IRB base this standard on the risks encountered by children of the same age and developmental stage as the subject population.

> Examples of minimal risk include single blood draw, physical exam, chest x-ray, surveys and certain investigational medical devices. FDA observes that investigational drugs are not likely to meet the minimal risk standard.

Minor increase over minimal risk: The draft guidance describes minor increase over minimal risk as "a slight increase over minimal risk that poses no significant threat to the child's overall health or well-being."

> Examples of minor increase over minimal risk include urine collection via a catheter, bone marrow aspirate with topical pain relief, and administration of a single dose of an investigational drug with adequate safety information.

C. How to Determine "Prospect of Direct Benefit"

Prospect of direct benefit refers to the potential benefit to the individual child from the research intervention or procedure. The IRB must determine that both (a) the risk is justified by the anticipated benefit to the individual child; and (b) the relation of the anticipated benefit to the risk is at least as favorable as available alternatives (Part 50.52). Of note in the draft guidance:

> – The level of certainty required for determining the prospect of direct benefit is not equivalent to the rigorous standards for confirming effectiveness. Thus, prospect of direct benefit can exist, and a study in children can begin, even if effectiveness in adults has not been established.
>
> – The potential benefit should result from the specific research intervention or procedure being studied, not from any accompanying physical exams or other ancillary interventions or procedures done as part of the trial.
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> – Potential sources of evidence to support the clinical benefit may include adult studies, animal or device modeling, and simulation data. FDA notes that for conditions that occur exclusively in children, nonclinical data from animal or in vitro models may be the only source of evidence.

D. Risk Analysis for Interventions or Procedureswith a Prospect of Direct Benefit (Part 50.52)

Under 21 CFR 50.52 (clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to subjects), the risk must be justified by anticipated benefit. Of note in the draft guidance:

> – IRBs should assess risk based on all available clinical safety data, such as data collected from (a) healthy adults; (b) adults with the same condition; and (c) from adults or children treated with the same drug or device for a different indication.
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> – If the above data are not available, nonclinical studies may be considered, such as (x) nonclinical studies on the maximum tolerated doses or device performance and safety; (y) juvenile animal studies to support the pediatric age groups being studied; and (z) nonclinical studies that are long enough to support treatment for chronic conditions.

E. Component Analysis: Research Interventions/Procedures and Placebo Arm

Minor Increase Over Minimal Risk Ceiling. The draft guidance explains that IRBs should perform a component analysis of risk. This is an evaluation of each intervention or procedure conducted solely for research purposes (including

administration of a placebo) to determine whether it offers prospect of direct benefit to the enrolled child. If the intervention or procedure does not offer the prospect of direct benefit, its risk should be limited to a minor increase over minimal risk and otherwise satisfy 21 CFR 50.53 (unless referred for review per 21 CFR 50.54 (see Section II F below)) .

Placebo Arm. The ethics of placebo arms can be tricky. Children in the investigational arm of a study may benefit from the investigational product and therefore have a prospect of direct benefit. Children in the placebo arms have no prospect of direct benefit. Therefore, the risk to children in the placebo arm should be limited to (a) minimal risk under 21 CFR 50.51, or (b) minor increase over minimal risk under 21 CFR 50.53, unless the study is referred for review under 21 CFR 50.54 . IRBs should consider the following factors in assessing a placebo arm under these two regulatory avenues:

- The placebo intervention;
- Routes of administration or procedures used for administration;
- Frequency and duration of administration of the placebo;
- Risk of withholding known effective therapy, if such therapy exists and will be withheld; and
- Use of rescue therapy, if appropriate.

Examples of risk assessments of placebo administration . According to the draft guidance, the following risk thresholds should generally apply:

- If an intravenous catheter will be placed for placebo administration, and is not necessary for clinical management or routine clinical care:
    i. a peripheral intravenous catheter: minimal risk or minor increase over minimal risk.
    ii. a central intravenous catheter: exceeds the minor increase over minimal risk threshold.
- Oral administration of placebo for a short period of time: minimal risk.
- Administration of placebo by a single injection: minimal risk.
- Administration of placebo by multiple injections or infusions: minor increase over minimal risk or, in some cases, exceeds this threshold.
- If known effective therapy is withheld, the risk of withholding must not exceed the minor increase over minimal risk threshold. If withholding or withdrawing known effective therapy may significantly harm the child, the risk may exceed this threshold, and the use of a placebo may not be justified.
- For placebo-controlled drug studies requiring administration over one or two years, the inclusion of appropriate risk mitigation strategies in a protocol may justify placebo administration that might otherwise exceed the minor increase over minimal risk threshold.

F. Referred FDA Review under 21 CFR 50.54

If an intervention or procedure in a pediatric study offers no prospect of direct benefit and exceeds the minor increase over minimal risk threshold, the IRB cannot approve the protocol under Part 50.51, 50.52, or 50.53. However, the clinical investigation may proceed under Part 50.54 if the IRB and the FDA Commissioner determine that:

- The research "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a

problem affecting the health or welfare of children; "

– The research will be conducted in accordance with sound ethical principles; and

– The assent of children and the permission of their parents or guardians is solicited per Part 50.55.

G. Parental/Guardian Permission and Child Assent

For all four regulatory avenues discussed above, the investigator must obtain permission from the parent(s) or guardian(s). Assent from the children must also be obtained if the IRB determines the children are capable of providing assent. The draft guidance observes that children age 7 or older are often considered capable of assent. While the draft guidance outlines the requirements of Part 50.55 for child assent and parent or guardian permission, for a comprehensive discussion of parent/guardian permission and child assent, FDA points the reader to FDA's draft Information Sheet on Informed Consent (July 2014). The 2014 draft document is availablehere.

H. Design Considerations, Study Procedure Assessment and Non-Therapeutic Procedural Sedation

Section IV of the draft guidance outlines additional considerations for IRB review, including supporting data, design considerations and study procedures. For study procedures, FDA provides additionalexamples of risk quantification for research procedures such as a single lumbar puncture vs. large organ biopsies, sedation not needed for the child's clinical care (i.e. non-therapeutic sedation), and MRI with and without contrast. The draft guidance also sets forth recommendations regarding non-therapeutic sedation.

III. FINAL THOUGHTS

For clinical investigations in children, there is a core tension between the importance of collecting data on medical products in children in order to improve their medical care and the importance of safeguarding children from risk to which they cannot legally consent. The ethical framework guiding the inclusion of children in clinical investigations, which draws on and is reflected in statutory law (specifically, 21 CFR Parts 50 and 56) as well as non-statutory principles such as the justice principles of the Belmont Report, aims to strike a crucial balance between protecting children from risk of harm involved in clinical trials and ensuring that adequate research is done on how drugs, biological products, and medical devices impact pediatric care.

The statutory classification of children as a vulnerable population means that (a) sponsors should draft protocols carefully in order to implement sufficient safeguards and ensure proper informed consent, and (b) IRBs should review protocols with equal care toward the level of risk the study involves, the potential benefits of the study for children, and the necessity of including children in the trial.

Litigation relating to pediatric clinical trials often allege ethical violations in the informed consent process. Lawsuits can arise even if assent and parental/guardian permission were obtained. Sponsors and IRBs need to understand what is required and what is recommended to ensure that child participants are properly protected and that both the participants and their parents/guardians are fully informed and have properly consented.

The draft guidance is available here.

[1] The author would like to thank Zoe Dettelbach for her contribution to this post.

If you have any questions or would like more information about these developing issues, please contact the following:

KATHERINE LEIBOWITZ
1-610-896-5788
Katherine.Leibowitz@LeibowitzLawTeam.com