# Demystifying the Nonclinical Elements For Determining “Prospect of Direct Benefit”

# About this Guide

To conduct clinical research in pediatric patients, the Food and Drug Administration (FDA)'s human subject protection regulations require that, with limited exceptions, research that includes some risk must offer a **prospect of direct benefit** (PDB) to the individual child to justify those risks.

This "how-to" guide authored by the Pediatric Inclusion Alliance ("PIA" or "Alliance") is intended to serve as a resource for industry and patient groups about how to put together the nonclinical data elements as part of a strong total data package to help make the case to FDA that a therapeutic candidate in its proposed protocol has a PDB.[1]

# Opportunity for Comment

This document was developed by a range of experts who are members of the Alliance and have deep experience and expertise in pediatric clinical trials. We want this resource to be as helpful and grounded in real world experience as possible. Therefore, we welcome external comments on this guide. **Please send any comments or suggestions to PediatricInclusion@leavittpartners.com by May 31, 2026.**

# About the Pediatric Inclusion Alliance

The mission of the Pediatric Inclusion Alliance is to advance multistakeholder and consensus-based policy workstreams that will together achieve the earliest possible pediatric inclusion in clinical trials for drugs, biologics, and devices across all diseases and conditions without compromising safety. Learn more about the Pediatric Inclusion Alliance by visiting us online at: https://leavittpartners.com/pediatric-inclusion-alliance/.

[1] None of the information contained in this document should be construed as individual company-specific legal or regulatory advice. Rather, it is offered as general considerations and recommendations when preparing the non-clinical elements of a proof of concept.

## Introduction

For far too long, children with diseases or conditions that may benefit from medication to treat the symptoms or underlying cause of their illness have unfortunately frequently had to wait years for access to safe, effective therapies, often already approved for adult populations. These therapies might well have been even more effective for younger patients if administered at the best time for them.

Regulatory agencies and drug developers are increasingly supportive of earlier inclusion of pediatric subjects in clinical development, and it is becoming more evident that all stakeholders are ready to clarify policies and address challenges as needed to advance this shared goal. This "how-to" guide aims to address one of the aspects of pediatric inclusion that can be particularly challenging for drug developers seeking to include children first in clinical trials—namely, justifying the prospect of direct benefit (PDB) for an individual clinical trial participant.

## What is "Prospect of Direct Benefit?"

Federal regulation requires that, depending on the level of risk involved, investigators consider the prospect of direct clinical benefit offered to a child participating in a trial and being exposed to an investigational drug, the knowledge likely to be generated from the research about the child's disease or condition, and the potential benefits of the experimental product compared to any other available treatments for the condition.

**Key Point:**

Sponsors must conduct a risk/benefit assessment to determine whether it is appropriate to enroll children in a clinical trial, and the level of evidence needed may vary based on the age groups most impacted by the disease or condition and the severity of the disease or condition.

It is important to recognize that federal regulation does not prevent the inclusion of children when the risk/benefit assessment properly illustrates the value of inclusion and there are proper safeguards in place. In cases of minimal risk, children can be enrolled in clinical trials that present a significant benefit to the child's disease community, rather than a direct benefit to the child (when the proper consent and assent are provided).

Acceptability for using nonclinical data to support the PDB depends on the context of the disease, the nature of the investigational treatment, and the strength and applicability of the nonclinical data.[2] While there is not a one size fits all for what goes into a PDB analysis, there are a number of common elements that feed into this analysis.

For a researcher or drug developer looking to include children in pediatric trials, it is important to map out their PDB strategy early. The strategy should be thoughtful, precise, and demonstrate cohesive reasoning for generating the evidence to justify the PDB. The strategy should incorporate a mapping of the data-modeling selected, and a benefit-risk analysis (including a chemistry and manufacturing controls (CMC) assessment) to allow the agency to make a determination of the PDB in children.

[2] M. Bhatnagar, et al. Prospect of Direct Benefit in Pediatric Trials: Practical Challenges and Potential Solutions. Pediatrics. May 2021. 147(5). https://pubmed.ncbi.nlm.nih.gov/33906929/

*The goal is to gather sufficient preclinical scientific data from multiple sources — animal models, preclinical testing of the same/similar drug in a closely related disease, preclinical testing of a same-class drug in the same disease, and/or data from adult human clinical trials to show that the PDB to the child receiving the treatment justifies the higher risk. Although the level of evidence needed by the FDA to support the PDB is less than that required to establish efficacy, the PDB is based on evidence to support the "structure" of the treatment, which includes the dose, duration, and method of administration.*[3,4]

## Key Questions for Determining Prospect of Direct Benefit Justification

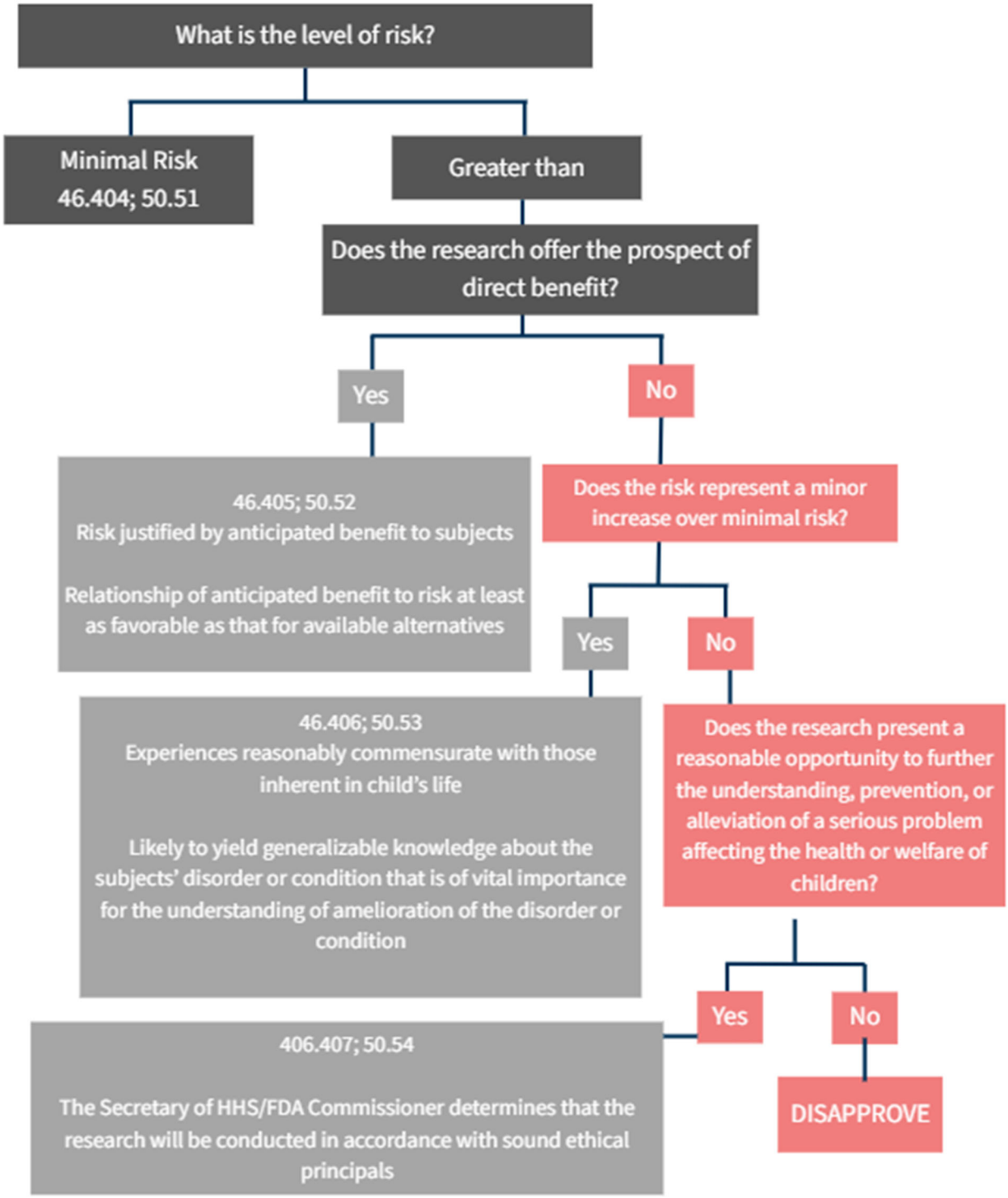
The elements of the strategy must directly answer two questions to determine if the PDB is justified:[5]

1. Does the experimental intervention offer a PDB; and
2. Is the PDB of sufficient probability, magnitude, and durability to show the expected risks are outweighed in the context of overall benefit.

[3] Melanie E. Bhatnagar. FDA. Slide presentation: Pediatric Clinical Investigations: Ethical Considerations. Slide 7. Sept 6, 2019. https://www.slideserve.com/vchoi/ethical-considerations-for-pediatric-clinical-investigations-powerpoint-ppt-presentation

[4] Michelle Roth-Cline. FDA. Slide presentation: Ethical Considerations in Evaluating Non-Therapeutic Studies in Children, Slide 16. Mar 29, 2012. https://www.fda.gov/media/84865/download

## Decision Tree for Risk Considerations for Pediatric Research




[1] Robert E. Shaddy, Scott C. Denne. American Academy of Pediatrics. Figure: Decision tree regarding risk considerations for pediatric research. Figure 1. 2012. https://pmc.ncbi.nlm.nih.gov/articles/PMC3369294/figure/fig1/

# Elements of the Strategy

To answer the first question, it is important for the strategy to include data modeling mapping and ensure the data supports a PDB for the intervention. To answer the second question, the strategy must also include a benefit risk analysis that shows the PDB is of sufficient probability, magnitude, and durability. Another critical element of the strategy is the CMC assessment that shows the treatment is of high quality. These three elements of the strategy are critical to addressing the questions of and justifying PDB.[5]

- ✓ **Data Modeling Mapping**: map which data models should be used to determine if the treatment offers the enrolled child a PDB.

- ✓ **Benefit Risk Analysis**: analysis of whether the risk level of treatment and procedure are justified by the potential benefit and whether the benefit risk balance is comparable to any available alternatives.

- ✓ **Chemistry, Manufacturing, and Controls (CMC) Assessment**: assessment of the quality of the treatment to ensure it meets or exceeds FDA's Current Good Manufacturing Practice (CGMP) regulations before it is given to pediatric patients.[6] Note that even with strong nonclinical data, if CMC is not supportive, FDA may not permit the clinical trial to move forward.

It is important to map out as many data modeling paths as you can to get to PDB in advance always keeping in mind these fundamental considerations.

- How is the nonclinical data as viewed through the regulatory lens?
- How does it translate to the clinic?
- How are these data relevant to the patient population?

## *Data Modeling Mapping*

When analyzing the proposed treatment to support PDB, it is imperative to consider scientific issues about which models to use, translatability methods/limitations, and at what dose to determine if evidence of efficacy in data models can be extrapolated to pediatrics to demonstrate potential benefits. For example, it is very important to map out feasible doses across models and humans prior to conduct of proof of concept

[5] Michelle Roth-Cline. FDA. Slide presentation: Ethical Considerations in Evaluating Non-Therapeutic Studies in Children, Slide 15. Mar 29, 2012. https://www.fda.gov/media/84865/download

[6] According to FDA, cGMP regulations for drugs "contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have."

(POC) studies, as a dose that may work in rodents may not necessarily be feasible (given limits of formulation/concentration, size of organ if allometric scaling, etc.). The nonclinical data and the results should be translatable to the patient population and what is known about the disease.

FDA has repeatedly said that nonclinical animal models or adult subjects should be studied prior to clinical trials involving children.[7] While, in April 2025, FDA announced plans to phase out animal testing requirements and use new approach methodologies (NAMs) for monoclonal antibodies and other drugs,[8] it is too soon to tell what the impact will be on preclinical data requirements to justify PDB.

> You'll want to ensure appropriate pediatric extrapolation as recommended in the E11A Pediatric Extrapolation guidance to show benefit. For example, if you want to dose pediatric patients, you should dose pediatric equivalent mice and follow them for an appropriate amount of time. Ideally then you'll have the data to show that you've intervened in a pediatric mouse and are seeing benefit, and this supports why we should dose pediatric humans. This will help with your PDB justification.

Data from these models are necessary to establish sufficient PDB. Moreover, data to justify the risk of the treatment will vary based on the severity of the disease and the adequacy of alternate treatments.

Data that could be used to justify PDB can be measured by using a clinical disease model to measure function or survival. If not available, then validated surrogate endpoints and changes in biomarkers (if available) may be used.[9] Either nonclinical models demonstrate PDB as standalone, or nonclinical models display a change on a surrogate endpoint, which is then supplemented with additional data linking the surrogate endpoint that is reasonably likely to predict clinical benefit.

[7] Robert 'Skip' Nelson. FDA. Slide presentation: Research Involving Children (Focusing on FDA Regulations), Slide 45. Nov. 4, 2015. https://os1.cc.nih.gov/sites/default/files/bioethics/bioethics-files/courses/pdf/2015/session6_nelson.pdf

[8] FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs. April 10, 2025. https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs Accessed on Dec. 12, 2025.

[9] Robert 'Skip' Nelson. FDA. Slide presentation: Research Involving Children (Focusing on FDA Regulations), Slide 46. Nov. 4, 2015. https://os1.cc.nih.gov/sites/default/files/bioethics/bioethics-files/courses/pdf/2015/session6_nelson.pdf

FDA has indicated dosing considerations should include the maximum recommended starting dose (MRSD) for "first-in-human" clinical trials which is based on "no observed adverse effect levels" (NOAEL) in animal studies and be converted to a human equivalent dose with the application of a safety factor.[10] For cell and gene therapy trials, alternate methodologies may be appropriate for serious diseases or for severely debilitating conditions. The highest non-severely toxic dose (HNSTD) may be another justifiable approach given some toxicities that may be acceptable given the overall severity and unmet need of the disease.[11] Other considerations for dosing may need to include whether are there differences between adolescents and young adults in terms of absorption, distribution, metabolism, and excretion.

Another consideration, if the disease has a significant phenotype, is whether to do a phenotyping study to assess probability of benefit and demonstrate the treatment will have a significant improvement (a statistically significant increase above that deficit, even if it is not full improvement) relative to the disease model. The data quality from phenotypic evaluations should mimic the controls, blinding, and data quality that FDA expects for POC studies, since that's ultimately where sponsors would want to test their hypothesis if the treatment has an effect on a key endpoint. This can be challenging since assessing the probability of benefit requires a suitable disease model that shows differences relative to wild-type animals.

[10] Robert 'Skip' Nelson. FDA. Slide presentation: Research Involving Children (Focusing on FDA Regulations), Slide 47. Nov. 4, 2015. https://os1.cc.nih.gov/sites/default/files/bioethics/bioethics-files/courses/pdf/2015/session6_nelson.pdf

[11] ASGCT and FDA Liaison Meeting. November 8, 2021. Slide 23. https://www.asgct.org/uploads/files/general/News/FINAL-combined-slides-redacted-2021-ASGCT-FDA-Liaison-Meeting.pdf

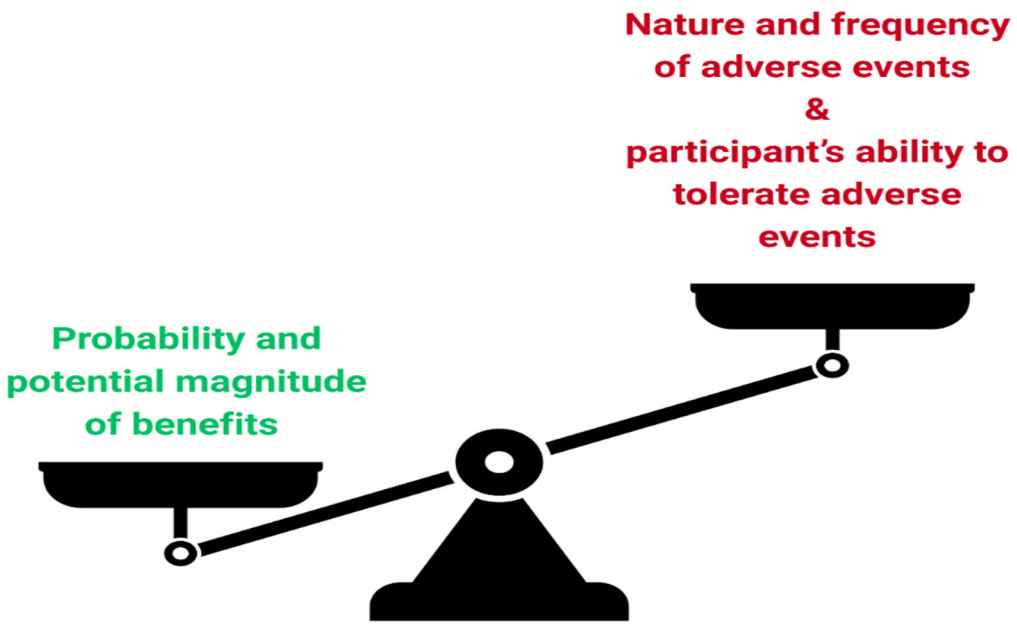
## EXAMPLE

- If you have an animal model that is only showing deficits and there is no biomarker, then you have one chance to get to PDB, and that's to show benefit.
- If you have a disease model that has both biomarkers and a phenotype, you potentially have two chances to get to a data package sufficient to demonstrate PDB.
    - You could either show direct benefit, and maybe the biomarker is supportive, or maybe there is the phenotype in the model isn't as clear, but then you can rely on the biomarker, because that's what may translate into humans.

### Questions to think about

- Has the disease progression modelling been characterized?
- What nonclinical model(s) are being selected?
- Is this the appropriate model?
- Does the disease have a statistically significant phenotype and is the sample size statistically significant?
- What happens when the proposed drug is introduced in a blinded manner? Does it show a difference relative to baseline?
- Can the biomarkers be measured and would any biomarkers qualify as a surrogate endpoint? See FDA's Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure
- Is the change on the biomarker demonstrating a validated surrogate endpoint?

*Benefit-Risk Analysis*




It is essential to demonstrate the potential benefit is justified in comparison to the risk when considering high-risk studies in children. Sponsors should conduct a benefit risk assessment. To demonstrate this, data will be needed from animal or adult human studies and on dosing and toxicities, as described above.[12]

When assessing benefits and risks FDA recommends considering the probability and potential magnitude of the benefits. For risks, consider the nature and frequency of expected adverse events (AE) as well as the participant's ability to tolerate AEs.[13] This calculus is similar to how FDA assesses risks in review of an new drug application, where the sponsor must articulate, as

[12] Michelle Roth-Cline. FDA. Slide presentation: Ethical Considerations in Evaluating Non-Therapeutic Studies in Children, Slide 32. Mar 29, 2012. https://www.fda.gov/media/84865/download

[13] Dr. Steve Winitsky, presentation (around the 6:50 mark)- https://fda.yorkcast.com/mediasite/Play/cb57417378a64a3b9fa702a5dc1bbf151d

part of its application, the probability, severity, and risk mitigations taken (e.g., starting human trials at a more tolerable dose).

It is expected that the benefit-risk analysis will be both quantitative and qualitative and can include the importance of direct benefit to the subject, the likelihood of avoiding greater harm from the disease, the degree of tolerable uncertainty, and the availability of alternative treatments.[14] It should include frank consideration of risk factors including harmfulness of the event, the type and probability of occurrence of the harm, the distribution of risk, the activity in which the risk is encountered, and whether the risk is voluntarily assume or involuntarily imposed.[15]

> ***For consideration***
> Potential approaches to dosing, such as Maximum Recommended Start Dose, No Observed Adverse Effect Level, Highest Non-Severely Toxic Dose, and Maximum Tolerated Dose, with the purpose of defining dose-limiting toxicity based on the overall nonclinical/translational assessment may not offer sufficient PDB to justify "first in-children" clinical trials, and may present greater risks (i.e., balancing risk and potential benefit).

[16]

[14] Michelle Roth-Cline. FDA. Slide presentation: Ethical Considerations in Evaluating Non-Therapeutic Studies in Children, Slide 17. Mar 29, 2012. https://www.fda.gov/media/84865/download

[15] Michelle Roth-Cline. FDA. Slide presentation: Ethical Considerations in Evaluating Non-Therapeutic Studies in Children, Slide 29. Mar 29, 2012. https://www.fda.gov/media/84865/download

[16] Robert 'Skip' Nelson. FDA. Slide presentation: Research Involving Children (Focusing on FDA Regulations), Slide 47. Nov. 4, 2015. https://os1.cc.nih.gov/sites/default/files/bioethics/bioethics-files/courses/pdf/2015/session6_nelson.pdf

**Questions to think about**

- "Are the data regarding the potential benefit of the drug sufficiently compelling to justify the potential (known, suspected, and unknown) risks?
- Is the balance of these risks and benefits at least as favorable as (evidence-based) alternative treatments (if any)?"

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When developing the strategy to justify PDB, the three evidence factors that sponsors need to demonstrate to FDA to show there is a positive benefit risk for pediatrics are probability, magnitude, and durability.

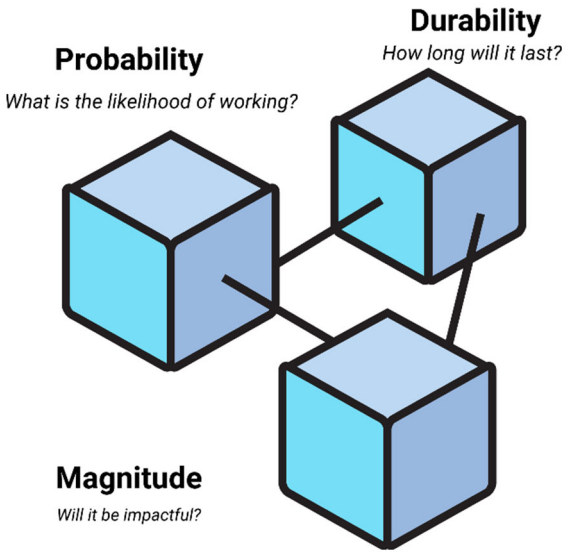
- Evidence to demonstrate the **probability** of benefit may come from animal model studies or previous human studies of the same product. Probability comes down to whether there is a statistically significant change in biomarker endpoints that would link to the benefit, or link to some type of outcome that would be translatable to the intended pediatric patient population and predictive of benefit.

> You need to think about the three dimensions (or interplay) of probability, magnitude, and durability and build these three elements of your strategy together.

[17] Robert 'Skip' Nelson. FDA. Slide presentation: Research Involving Children (Focusing on FDA Regulations), Slide 44. Nov. 4, 2015. https://os1.cc.nih.gov/sites/default/files/bioethics/bioethics-files/courses/pdf/2015/session6_nelson.pdf

- The potential **magnitude** of the benefit can be informed by both qualitative and quantitative elements, such as endpoints or other data that show a statistically significant difference, and also the patient's perspective on what constitutes a significant, meaningful change.

- **Durability**, or how long the benefit of the treatment is expected to last, will differ depending on the part of the body targeted. As FDA's 2022 guidance notes in the discussion of durability of one-time treatments like cell and 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."[18] For any investigational product, it is important to know the baseline level and ensure evidence gathering is extended out far enough to allow for data to be measured for an adequate timeframe to make a conclusion on the durable benefit. For example, if the treatment targets the liver, which is growing, and data is coming from a mouse model, the mice will need to be followed for a long enough time that would link to years, if not decades, in humans. On the other hand, if the treatment is targeting the central nervous system and neurons that aren't dividing, the mice may not need to be followed for as long of a time period. Demonstrating durability is especially critical for certain treatments, such as gene therapies, that can currently only be dosed once. [19]




[18] Ethical Considerations for Clinical Investigations of Medical Products Involving Children. FDA Draft Guidance for Industry, Sponsors, and IRBs. Sept. 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children

[19] Dr. Steve Winitsky, presentation (around the 6:40 mark)- https://fda.yorkcast.com/mediasite/Play/cb57417378a64a3b9fa702a5dc1bbf151d

**Questions to think about**

- Probability
  - Which model(s) is best suited for the pre-clinical studies?
  - What data will be needed? (what to measure)
  - What endpoints to use?
  - Is a phenotyping study possible?
  - What sources will be used to obtain data?
  - How will data be collected?
  - What is the statistically significant sample size?
- Magnitude
  - Have patients provided their perspectives on what is clinically meaningful?
- Durability
  - What part of the body is targeted?
  - What is the baseline?
  - How long will follow through need to be?
  - Is the therapy a one-time or repeated dose?

## *Chemistry, Manufacturing, and Controls (CMC) Assessment*

Chemistry, Manufacturing, and Controls (CMC) are not often discussed in the context of assessing benefit-risk but are actually quite an important component of PDB and a sponsor's data package. CMC speaks to the quality of product that is being put into pediatric patients. FDA has issued regulations and guidances to help industry understand and comply with cGMPs.[20]

> When dosing a human child, always plan to meet or exceed FDA's quality standards.

Having high quality CMC practices requires having good characterization and robust analytics. It is important for a sponsor to understand their impurities profile which feeds into the above mentioned the benefit risk analysis. A comparability mapping exercise should be done well in advance of the clinical trial and include

[20] FDA. Pharmaceutical Quality Resources. https://www.fda.gov/drugs/development-approval-process-drugs/pharmaceutical-quality-resources

considerations for bridging, planned toxicity studies, and ensuring the CMC looks comparable to what was proposed for the drug. It will need to include a scale-up plan, considering costs, for therapy production. To maintain uniform management and oversight of quality, it is important to have in place well defined CMC practices and standard operational procedures such as conducting oversight of partners, blinding all studies, reviewing all nonclinical data, and conducting trainings.

## Chemistry, Manufacturing, and Controls (CMC) Assessment Checklist

- ✓ Good characterization and robust analytics
- ✓ A comparability mapping exercise that considers for bridging, planned toxicity studies, and initial proposal of the drug
- ✓ A scale-up plan, considering costs, for therapy production
- ✓ Well-defined CMC practices and standard operational procedures (e.g. conducting trainings)

# Engagement

## *Patients*

It is important for sponsors to engage with the patient community early and take a patient-centric approach to inform your development program and strategy. Patients are the most knowledgeable about living with the burden of their disease and their input is essential. Patient groups may be able to contribute in several ways and sponsors can leverage these contributions to justify PDB. Patient groups may be able to guide characterization of disease progression modelling or hold a patient-focused drug development meeting to capture and summarize the patient voice. Many patient groups are eager to participate in sponsor meetings with FDA and could provide direct insights to the agency on what is clinically meaningful to patients and speak to the significance of the potential benefit and tolerance of risk, providing additional substantiation of the benefit-risk assessment.

**EXAMPLE**

In a patient with a motor deficit who has a sleep disturbance, will better sleep improve the patient's life and be clinically meaningful? To answer these types of questions, a sponsor can utilize the top 3-5 patient and caregiver concerns identified in the patient's voice through the Patient Focused Drug Development (PFDD) process to not only inform their strategy but also provide justification to the agency on prospect of direct benefit.

## *Internal to a Company*

Another key piece is that the PDB strategy is not solely a nonclinical exercise. It requires thoughtful collaboration with internal teams like regulatory, clinical, and CMC and with key stakeholders (key opinion leaders, advocacy leaders, etc.). The nonclinical studies should be designed "with the end in mind," as this data is ultimately meant to enable the intended pediatric clinical trial.

## *Food and Drug Administration*

Early and regular engagement with FDA is critical. FDA's Center for Biologics Evaluation and Research (CBER)[21] and Center for Drug Evaluation and Research (CDER)[22] provide information on how to engage during the pre-investigation phase. FDA also has guidance on formal meetings with sponsors.[23] In general, the ideal time to engage with FDA on a PDB strategy is within an INTERACT meetings, [24] where the sponsor can outline their disease-specific PDB and translational strategy, as well as seek feedback on the pivotal POC study design to ensure data collected may be supportive of PDB. Then at pre-IND meetings, sponsors can share the output of the data with FDA to gain buy-in for PDB and subsequent design of toxicology studies.

When discussing justification of PDB with the agency, it is important not only to have robust data, but also communicate the high unmet need for patients living with the disease of focus on a personal level. This can be done by sharing personal stories, case studies, PFDD materials, and information from patient groups or, as mentioned above, by inviting patient groups to join the meeting with FDA. FDA encourages sponsors to incorporate the patient input into drug development and has issued several guidances on how to do this.[25]

[21] FDA/CBER OTP Pre-IND Meetings
[22] FDA/CDER's Pre-Investigational New Drug Application (IND) Consultation Program via CDER NextGen Portal
[23] Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. Draft Guidance for Industry. Sept. 2023.
[24] FDA. OTP INTERACT Meetings. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-interact-meetings
[25] FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical Accessed on Dec. 12, 2025.

# Conclusion

For ethical reasons, in order to obtain FDA approval to conduct clinical trials in children, a demonstration of prospect of direct benefit (PDB) is required when there is more than minimal risk involved. When crafting your strategy, you need to be thoughtful and precise and demonstrate cohesive reasoning to justify PDB. The strategy should incorporate a mapping of the data modeling selected and a benefit-risk analysis which provides evidence of probability, magnitude, and duration and includes a robust CMC assessment. Having a robust strategy with these three elements is necessary to show evidence of and justify prospect of direct benefit. Finally, it is important to take a patient-centric approach, engaging early and often with patient groups. Similarly, it is critical and even expected to engage with FDA early and regularly.

# Appendix: Summaries of and Links to Resources

1. **21 CFR 50, subpart D Additional Safeguards for Children in Clinical Investigations.** Summarizes the ethical/regulatory framework for enrolling children in FDA-regulated clinical investigations, defining risk categories and when a prospect of direct benefit is required. Relevant information located at §50.51–§50.53 (risk categories and PDB criteria), §50.55 (assent/permission).

2. **21 CFR 58 Good Laboratory Practice for Nonclinical Laboratory Studies.** Establishes GLP standards for nonclinical studies that support applications, ensuring data quality that highlights benefit–risk decisions for pediatric trials. Relevant information located in Subpart B–D (organization, facilities, equipment) for study integrity relevant to PDB justifications.

3. **Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. Guidance for Industry.** October 2000. Sets guidance for FDA standards for Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, including clarity on the 120-day clock for submission of the toxicology information. Relevant information on pages 3 and 4.

4. **S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Guidance for Industry.** May 2012. Guides the design of nonclinical programs (species selection, dose, duration) for biologics that frequently underlie pediatric development and PDB rationale. Relevant information in Sections 3–4 (toxicology program design, dose selection) to support probability/magnitude elements for PDB.

5. **Preclinical Assessment of Investigational Cellular and Gene Therapy Products. Guidance for Industry.** November 2013. Details preclinical expectations for CGT products (pharmacology, biodistribution, tumorigenicity), directly informing pediatric PDB and benefit–risk justifications. Relevant information located in Sections IV–VI (Biodistribution, Toxicology, Dose/Regimen considerations).

6. **Ethical Considerations for Clinical Investigations of Medical Products Involving Children. Draft Guidance for Industry, Sponsors, and IRBs.** September 2022. FDA's overarching ethics framework for pediatric enrollment (scientific necessity, risk thresholds, PDB). Aligns IRB decisions with Subpart D. Relevant information located in Sections III–V (Scientific necessity, Risk categories, PDB assessments). See also the companion "Snapshot" below.

7. **Snapshot: Ethical Considerations for Clinical Investigations of Medical Products Involving Children.** A digest of the draft guidance that walks through steps for deciding pediatric enrollment and the PDB logic. Relevant information located on the "Steps for Considering Enrollment" diagram; bullets on Subpart D categories and PDB cues.

8. **Podcast.** Audio overview reinforcing when and how to include children, highlighting benefit–risk thinking and PDB concepts. Relevant information located in the episode show notes timestamps for segments on risk categories and PDB.

9. **Benefit-Risk Assessment for New Drug and Biological Products. Guidance for Industry.** October 2023. Explains FDA's structured benefit–risk framework used in reviews; sponsors can mirror this logic when presenting pediatric PDB rationales. Relevant information located in Sections II–III (Framework and Decision Context); examples illustrating probability, magnitude, and uncertainty.

10. **General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products. Draft Guidance for Industry.** September 2022. Covers PK/PD, modeling/simulation, and dose selection in children—core to articulating PDB and managing risk. Relevant information located in Sections III–V (Exposure–response, M&S, dosing strategies) and Appendices for age-group considerations.

11. **Research Involving Children as Subjects and Not Otherwise Approvable by an Institutional Review Board: Process for Referrals to Food and Drug Administration and Office for Human Research Protections. Draft Guidance for Institutional Review Boards, Investigators, and Sponsors.** March 2023. Describes the referral pathway for studies exceeding standard Subpart D categories; frames rare cases where pediatric research may proceed under special review. Relevant information located in Process overview and criteria sections.

12. **Informed Consent. Guidance for IRBs, Clinical Investigators, and Sponsors.** August 2023. Details consent/assent expectations, parental permission, and readability critical to operationalizing Subpart D decisions in pediatrics. Relevant information located in Sections on Children's Assent and Parental Permission; check Appendices for documentation elements.

13. **CBER's OTP Learn Webinars.** On-demand sessions addressing preclinical, CMC, and clinical design for CGTs with segments that translate directly to pediatric PDB and benefit–risk planning. Relevant information located in select sessions titled “Pediatric,” “Risk/Benefit,” “Dose,” or “Preclinical”; scan agendas/descriptions for those keywords.

14. **FDA/CBER Preclinical Considerations for Cell and Gene Therapy Products (virtual meeting).** March 2020. Walks through CGT preclinical packages (biodistribution, persistence, off-target risks) that are frequently leveraged to argue PDB in rare pediatric conditions. Relevant information located in the sections on toxicology and biodistribution methods; scrub to mid-talk (~20–40 min) where study design case examples are often discussed.

15. **Pediatric Clinical Trials.** Provides an overview of pediatric trial design under Subpart D, including how IRBs and FDA evaluate benefit–risk and when PDB is necessary. Relevant information located (~2 min) including segment discussing Subpart D categories and risk vs. potential benefit.

16. **FDA Webcast. Early-Phase Trials of Cellular and Gene Therapies.** Focuses on first-in-human/early-phase considerations (starting dose, escalation, stopping rules) that map to pediatric benefit–risk narratives. Relevant information located in sections on starting dose rationale and DLT definitions; (~10:35 min for pediatric population).

17. **FDA Webcast. The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND.** Explains how CMC (potency, purity, comparability) underpins safety/benefit

assumptions for pediatric dosing and durability claims (a PDB dimension). Relevant information located in potency assay and comparability segments; (~5:15 min) for additional guidance on what to do with human cells.

18. **CDER's Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D).** Resource hub for rare-disease development tactics including patient engagement and trial flexibility that can strengthen pediatric PDB and benefit–risk cases. Relevant information located in modules on natural history, endpoints, and patient input; scan case studies for pediatric-relevant decisions.

19. **FDA's Investigational New Drug (IND) Application Webpage.** Central gateway to IND content, timelines, and contacts; ideal for planning pre-IND engagement on pediatric PDB strategies. Relevant information located in "Pre-IND Consultation Program" and "Guidance Documents for INDs" sections at the top navigation.

20. **FDA. The Drug Development Process. Step 2: Preclinical Research.** Plain-language overview of preclinical work (in vitro/in vivo, safety).

21. **NIH/NCATS Toolkit for Patient-Focused Therapy Development.** Guidance for opportunities to capture patient voice (what's meaningful benefit, tolerable risk), which FDA encourages sponsors to incorporate into pediatric PDB narratives. Relevant information located in "Give Input on the Informed Consent Process," "Perform Patient Preference Studies," and "Help Industry with Clinical Trial Design."

22. **M. Bhatnagar, et al. Prospect of Direct Benefit in Pediatric Trials: Practical Challenges and Potential Solutions.** *Pediatrics.* May 2021. 147(5). Research paper clarifying scientific criteria for PDB (adult-to-pediatric extrapolation, acceptable uncertainty, and evidence sources). https://pubmed.ncbi.nlm.nih.gov/33906929/

23. **Melanie E. Bhatnagar. FDA. Slide presentation: Pediatric Clinical Investigations: Ethical Considerations.** September 6, 2019. Slide deck discussing ethics in pediatric clinical investigations under Subpart D, with prompts for quantifying probability, magnitude, and durability of benefit. https://www.slideserve.com/vchoi/ethical-considerations-for-pediatric-clinical-investigations-powerpoint-ppt-presentation

24. **Robert 'Skip' Nelson. FDA. Slide presentation: Research Involving Children (Focusing on FDA Regulations).** November 4, 2015. Authoritative walkthrough of Subpart D categories, dosing concepts (MRSD/NOAEL/HNSTD), and how these feed pediatric benefit–risk and PDB. Relevant information located on ~Slides 45–47 (dose rationale, risk thresholds) and the Subpart D category charts. https://os1.cc.nih.gov/sites/default/files/bioethics/bioethics-files/courses/pdf/2015/session6_nelson.pdf

25. **Michelle Roth-Cline. FDA. Slide presentation: Ethical Considerations in Evaluating Non-Therapeutic Studies in Children.** March 29, 2012. Frames key questions FDA/IRBs ask when weighing benefit–risk without direct benefit pathways and contrasts with when PDB is required. Relevant information located on Slides 12, 16, 20, 21, 34 for risk assessment and PDB-related

decision prompts; also Slides 15–17, 29–36 for structured questions on benefit–risk. https://www.fda.gov/media/84865/download

26. **FDA. Benefit-Risk Assessment for New Drug and Biological Products. Guidance for Industry.** P. 8. October 2023. Guidance for drug sponsors and other stakeholders on how considerations about a drug's benefits, risks, and risk management options factor into premarket and postmarket regulatory decisions. Relevant information located in Sections IV and V. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products