# Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients Guidance for Industry

## *DRAFT GUIDANCE*

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For questions regarding this draft document, contact (CDER) Julia Beaver at 240-402-0489 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Oncology Center of Excellence**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

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# Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients
# Guidance for Industry

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# Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients

## Guidance for Industry[1]

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## I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products[2] regulated by CDER and CBER for the treatment of cancer.[3] Specifically, this guidance includes recommendations regarding the inclusion of pediatric patients (i.e., children and adolescents). This guidance is intended to assist stakeholders, including sponsors and institutional review boards (IRBs), responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient

[1] This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

[3] Topics of the other three guidances are related to eligibility criteria for patients with human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infections; with organ dysfunction or prior or concurrent malignancies; and with brain metastases.

accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.[4,5]

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice without jeopardizing patient safety. Early evaluation and development of potentially effective drugs, particularly targeted drugs, in pediatric patients may provide information on safe and effective use, therefore reducing risks associated with off label use, and accelerate the development of effective, innovative therapies for pediatric patients.

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.

## II. BACKGROUND

This guidance discusses minimum age eligibility criteria for pediatric patients in cancer clinical trials and addresses specific situations in which the inclusion of pediatric patients may be appropriate (based on disease biology and clinical course, molecular target of the investigational drug, and/or its molecular mechanism).

Historically, pediatric patients have not been included in adult clinical trials, which generally specify 18 years as the minimum age of eligibility. Pediatric trials of the same drug generally have been initiated after the completion of one or more adult clinical trials, or after the initial approval in adults, delaying development of and access to potentially effective new cancer drugs for the pediatric population. In some cases, separate pediatric trials may have been infeasible because the disease occurs so rarely in pediatric patients. This delay in or absence of formal evaluation in a clinical trial results in product labeling that includes no pediatric-specific information about dose, safety, efficacy, and long-term effects to inform patients and providers on a drug's use in this population. Designing clinical trials that include pediatric patients and then including this information in the labeling promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice.

This guidance focuses on providing recommendations for eligibility criteria for pediatric populations including both children (for purposes of this guidance, ages two years to less than twelve years) and adolescents (for purposes of this guidance, ages twelve years to seventeen years).

[4] Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, NEJM, 376:1504-1505.

[5] Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, JCO, 35(33): 3737-3744.

## III. RECOMMENDATIONS

Eligibility of a specific pediatric population for a cancer clinical trial should be considered when there is clinical evidence or a strong scientific rationale to suggest that pediatric patients with a specific cancer diagnosis, histologic subtype, or tumor associated with the same relevant molecular target may benefit and when there is compelling nonclinical and/or adequate clinical information to sufficiently justify patient risk.

### A. Considerations for including pediatric patients in adult cancer clinical trials

#### *1. Ethical considerations*

There are several important ethical considerations specific to including pediatric patients in clinical trials outlined in the FDA regulations addressing human subject protection at 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations. These safeguards restrict the allowable risk to which a pediatric patient may be exposed to an investigational agent to certain situations, including those in which the interventions or procedures in the trial offer a prospect of direct clinical benefit to the individual subject. Use of an investigational agent in an oncology trial should be restricted to situations in which there is the prospect of direct clinical benefit to the individual pediatric patient. These clinical investigations may involve children if: (1) the risk is justified by the anticipated benefit to the subject, (2) the anticipated risk-benefit profile is at least as favorable as that presented by available alternative treatments, and (3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.[6]

Furthermore, under 21 CFR 56.111(c), in order to approve research in which some or all of the subjects are children, an IRB must determine that all research complies with 21 CFR part 50 subpart D.[7] Protocols that enroll pediatric patients should include pediatric oncology expertise for the design and conduct as well as adequate pediatric expertise in IRB review.

#### *2. Regulatory considerations*

Sponsors may be able to meet the requirements in sections 505A and 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[8,9] by including pediatric patients in adult clinical trials as discussed in this guidance.

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[6] See the specifics of these regulations under 21 CFR part 50, subpart D.

[7] Similar principles are outlined in the HHS human subject protection regulations at 45 CFR subpart 46, subpart D and 45 CFR 46.111(b).

[8] By convention, sections 505A and 505B of the FD&C Act are referred to by the names of the legislation that created them, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), respectively. FDA will adopt this naming convention in this guidance.

[9] For more information, see the Food and Drug Administration, Status Report to Congress, July 2016, Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, available at https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM509815.pdf, accessed on February 26, 2019.

### *3. General considerations for all trial phases*

Sponsors seeking to include pediatric patient populations should evaluate pediatric formulations taking into account the age, size, physiologic condition, and treatment needs of pediatric patients to be studied. Depending upon the mechanism of action of the drug and its potential for impacting development, growth, and causing late effects, prospective long-term follow-up of pediatric patients may be warranted. Additionally, monitoring for clinically important age-related differences in the safety profile of the drug should be conducted.

#### a. Considerations for children

Types of evidence that could support inclusion of patients from two years of age[10] to under age twelve years include:

- Clinical studies: Natural history and preliminary adult studies demonstrate children will likely exhibit similar responses to the investigational drug based on a clinical efficacy endpoint and concerns for the potential for severe growth and developmental toxicities are absent. Assessment of data, if available, from adult clinical programs may support decisions related to enrolling children.

- Nonclinical studies: *In vivo* and *in vitro* preclinical data (including *in silico* or mechanism-based *in vitro* evidence), particularly when conducted using pediatric tumor model systems may help increase confidence to support inclusion of pediatric patients. Modeling and simulation should be used to understand potential differences in pharmacokinetic (PK) and pharmacodynamic (PD) as well as dose selection.

- Sufficient non-clinical or early clinical experience in adults that suggests minimal risk of adverse effects on growth and development, and that can be used to guide benefit-risk assessment for children.

- Predictive biomarkers when available.

- Evidence from other drugs in the same pharmacological class or with similar mechanism of action.

Presentation of more than one of these types of evidence increases the strength of the evidence for including children in adult clinical trials.

[10] Generally, because infants including neonates and young children < 2 years of age may be particularly vulnerable to expected and unanticipated toxicity due to developmental concerns and age-dependent maturation of metabolic enzyme systems and organ function, children < 2 years should not be included in adult cancer trials. In rare instances, infants beyond the neonatal period may be appropriate candidates for select new drugs. However, enrollment of children < 2 years of age is best reserved for exceptional cases and only after consultation with the FDA.

b. Considerations for adolescents

As discussed in the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials*,[11] sponsors should consider including adolescents (i.e., ages twelve years to seventeen years) in disease- and/or target-appropriate adult cancer clinical trials at all stages of development when appropriate conditions are met (see sections III.4.b and III.5).

*4. Early phase trial considerations*

FDA encourages including pediatric patients for conditions without known curative options in early-phase trials that assess dose, safety, and PK in a variety of tumor types when compelling nonclinical data and/or early adult clinical data suggest activity.

Prospective planning to include pediatric patients in select first in human (FIH) studies intended for adults can be accomplished by designing studies to include an expansion cohort,[12] which would begin enrollment of pediatric patients when adequate data on dose and safety in adults are available to assure that the clinical trial provides the prospect for direct clinical benefit to pediatric patients to justify the risks. In addition to evidence of activity, the study drug dosage and the duration of treatment must be expected to support a prospect of direct clinical benefit to children.

Potential ways to include pediatric patients after a sufficient number of adult patients have been evaluated to provide adequate safety and toxicity data include:

- Enrolling a cohort of pediatric patients starting one dose level behind the highest dose level studied in adults in which there are no dose-limiting toxicities identified.

- The pediatric starting dose should be lower than the adult maximally tolerated dose (particularly for monoclonal antibodies) (i.e., the pediatric starting dose may be the adult recommended phase 2 dose (RP2D) if the dose is not the adult maximally tolerated dose).

- A limited dose escalation may occur in the pediatric cohort depending on the therapeutic product and the clinical indication(s) as well as the specific age eligibility for the pediatric cohort.

- In general, for children < 12 years of age and for adolescents < 40 kg defined adult flat doses would be converted to body surface area or body weight adjusted dosing.

[11] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[12] For more information, see the draft guidance for industry *Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (August 2018). When final, this guidance will represent the FDA's current thinking on this topic.

- Enrolling pediatric patients in a separate cohort that will accrue concurrently with the adult cohort when sufficient information to permit dose modeling based on adult PK and exposure data are available.

As discussed in the draft guidance for industry *Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics*,[13] in exceptional circumstances, substantive nonclinical evidence of activity in tumor-derived cell lines or patient-derived xenografts of pediatric tumors alone may provide sufficient justification for enrollment of a pediatric cohort before the availability of full clinical data in adults. In these situations, sponsors should consider staged enrollment of older children or adolescents before younger children.

a. Considerations for children

In situations where there may be a concern regarding differential efficacy between adults and pediatric patients for the same or different indication, sponsors could consider enrolling an expanded population with patients under 12 years of age with the goal of including them in the safety analysis but not in the primary adult efficacy analysis.

Possible strategies for the evaluation of efficacy in the pediatric population or indication(s) include:

- Continue to enroll restricted and expanded populations in the same clinical trial, and analyze efficacy separately if the biology/clinical course of the disease for which an indication is sought differs in adults and children.

- Use an expanded cohort design to build knowledge including assessment of safety and efficacy in particular populations. This approach would be particularly useful when the adult and pediatric indications ultimately under evaluation differ and in the setting of histology/tissue agnostic development strategies.

b. Considerations for adolescents

There should be a strong biologic rationale and absence of potentially curative therapies to support enrollment of adolescents in early phase adult trials, but given similarities in drug exposure between adolescents and adults (based on similar body weight and metabolic processes), adolescents may be enrolled concurrently with adult patients after some initial adult PK and toxicity data are obtained.[14]

[13] When final, this guidance will represent the FDA's current thinking on this topic.

[14] For more information, see the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019).

### *5. Late phase trial considerations*

The minimum age of eligibility specified in late-phase trials should be tailored to the biology of the disease under study, the scientific objectives of the trial, and the existing data regarding the mechanism of action and safety profile of the drug.