Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Guidance for Industry, Sponsors, and IRBs

DRAFT GUIDANCE

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Ethical Considerations for Clinical Investigations of Medical Products Involving Children
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Clinical investigations[1] in children are essential for obtaining data on the safety and effectiveness of drugs, biological products,[2] and medical devices (collectively referred to as "medical products" herein) in children and to protect children from the risks associated with exposure to medical products that may be unsafe or ineffective. Children[3] are a vulnerable population who cannot consent for themselves and who therefore are afforded additional safeguards when participating in a clinical investigation. Such safeguards are an essential requirement for the initiation and conduct of pediatric investigations as part of a medical product development program. This guidance describes the FDA's current thinking regarding ethical considerations for clinical investigations of medical products in children.[4] Clinical investigations involving FDA-regulated products that are not medical products may have similar ethical considerations to those discussed in this guidance but are outside the scope of this guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] FDA's regulations at 21 CFR 50.3(c) define the term *clinical investigation* as "any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the Act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." See also 21 CFR 56.102(c). In this guidance, the terms *trial*, *clinical trial,* and *study* have the same meaning as the term *clinical investigation*.

[2] For purposes of this guidance, references to drugs include drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] FDA's regulations at 21 CFR 50.3(o) define *children* as "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted." For the purposes of this guidance, *children* include neonates, infants, children, and adolescents who have not reached the legal age of consent in their local jurisdiction.

[4] See section II for information regarding the regulatory requirements.

II. BACKGROUND

The ethical principles for the protection of human subjects in FDA-regulated clinical investigations are reflected in the requirements in 21 CFR parts 50 and 56; additional safeguards for children are included in 21 CFR part 50, subpart D (*Additional Safeguards for Children in Clinical Investigations)*. Institutional review boards (IRBs) are required to follow these regulations when reviewing clinical investigations of FDA-regulated medical products that are intended to enroll children. 21 CFR part 50, subpart D parallels the Department of Health and Human Services regulations found in 45 CFR part 46, subpart D, *Additional Protections for Children Involved as Subjects in Research*.

All FDA-regulated clinical investigations of medical products are subject to the requirements in parts 50 and 56 regardless of whether they require an investigational device exemption (IDE) or an investigational new drug application (IND).[5] For studies requiring an IDE or an IND, sponsors are encouraged to discuss their investigational plan, including plans for pediatric drug development, with the relevant review division prior to submitting a protocol to the IDE or IND.[6]

III. ETHICAL FRAMEWORK

In accordance with 21 CFR 50.50, IRBs must review clinical investigations involving children as subjects and approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of subpart D.

- 21 CFR 50.51 (clinical investigations not involving greater than minimal risk) requires that the IRB find that no greater than minimal risk to children is presented (see section III.B) and adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians (see section III.G).

- 21 CFR 50.52 (clinical investigations involving greater than minimal risk but presenting the *prospect of direct benefit* to individual subjects) requires that the IRB find that the risk is justified by the anticipated benefit to subjects (see section III.C), the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches (see section III.C), and adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians (see section III.G).

[5] 21 CFR 50.1 and 56.101.

[6] For additional information regarding clinical investigations of drugs involving children, see the ICH guidance for industry *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (*April 2018). See also the FDA guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- 21 CFR 50.53 (clinical investigations involving greater than minimal risk and no *prospect of direct benefit* to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition[7]) requires that the IRB finds that:

    - The risk represents a *minor increase over minimal risk* (see section III.B);

    - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, physiological, social, or educational situations (see section III.B);

    - 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; and

    - Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians (see section III.G).

  For children to be exposed to the level of risk described in 21 CFR 50.53, the children should either have or be at risk for the specific disorder or condition that will be studied in the clinical investigation.[8] Objective or empiric data should support that the condition proposed for study has the potential to negatively impact the child's health and well-being or increase the risk of developing a health problem in the future, as well as that collection of the data will enhance understanding towards prevention, diagnosis, improvement, or treatment of the condition.

The following are the fundamental concepts for the ethical framework in 21 CFR part 50, including subpart D, and 21 CFR part 56, and that IRBs should consider when reviewing clinical investigations that include children.

A. Principle of Scientific Necessity

The principle of scientific necessity[9] is encompassed in two regulatory requirements: the equitable selection of subjects (21 CFR 56.111(a)(3)) and minimization of risk (21 CFR 56.111(a)(1)). The concept is also grounded in the ethical principles of the Belmont Report,[10] specifically that of justice. IRBs should consider the scientific necessity of conducting a clinical investigation in children. It may be more efficient to consider scientific necessity prior to

[7] For the purposes of this guidance, references to *disorder* and *condition* include *diseases*.
[8] Institute of Medicine (2004); *Committee on Clinical Research Involving Children, Ethical Conduct of Clinical Research Involving Children*; Field MJ, Behrman RE, editors. Washington DC: National Academies Press. Recommendation 4.3. Available at https://www.ncbi.nlm.nih.gov/books/NBK25542/ (accessed September 19, 2022).
[9] Roth-Cline M, Nelson R. The ethical principle of scientific necessity in pediatric research. *Am J Bioeth*. 2014;14(12):14–15.
[10] The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 1979, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, available at https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html (accessed September 19, 2022).

assessing risk and benefit under 21 CFR part 50, subpart D. 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. For example, 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.[11]

Regarding the equitable selection of subjects, IRBs should consider the purposes of the research and the setting where the research will be conducted and should be aware of the unique challenges of research involving children.[12] 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.

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.

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

Any intervention or procedure, including the administration of an investigational drug or use of an investigational medical device, undertaken as part of a clinical investigation in children may be associated with risk. The regulations at 21 CFR part 50, subpart D include two categories of risk for procedures or interventions in a clinical investigation that do not offer a *prospect of direct benefit*:

- *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 (21 CFR 56.102(i)). 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. The experiences of a normal 2-year-old may be very different than the experiences of a normal 16-year-old. The duration of the exposure to the risk, the characteristics of the risk, and the reversibility of harm should

[11] See the guidance for industry and FDA staff *Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices* (June 2016) and the ICH guidance for industry *E11(R1)*. For additional information on pediatric extrapolation, see the ICH draft guidance for industry *E11A Pediatric Extrapolation* (August 2022) (when final, this guidance will represent the FDA's current thinking on this topic).

[12] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

also be considered. Examples of minimal risk interventions or procedures may include a single blood draw, physical exam, chest x-ray,[13] or surveys.[14] Given that investigational drugs generally are considered to have the potential to cause harm, the use of an investigational drug in a clinical investigation that includes children is unlikely to be considered minimal risk under 21 CFR part 50, subpart D. Investigational devices, however, can vary significantly in design and intended use (e.g., monitoring, diagnostic, or therapeutic devices). Depending on the investigational device (e.g., diagnostic versus therapeutic) and how it is used in the investigation, there could be device investigations that meet the criteria for minimal risk under 21 CFR part 50, subpart D.

- *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.[15] 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 setting and the experience level of the investigator are important factors to consider when making an assessment as to whether an intervention or procedure meets criteria as a *minor increase over minimal risk*.[16] Examples of interventions or procedures that might be considered a *minor increase over minimal risk* are a urine collection via a catheter, or bone marrow aspirate with topical pain relief,[17] or administering a single dose of an investigational drug with adequate safety information (see section IV.B).

See section IV for additional information regarding risk categories related to the design of the clinical investigation and research related procedures.[18]

C. Prospect of Direct Benefit

The level of certainty required for determining that a *prospect of direct benefit* exists is not commensurate with the rigorous standards for confirming effectiveness.[19] Consequently, effectiveness in adults does not need to be established before studies in children may begin. *Prospect of direct benefit* refers to the potential benefit to the individual child from exposure to

[13] Institute of Medicine (2004); *Committee on Clinical Research Involving Children, Ethical Conduct of Clinical Research Involving Children;* Field MJ, Behrman RE, editors. Washington DC: National Academies Press. Table 4.1, page 135.
[14] See the *Federal Register* of November 9, 1998 (63 FR 60353 at 60355).
[15] Department of Health Education and Welfare, Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. See the *Federal Register* of January 13, 1978 (43 FR 2084 at 2112).
[16] For information on reviewing the qualifications of investigators, see the guidance for IRBs, Clinical Investigators, and Sponsors on *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed* (August 2013).
[17] See footnote 13.
[18] Additional recommendations related to risk are included in The Secretary's Advisory Committee on Human Research Protections (SACHRP): Appendix B: Recommendations regarding risk in research involving children, July 28, 2005. Available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2005-july-28-letter-appendix-b/index.html (accessed September 19, 2022).
[19] Bhatnagar M, Sheehan S, Sharma I, Baer G, Green D, McCune S, Joffe S, Snyder D, 2021, Prospect of Direct Benefit in Pediatric Clinical Trials: Practical Challenges and Potential Solutions, Pediatrics, 147(5) e2020049602.

the research intervention or procedure in the clinical investigation in question (21 CFR 50.52). *Prospect of direct benefit* should result from the research intervention or procedure being studied (e.g., the investigational drug or medical device) and not from ancillary interventions or procedures, such as physical exams done as part of the trial. For research interventions or procedures that are considered to offer *prospect of direct benefit*, the IRB must find not only that the risk is justified by the anticipated benefit to the child, but the relation of the anticipated benefit to the risk is at least as favorable as any available alternatives (21 CFR 50.52). When evaluating if an intervention or procedure offers a *prospect of direct benefit,* the IRB should consider whether the evidence establishing proof of concept about a potential beneficial effect is sufficient, and whether the proposed dose (particularly for drugs) and duration of exposure to the intervention or procedure are adequate to offer a potential clinical benefit to the individual child. For a medical device clinical investigation, the device characteristics should be compatible with the child's age and developmental stage such that a benefit is anticipated.[20]

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. Animal or relevant device modeling and simulation data may provide evidence of *prospect of direct benefit*; and, in conditions that exist in both pediatric and adult populations, may preclude or mitigate the need to preliminarily collect relevant adult data. For pediatric conditions with a phenotype that extends into adulthood, demonstration of a drug's favorable effect on a biomarker(s) or surrogate endpoint(s) linked to the causal pathway of the disease in adults may also support *prospect of direct benefit* in children. For conditions with manifestations that occur exclusively in children, collection of adult data evaluating the drug or device may not be available or feasible, and 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*.

See section IV for additional information regarding *prospect of direct benefit* related to the design of the clinical investigation and research related procedures.

D. Assessment of Risk for Interventions or Procedures with a Prospect of Direct Benefit

21 CFR 50.52(a) requires that the IRBs find that the risk is justified by the anticipated benefit to subjects. Assessment of the risk is predicated on adequate safety data. All available clinical safety data—such as data collected from healthy adults, if appropriate; adults with the same condition; or adults or children treated with the same drug or device for a different indication—should be included in the risk analysis. However, if such information is not available, as may be the case for pediatric conditions that present solely or primarily in childhood, safety information

[20] See the guidance for industry and FDA staff *Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices*.

may be limited to nonclinical studies,[21] which could include:

- Nonclinical studies to evaluate maximum tolerated doses or device performance and safety,
- Juvenile animal studies to support the pediatric age groups being studied, and/or
- Nonclinical studies of sufficient duration to support treatment for chronic conditions.

E. Component Analysis

A research protocol, including a protocol studying a pediatric condition, may, and usually does, 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 and 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).[22] 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 unless the protocol is referred for review, as per 21 CFR 50.54 (see section III.F).

Failure to carefully evaluate the different components of a clinical investigation may result in an intervention or procedure that does not offer *prospect of direct benefit* exceeding the allowable ceiling of a *minor increase over minimal risk*. For example, for children enrolled in the active study arm of a placebo-controlled clinical investigation, there is *prospect of direct benefit* 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. Factors to consider when assessing risk to children in the placebo arm of the trial (evaluated under 21 CFR 50.51 as minimal risk or 21 CFR 50.53, as a *minor increase over minimal risk*) are:

- The placebo intervention (e.g., sugar pill, saline);
- Routes of administration (e.g., oral, infusion, topical) or procedures used for administration (e.g., placement of peripheral catheter);
- 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.[23]

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[21] For information on the design and conduct of nonclinical studies, see guidance for industry *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment* (October 2019); guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006); guidance for industry *Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals* (March 2019); ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010); ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018); ICH guidance for industry *S11 Nonclinical Safety Testing in Support of Development of Paediatric Medicines* (May 2021); and draft guidance for industry and FDA staff *General Considerations for Animal Studies for Medical Devices* (October 2015) (when final, this guidance will represent the FDA's current thinking on this topic).

[22] Final Rule, Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products, 78 FR 12937 at 12942 (February 26, 2013) and 43 FR 2084 at 2086 (January 13, 1978).

[23] Momper JD, DJ Green, K Park, GJ Burckart, DL Snyder, 2021, Ethical Considerations for Pediatric Placebo-Controlled Trials: FDA Outcomes and Perspectives. TIRS, 55(2): 282-303.

The risks associated with administration of a placebo in a clinical investigation should be part of the component analysis of risk. For example, if an intravenous catheter will be placed solely to administer placebo and is not needed for clinical management or is not needed for routine clinical care, the risk of the insertion and management of the catheter should be considered as part of the risk assessment. A peripheral intravenous catheter should generally be considered as minimal risk or a *minor increase over minimal risk*, whereas a central intravenous catheter should generally be considered to exceed the *minor increase over minimal risk* threshold.[24] Oral administration of a placebo for a short time period should generally be considered minimal risk. A placebo administered by a single injection could be considered minimal risk; it is possible that multiple injections or infusions could be considered as a *minor increase over minimal risk*, but in other circumstances multiple injections or infusions would exceed the *minor increase over minimal risk* threshold. If known effective therapy is withheld, the risk associated with withholding therapy should not exceed a *minor increase over minimal risk*. If withholding or withdrawing a known effective therapy may result in significant harm to the child, the risk may exceed the *minor increase over minimal risk* threshold, and the use of a placebo may not be justified.[25, 26] 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.[27]

F. Potential for Review per 21 CFR 50.54

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. FDA regulations include provisions under which a clinical investigation that is not otherwise approvable by an IRB may proceed if the following criteria are met[28]:

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[24] As an example, in 2017 an IRB referred a protocol involving placebo administration via a central access venous device to FDA for review per 21 CFR 50.54. FDA consulted with its Pediatric Advisory Committee and Pediatric Ethics Subcommittee (PAC/PES). A summary of the deliberations of the PAC/PES, the recommendation from FDA's Office of Pediatric Therapeutics to the Deputy Commissioner for Medical Products and Tobacco, and the decision by the Deputy Commissioner is available at https://www.fda.gov/media/105555/download (accessed September 19, 2022).

[25] ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), page 15.

[26] World Medical Association. (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. First adopted in Helsinki, Finland, in 1964. Available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed September 19, 2022).

[27] For examples, see Minutes from the May 11, 2018 joint meeting of the Pediatric Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee, regarding the use of randomized, blinded placebo-controlled trials for products intended for the treatment of achondroplasia, available at https://www.fda.gov/media/114640/download (accessed September 19, 2022); Meeting Minutes from the May 18, 2017 joint meeting of the Pediatric Advisory Committee and Pediatric Ethics Subcommittee, regarding a clinical investigation of a product intended to treat Duchenne Muscular Dystrophy, available at https://www.fda.gov/media/107320/download (accessed September 19, 2022); and footnote 23.

[28] For additional information see the guidance for clinical investigators, institutional review boards, and sponsors *Process for Handling Referrals to FDA Under 21 CFR 50.54 Additional Safeguards for Children in Clinical Investigations* (December 2006).

- The 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; and

- 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 either:

  – The research in fact satisfies 21 CFR 50.51, 50.52, or 50.53; or

  – The following three conditions described in 21 CFR 50.54 are met:

    1) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

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

    3) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 21 CFR 50.55.

G. Parental/Guardian Permission and Child Assent

A clinical investigator must obtain permission from the parent(s) or guardian(s) when a child is enrolled in a clinical investigation (21 CFR 50.55(e)).[29] The parental/guardian permission form must address the required elements of consent, as well as appropriate additional elements (see 21 CFR 50.25) to allow the parent(s) or guardian to make an informed decision. 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 as the situation requires.[30]

Assent means a child has provided affirmative agreement to participate in a clinical investigation; mere failure to object should not be construed as assent (21 CFR 50.3(n)). Unless the IRB waives the requirement, adequate provisions must be made for soliciting assent from the children if the IRB determines that the children are capable of providing assent (21 CFR

[29] FDA's regulations include limited exceptions from the general requirements for informed consent. See 21 CFR 50.23 and 50.24 and guidance for institutional review boards, clinical investigators, and sponsors *Exception from Informed Consent Requirements for Emergency Research* (April 2013). Of note, FDA does not intend to object to an IRB waiving or altering informed consent requirements for certain minimal risk clinical investigations involving children, as described in guidance for sponsors, investigators, and institutional review boards *IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* (July 2017).

[30] For additional information on the informed consent process, see draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet* (July 2014). When final, this guidance will represent the FDA's current thinking on this topic.

50.55(a)). Children 7 years of age and older are often considered capable of assent;[31] however, the age, maturity, and psychological state (mental capacity and developmental stage) of the child involved in the research must be considered (21 CFR 50.55(b)).

Assent of the children is not a necessary condition for a clinical investigation to proceed if the IRB finds either 1) that the children's capability is so limited they cannot reasonably be consulted or 2) that the intervention or procedure involved in the clinical investigation holds out a *prospect of direct benefit* that is important to the health or well-being of the children and is available only in the context of the clinical investigation (21 CFR 50.55(c)). Even if the IRB determines that the children are capable of assenting, assent may be waived under 21 CFR 50.55(d) if the IRB finds and documents that all the following criteria are met:

- The clinical investigation involves no more than minimal risk to the subjects;
- The waiver will not adversely affect the rights and welfare of the subjects;
- The clinical investigation could not practicably be carried out without the waiver; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Ultimately, the IRB determines whether assent is required and how assent is obtained.

IV. APPLICATION OF SUBPART D TO PEDIATRIC CLINICAL INVESTIGATIONS

IRBs should consider the following when determining if the regulatory criteria for clinical investigations involving children have been met.

A. Data to Support Conducting Pediatric Clinical Investigations

Multiple sources of information may be used to inform the design of an acceptable pediatric clinical investigation. Information from nonclinical studies, bench testing or modeling and simulation (especially in the case of devices), and literature may be used to assess the potential risks and benefits of initiating the investigation in children. Depending on the quality and applicability of these data, collection of relevant adult data prior to initiation of a trial in pediatric subjects may not always be necessary. If relevant adult data are available, those data may inform the trial design for pediatric subjects (see Principle of Scientific Necessity, section III.A). Early inclusion of children in medical product development or initiation of clinical trials directly in children may be appropriate.

In some cases, adult studies may not be ethical or feasible. For example, for a rare disease with high pediatric mortality, there may be few adults with the disease, or adults may have a less severe form with limited applicability to the more severe pediatric form.

[31] See the *Federal Register* of January 13, 1978 (43 FR 2084 at 2110).

B. Design Considerations for Clinical Investigations

Clinical investigations involving children should be designed to maximize the amount of information gained and minimize the number of subjects involved.

The risks posed by the drug or device in a pediatric clinical investigation may vary depending on the particular subgroup of pediatric patients. Factors to consider when designing a clinical investigation and assessing the potential risks to children involved in the study include the:

- Age and degree of physiological maturity of the child;
- Nature and natural history of the clinical condition to be treated;
- Current severity of the condition to be treated in the child;
- Presence of other complicating clinical conditions;
- Safety and effectiveness of the drug or device that may have been demonstrated in older subjects, or that is expected based on other clinical or nonclinical investigations; and
- Likely duration of drug or device use and its impact on the growth and development of the child, including behavioral and psychosocial effects.

The following sections provide additional design considerations for clinical investigations of drugs and clinical investigations of medical devices.

1. Clinical Investigations of Drugs

To offer a *prospect of direct benefit*, any dose planned for use in a pediatric clinical investigation should have the potential to have a therapeutic effect based on available scientific information.[32] If there are adults with the disease, pharmacokinetic (PK) and pharmacodynamic (PD) data in adults may provide useful information to help establish a potentially effective dose for use in children.

If there are a limited number of adults with the condition, PK and PD data from clinical trials in healthy adult volunteers[33] or in adults or children using the product for other indications may be informative in helping to establish initial dosing for children with the condition under study. Such information may also provide some evidence of drug activity to support *prospect of direct benefit* if the activity assessment is relevant to the pediatric population of interest. Extending a dose for a product from another patient population (or different indication) to the new pediatric population should be based on a sound scientific assessment, particularly addressing how the exposure-response for effectiveness and safety in the other population was used to predict the exposure-response relationship in the pediatric population of interest.

Nonclinical studies in disease-specific animal models of a pediatric condition or in vitro data could be used to support an initial pediatric dose if the PD effect on important aspects of the

[32] These considerations also apply to investigational gene therapies. For these trials, a single dose of vector is generally administered, with the possibility of a long-lasting duration of action and resulting benefit; the study dose will need to be in the potentially therapeutic range.

[33] Testing in adult normal, healthy volunteers is generally not acceptable for gene therapy trials. See the guidance for industry *Human Gene Therapy for Rare Diseases* (January 2020).

condition in question can be translated into an equivalent human dose that is anticipated to be effective and offers *prospect of direct benefit*. This should be based on scientific criteria that estimate the relationship between the PD effect in the nonclinical model and human physiology.

Clinical investigations should be of sufficient duration to offer a potential clinical benefit to the individual child. This judgement is similar to that made when exposing children to a treatment in clinical practice. Of note, 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*.[34, 35] In this case, the study intervention does not offer benefit but may contribute to generalizable knowledge about the child's disorder or condition.

Multiple-dose studies[36] 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. Such adaptive designs could combine prospectively planned dose ranging or dose titration with continued dosing after a dose is established.[37]

2. Clinical Investigations of Medical Devices

Compared to drugs, devices present different challenges due to the range of technology they incorporate and their varying applications. The available clinical data for the device (e.g., published studies and reports and actual use information) should be considered when designing the clinical trial to maximize the amount of information gained and minimize the number of subjects involved. For indications involving both adults and children, it may be possible to design a single pivotal study that includes both pediatric and adult subjects to reduce the burden of multiple studies and to optimize the sample sizes for both the pediatric and adult study populations. Further, while every effort should be made to gather data that adequately address each targeted pediatric subgroup for the proposed indication for use, in some cases, the expected benefit and safety can be determined without separate studies in each subgroup. That is, it may

[34] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.
[35] Roth-Cline M, Nelson RM. Microdosing Studies in Children: A US Regulatory Perspective. Clinical Pharmacology and Therapeutics. 2015; 98(3): 232-233.
[36] Given the complexity of gene therapy products, multiple dose PK studies are unlikely to be conducted. Please contact CBER for additional considerations that may apply.
[37] Guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019).

be extrapolated from one age group to another.[38] In other cases, such as with neonates, clinical data gathered specifically in that subgroup will likely be needed.[39]

C. Study Procedures in Pediatric Clinical Investigations

In the context of a clinical investigation, procedures that are carried out as part of routine clinical care of a child generally are considered to offer a clinical benefit and do not require evaluation as a research intervention under the regulations. Procedures that are carried out solely for research purposes and do not offer *prospect of direct benefit* must meet the minimal risk criteria (21 CFR 50.51) or no more than a *minor increase over minimal risk* criteria (21 CFR 50.53) in order to be included in a clinical investigation unless referred for review under 21 CFR 50.54 (see section III.F).

The potential for harm and the invasiveness and frequency of the planned procedures should be considered when assessing the risk. A single lumbar puncture or a single muscle biopsy have been considered, in many circumstances, to constitute a *minor increase over minimal risk*.[40] However, large organ biopsies—such as liver or kidney biopsies—when done for research purposes only have generally been considered to exceed a *minor increase over minimal risk*, and should not be done in children unless the procedure is performed as part of the routine clinical care for that child in the treatment of their condition. When considering the risk of a procedure, the risk of any sedation not needed for the child's clinical care (i.e., non-therapeutic procedural sedation, see section IV.C.1) or the risk of use of a contrast agent should also be considered. For example, a single MRI without contrast could be considered minimal risk, but the addition of contrast or sedation to the procedure is likely to constitute at least a *minor increase over minimal risk*, depending on the type of contrast being used and the risk of the sedation.

1. Procedural Sedation in Pediatric Clinical Investigations

Procedures in children in a clinical trial may require sedation and the risks of sedation needed for non-beneficial "research-only" (non-therapeutic) procedures should be considered. The Pediatric Ethics Subcommittee of FDA's Pediatric Advisory Committee met in March 2015 to discuss the use of non-therapeutic procedural sedation and came to the following areas of agreement when considering the use of sedation for a non-therapeutic procedure:[41]

- Procedures should be performed at a high-volume center with a dedicated pediatric sedation service;

[38] See footnote 20.
[39] For additional information, see the guidance for industry and FDA staff *Premarket Assessment of Pediatric Medical Devices* (March 2014).
[40] Snyder D, Lee C, and Nelson R. (2018). Invasive Placebos, Patient Burdens and Community Advocacy: A Federal Ethics Panel Protocol Review. In Kodish, E and Nelson, R. (Eds). Ethics and Research with Children, A Case-Based Approach (2nd ed.). New York, NY: Oxford University Press.
[41] Minutes of the Pediatric Ethics Subcommittee of FDA's Pediatric Advisory Committee, March 23, 2015. http://wayback.archive-it.org/7993/20180127092544/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM510177.pdf (accessed September 19, 2022).

- There should be rigorous scientific justification for the need for the non-therapeutic procedures;
- The approach to procedural sedation and risk minimization procedures should be described in the protocol;

- Children with chronic conditions that may place them at higher risk from procedural sedation should be carefully evaluated and potentially excluded from the protocol;

- The non-therapeutic procedure should be terminated if complications of sedation arise or the level of sedation is inadequate, as it would be inappropriate to escalate the approach to procedural sedation beyond what would be considered a *minor increase over minimal risk* rather than to stop the procedure;

- If a particular procedure in a particular patient population is normally accompanied by sedation when performed for clinical reasons, sedation should not be withheld in the non-therapeutic research setting to avoid its risks and thereby attempt to enhance the procedure's approvability under federal research regulations; and

- There should be clear communication with potential subjects (and their parents/guardians) regarding the non-therapeutic nature of the procedures and procedural sedation in child assent and parental permission documents.

FDA recommends that sponsors use these recommendations for minimizing risk in designing and implementing protocols that include non-therapeutic procedural sedation. These recommendations will also aid IRBs when assessing the risk to children. The IRB should consider the cumulative risk if more than one procedure with non-therapeutic procedural sedation is planned. If the IRB determines that the procedure(s) is integral to answering the scientific question and ethical to perform, but that it constitutes more than a *minor increase over minimal risk*, review under 21 CFR 50.54 will be required before the clinical investigation may proceed.