U.S. FOOD & DRUG ADMINISTRATION

Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Draft Guidance for Industry, Sponsors, and IRBs

What is covered in this guidance?

This draft guidance describes the FDA's current thinking regarding ethical considerations for clinical investigations of medical products in children and provides a detailed description of the additional human subject protection regulations that are included in 21 CFR 50, subpart D (Additional Safeguards for Children in Clinical Investigations).

Why is this guidance important?

Clinical investigations in children are essential for obtaining data on the safety and effectiveness of drugs, biological products, and medical devices in children and to protect children from the risks associated with exposure to medical products that may be unsafe or ineffective. Children are a vulnerable population who cannot consent for themselves and therefore are afforded additional safeguards when participating in a clinical investigation. This draft guidance is intended to assist industry, sponsors, and institutional review boards (IRBs) when considering the enrollment of children in clinical investigations of medical products.

How is this snapshot helpful?

This snapshot provides an overview of the draft guidance to:

- Summarize the steps for considering enrollment of children in a clinical investigation using the ethical framework in 21 CFR 50, subpart D
- Present a high-level perspective of the draft guidance contents
- Consolidate information in the draft guidance into a brief and easy-to-read resource

Who are *children*? For the purposes of this draft guidance, *children* include neonates, infants, children, and adolescents who have not reached the legal age of consent in their local jurisdiction.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about ethical considerations for clinical investigations of medical products involving children, **read the guidance**.

Steps for Considering Enrollment of Children in a Clinical Investigation Using the Ethical Framework in 21 CFR Part 50, Subpart D

STEP 01

SCIENTIFIC NECESSITY

Consider the principle of scientific necessity (see draft guidance section III.A)

Children should not be enrolled into 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.

[EXAMPLE] Pediatric Extrapolation

For products that are being developed for use in adults and children, 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.

STEP 02

ETHICAL FRAMEWORK

Review the clinical investigation to determine whether it satisfies the criteria described in 21 CFR 50.51, 50.52, or 50.53 (see draft guidance section III)

21 CFR

50.51 Clinical investigations not involving greater than **minimal risk**

50.52 Clinical investigations involving greater than minimal risk but presenting the **prospect of direct benefit** to individual subjects

50.53 Clinical investigations involving greater than minimal risk (but no more than a **minor increase over minimal risk**) and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition

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STEP 02

21 CFR Section Comparison Table

21 CFR	50.51	50.52	50.53
Definitions	**Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests	**Prospect of direct benefit** refers to the potential benefit to the individual child from exposure to the research intervention or procedure being studied (e.g., the investigational drug or medical device) in the clinical investigation	**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
Interpretation	• The standard of minimal risk should be interpreted as those risks encountered in the daily life of normal, average, healthy, children living in safe environments and indexed to the experiences of children of the same age and developmental stage as the subject population • Given that investigational drugs generally are considered to have the potential to cause harm, an investigational drug utilized in a clinical investigation that includes children is not considered minimal risk	• Prospect of direct benefit refers to potential clinical benefit directly from the research intervention or procedure, not from ancillary interventions or procedures done as part of the trial • An IRB must find not only that the risk is justified by the anticipated benefit to the child, but also the relation of the anticipated benefit to the risk is at least as favorable as any available alternatives • Assessment of risk is predicated on adequate safety data. All available relevant clinical and/or nonclinical safety data should be included in the risk analysis	• 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 • The intervention or procedure must be 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
Examples	Procedures considered "minimal risk" may include single blood draw, physical exam, chest x-ray, surveys	Data are required to establish proof of concept and support that the proposed dose (or device characteristics) and duration of exposure to the intervention or procedure are adequate to offer potential clinical benefit **(see Assessment of Prospect of Direct Benefit)**	Procedures that might be considered a "minor increase over minimal risk" may include urine collection via a catheter, bone marrow aspirate with topical pain relief, a single lumbar puncture, a single dose of an investigational drug with adequate safety information
Take Home Points	• Healthy children may be enrolled • Not appropriate for trials of investigational medical products	• The child must have the prospect of benefiting from the intervention and the anticipated benefit must justify the risks • Common basis for IRB approval of trials of investigational medical products	• The child must have the disorder or be at risk for the disorder, the knowledge to be gained about the disorder must be vital, and the risk must not pose a significant threat to the child's health

STEP 02

☑ ASSESSMENT OF PROSPECT OF DIRECT BENEFIT

The necessary evidence to determine prospect of direct benefit for a pediatric clinical investigation may be based on one or more sources of information. When adult data are available in conditions that exist both in adults and children, evidence of clinical benefit from the drug or device in adults can provide support for prospect of direct benefit before clinical investigations are initiated in children. For conditions whose manifestations occur primarily or exclusively in children, collection of adult data evaluating the drug or device may not be available or feasible. In those cases, nonclinical data obtained in a relevant animal or in vitro model for the condition of interest may often be the only source of information to support prospect of direct benefit. Relevant animal or device modeling and simulation data may provide evidence of prospect of direct benefit and may preclude or mitigate the need to preliminarily collect relevant adult data. (See draft guidance sections III.C and IV.A.)

STEP 03

COMPONENT ANALYSIS

Conduct a component analysis of the clinical investigation to determine whether each intervention or procedure satisfies the regulatory requirements under 21 CFR 50, subpart D (see draft guidance section III.E)

A research protocol may include multiple research-related interventions or procedures, some that offer prospect of direct benefit and some that do not. Any intervention or procedure conducted solely for research purposes (not needed for clinical management or routine clinical care) should be evaluated separately to determine whether it offers prospect of direct benefit to the enrolled child (known as a "component analysis" of risk). If a specific intervention or procedure does not offer prospect of direct benefit, the risk of the intervention or procedure should be limited to a minor increase over minimal risk, and meet the other conditions outlined under 21 CFR 50.53.

[EXAMPLE] Placebo

The risks associated with the administration of a placebo in a clinical investigation should be part of the component analysis of risk. For children enrolled in the active study arm of a placebo-controlled clinical investigation, there is prospect of direct benefit that is offered by the investigational medical product; for children in the placebo arm, however, there is no prospect of direct benefit from the placebo intervention or procedure. See the draft guidance for a discussion of factors to consider when assessing risks to children in the placebo arm of a trial.

[EXAMPLE] Nontherapeutic Procedural Sedation

Procedures in children in a clinical trial may require sedation and the risks of sedation needed for nonbeneficial "research only" (nontherapeutic) procedures should be considered. See the draft guidance to review the considerations for the use of sedation for nontherapeutic procedures agreed upon by the Pediatric Ethics Subcommittee of the FDA's Pediatric Advisory Committee in March 2015.

POTENTIAL FOR REVIEW PER 21 CFR 50.54

If the protocol does not meet the criteria under 50.51, 50.52, or 50.53, IRBs may consider the potential for review per 21 CFR 50.54.

For example, if an intervention or a procedure in a pediatric protocol exceeds a minor increase over minimal risk and does not offer prospect of direct benefit, the protocol is not approvable by an IRB under 21 CFR 50.51, 50.52, or 50.53.

If an IRB finds 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 IRB can refer the protocol to the FDA for review and consultation with a panel of experts and for public review and comment in accordance with the provisions under 21 CFR 50.54 (see draft guidance section III.F).

PARENTAL/GUARDIAN PERMISSION AND CHILD ASSENT

Evaluate the trial's requirements and processes for permission and assent (see draft guidance section III.G)

A clinical investigator must obtain permission from the parent(s) or guardian when a child is enrolled in a clinical investigation (21 CFR 50.55(e)). The parental/guardian permission form must address the required elements and appropriate additional elements of consent (see 21 CFR 50.25) to allow the parent(s) or guardian to make an informed decision. Unless the IRB waives the requirement, adequate provisions must be made for soliciting assent from the child if the IRB determines that the child is capable of providing assent (21 CFR 50.55(a)).

Informed consent is a process; parents, guardians, and assenting children should be given the opportunity to ask questions when considering study participation and continue to be provided information as the study progresses and the situation requires.

[EXAMPLE]

> Children 7 years of age and older are often considered capable of assent; however, the age, maturity, and psychological state (mental capacity and developmental stage) of the child involved in the research must be considered.

☑ CODE OF FEDERAL REGULATIONS (CFR)

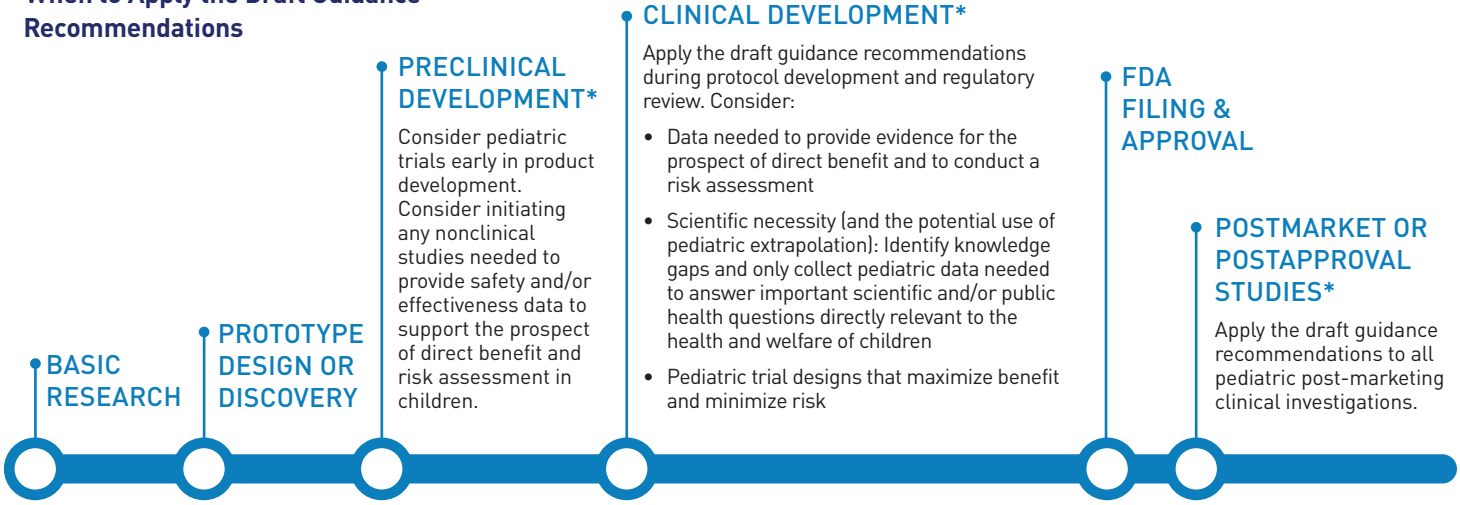
for the protection of human subjects involved in FDA-regulated research

21 CFR Part 50 Protection of Human Subjects
- 21 CFR 50, Subpart A General Provisions
- 21 CFR 50, Subpart B Informed Consent of Human Subjects
- 21 CFR 50, Subpart D Additional Safeguards for Children in Clinical Investigations

21 CFR Part 56 Institutional Review Boards

Drug Development Timeline

*** When to Apply the Draft Guidance Recommendations**



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Speaker: Donna L. Snyder, MD, MBE

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To learn more about ethical considerations for clinical investigations of medical products involving children, **read the guidance**.

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