



What do you need to know about the special protections for pediatric subjects?

Robert 'Skip' Nelson, MD PhD

Deputy Director and Senior Pediatric Ethicist

Office of Pediatric Therapeutics, Office of the Commissioner

Food and Drug Administration, Silver Spring MD

<Robert.Nelson@fda.hhs.gov>

Introduction

- Over the past 20 years, we have evolved from a view that we must protect children from research to a view that we must protect children through research.
- We have a professional obligation to ensure that there are adequate data to support the safe and effective use of drugs, biologics and devices in infants, children and adolescents.
- The critical need for pediatric research on drugs, biologics and devices reinforces our responsibility to assure that children are only enrolled in research that is both scientifically necessary and ethically sound.
- Children are widely considered to be vulnerable persons who, as research participants, require additional (or special) protections beyond those afforded to competent adult persons.

Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
- “Low Risk” Pathway
- “Higher Risk” Pathway
- Parental Permission and Child Assent
- Clinical Hold (“unreasonable risk”)

Basic Ethical Framework in Pediatrics

1. Children should only be enrolled in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults).
2. Absent a prospect of direct therapeutic benefit to the children enrolled in a clinical trial, the risks to which those children would be exposed must be “low” (i.e., knowledge does not justify more than “low” risk).
3. Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care.
4. Vulnerable populations who are unable to consent for themselves (including children) should have a proxy to further protect them from harm (usually a parent or guardian) and who may consent on behalf of the vulnerable subject.

Who are “children”?

- Labeling regulations for drugs/biologics:
 - 0 to < 17 years [21 CFR 201.57(c)(9)(iv)]
- Pediatric Medical Device Safety Improvement Act:
 - 0 to 21 years [Section 301(E)(i)]
- Additional protections: “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” [21 CFR 50.3(o)]

“Nested” Protections

1: Scientific Necessity

4: Parental Permission



4: Child Assent

2,3: Appropriate Balance of Risk and Benefit

1. Principle of Scientific Necessity

- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children.
- Equitable selection (*prima facie* obligation)
 - Subjects capable of informed consent (i.e., adults) should be enrolled prior to children
 - Do not enroll children unless essential (i.e., no other option, whether animal or adult human).

General Justification of Research Risk (Adult and Pediatric)

- General Criterion for IRB approval of research.
 - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
 - *21 CFR 56.111(a)(2)*
- ✓ This criterion is modified by the additional safeguards for children enrolled in FDA-regulated clinical investigations in that there is a limit to the risk that knowledge can justify.

Additional Safeguards for Children

21 CFR 50 subpart D

2,3: Appropriate Balance of Risk and Benefit

- Research involving children either
 - must be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child, or
 - *21 CFR 50.51/53*
 - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
 - *21 CFR 50.52*

Linking Science and Ethics

- To conduct a pediatric clinical trial, the ethical challenge is to establish sufficient evidence using either preclinical animal models or adult human clinical trials[†] to conclude:
 - *“Low Risk” Pathway*: Absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably “low” risk (minimal, minor increase over minimal), or...
 - 21 CFR 50.51/50.53 (cf. ICH E-6 §4.8.14)
 - *“Higher Risk” Pathway*: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify “higher” risks.
 - 21 CFR 50.52

[†] Data also may come from post-marketing pediatric (i.e., "off label") and/or adult data

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 - Prospect of Direct Benefit; Component Analysis
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Prospect of Direct Benefit (PDB)

- A “direct benefit” may improve the health or well-being of the individual child and results from the research intervention being studied (and not from other clinical interventions included in protocol).
- What evidence (either from adult humans or animal models) is available about this intervention/product?
 - Do these data make us reasonably comfortable that children might benefit from this intervention/product?
 - Is the dose and duration of treatment with the investigational drug long enough to offer the intended benefit?
 - For diagnostic procedures, would the procedure normally be done as part of routine clinical care? Would the data potentially impact on clinical care?

Component Analysis

- “To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively.”
 - The National Commission 1978

Steps of Component Analysis

1. Analyze the protocol to determine whether each research intervention and/or procedure contained in protocol does or does not offer the enrolled child a prospect of direct benefit.
2. Assess risk level of those interventions and/or procedures that do not offer the child a prospect of direct benefit. This risk level must not exceed a minor increase over minimal risk (21 CFR 50.53).
3. Assess whether the risks of those interventions and/or procedures that do offer a prospect of direct benefit are justified by those potential benefits, and that this balance of risks and potential direct benefits are comparable to any available alternatives (21 CFR 50.52).

Why is component analysis important?

- Failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the allowable ceiling of a minor increase over minimal risk (absent referral under 21 CFR 50.54).

Case Study

- Multinational, placebo-controlled, study of an investigational product, in children ≥ 7 years old
 - Product (or placebo) administered (double blind) by IV infusion over 4 hours each day for 14 days
 - PICC used at 19 (of over 100) sites, approved by 12 IRBs
- PICC presents more than a minor increase over minimal risk
 - PICC use justified in children receiving the active product due to the prospect of direct benefit from the infusion
 - Children receiving placebo via PICC offered no prospect of direct benefit, but exposed to greater than minor increase over minimal risk
- Thus, PICC insertion and use in the placebo group was not in compliance with 21 CFR 50, subpart D.

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Minimal Risk

- “Minimal risk” was originally defined as those risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.”
- The phrase “of healthy children” was subsequently deleted, but most ethicists and all US federal advisory panels believe the original definition is better.
- Administration of an experimental drug/biological product is neither “normal” or “routine” and is thus not “minimal” risk.

Defining Acceptable Risks

- The definition of risk as a product of “probability” times “magnitude” gives the misimpression that risk assessment can be purely quantitative.
- The disvalue of a harm (or risk) cannot be quantified to where a uniform or comparative standard can be established.
- Defining “minimal risk” by using as a “reference” either “daily life” or “routine examinations” reduces a moral evaluation to a comparison of “factual” risks.
- The fact that a risk occurs outside of the research setting (whether in “daily life” or during “routine examinations”) does not make that same risk morally acceptable in the research context.

Minor Increase over Minimal Risk

- "Minor increase" refers to a risk which, while it goes beyond the narrow boundaries of minimal risk..., poses no significant threat to the child's health or well-being."
- "Given this conservative limit, the... promise of [substantial future benefits to children other than the subject] does justify research which goes beyond, but only slightly beyond, minimal risk."
- Interventions/procedures that do not present a prospect of direct benefit must present a "low" (e.g., minor increase over minimal) risk, and limited to children with a "disorder or condition" in 21 CFR 50.53 (absent a federal exception).

How is “disorder or condition” defined?

- The US federal research regulations offer no definition of either “disorder” or “condition.”
- A Proposed Definition
 - “A specific (or set of specific)... characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children’s health and well-being or to increase their risk of developing a health problem in the future.”

Institute of Medicine (US): Recommendation 4.3[†]

- Key Concept: “at risk” for disorder or disease.

Example: OTC[†] Cough & Cold Products

- Single-dose PK studies of OTC cough and cold products are necessary to establish the correct dose to be used in subsequent efficacy studies.
- Based on available data, a single dose of an OTC cough and cold product may not offer a prospect of direct benefit to the enrolled child, but can be considered “low” risk (but not “minimal” risk).
- Enrolled children must have a disorder or condition.
 - Children who are symptomatic from a cold have a condition (disease).
 - Asymptomatic children may be “at risk” for a cold based on empirical data that clearly defines an “at risk” population (using US data).
 - *Frequency Criterion*: >6 infections per year for children aged 2 to <6 yrs and >4 infections per year for children aged 6 to <12 yrs.; AND,
 - *Crowding Criterion*: ≥4 persons living in the home OR ≥3 persons sleeping in one bedroom; AND,
 - *Exposure Criterion*: another ill family member in the home OR a child in the family who is attending preschool or school with ≥6 children in the group.

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 - Timing of pediatric studies; “first-in-children” studies; evaluation of placebo controls
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“Higher Risk” Pathway

- Any clinical investigation... in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject... may involve children as subjects only if:
 - a) The risk is justified by the anticipated benefit to the subjects;
 - b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

21 CFR 50.52

Prospect of Direct Benefit (PDB)

- The level of evidence necessary to support PDB (“proof of concept”) is lower than the level of evidence required to establish efficacy.
 - “Proof of concept” may be based on animal or adult human data, using a “clinical” endpoint or a “surrogate” based, for example, on disease pathophysiology.
- Whether experimental intervention offers PDB separate from whether that PDB of sufficient probability, magnitude and type to justify the anticipated risks of the intervention, given the overall clinical context.
 - Risk/benefit evaluation is a complex quantitative and qualitative judgment that is similar to clinical practice.
 - Contextual justification of risk by PDB can include:
 - Importance of “direct benefit” to subject; possibility of avoiding greater harm from disease; degree of “tolerable” uncertainty; justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments; should have “as good a chance for benefit as the clinical alternatives”

The Role of Adult Human Data

- “Equitable selection” does not imply that adult studies must be completed before beginning pediatric studies.
- We need sufficient “proof of concept” for prospect of direct benefit (PDB) that justifies exposing children to the known (and unknown) risks of the intervention (21 CFR 50.52).
- Adults should be enrolled prior to adolescents and younger children to obtain data in support of this judgment.
- Once *sufficient adult data* exist to make this judgment, pediatric development should proceed without further delay.
- Whether we need an “adequate and well-controlled” study in pediatrics depends on our ability to “extrapolate” efficacy.

Enrollment of Adolescents in HIV Vaccine Trial

Selected Recommendations (August 14, 2007)

- Not enroll adolescents until after interim efficacy and cell-mediated immunity (CMI) analysis of adult data
 - Require trend in favor of experimental HIV vaccine
- If extrapolation appropriate, base adolescent sample size on descriptive CMI data from interim analysis
 - Descriptive comparison between adult and adolescent immune response data could serve as bridge for extrapolation of efficacy
 - Reasonable to increase adolescent sample to improve power to detect a significant safety signal at an incidence of <1-3%
- Extrapolation of efficacy would permit concurrent labeling based on supporting dosing and safety data.

“First-in-Children” under 21 CFR 50.52

- Can one infer a sufficient prospect of direct benefit from animal studies alone to justify a “first-in-children” clinical trial under 21 CFR 50.52?
 - Necessary data to establish sufficient prospect of direct benefit (PDB) to justify the risks varies with the severity of the disease and the adequacy of alternate treatments.
- Proposal: Sliding Threshold
 - Structure (generally insufficient for PDB)
 - Function (based on mechanism of action)
 - Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
 - Transgenic Technology (human target + mouse)
 - Clinical Disease Model
 - Surrogate endpoints
 - Clinical endpoint (e.g., survival) (FDA “Animal Rule”)

Maximum Recommended Starting Dose (MRSD) for “first-in-human” clinical trials

- MRSD frequently based on “no observed adverse effect levels” (NOAEL) in the tested animal species, with conversion of NOAELs to a human equivalent dose following the application of a safety factor.
- But the risk/potential benefit for NOAEL “safe starting dose” may not be equivalent to MRSD dose associated with the greatest efficacy in animal studies.
- Thus, a NOAEL-based dose may not offer sufficient PDB to justify “first-in-children” clinical trial, while the MRSD may present greater risks.

Placebo (Sham) Controls in Pediatrics

- Sham procedures (and placebos) do not offer any prospect of direct benefit to the enrolled child.
- Two types of risk
 - Risk of placebo itself may be “minimal” unless placebo is invasive (e.g. sham injections)
 - Risk of harm from not receiving “proven” or “effective” treatment.
- Both types of risk must be no greater than a “minor increase over minimal risk” (21 CFR 50.53)
 - This approach consistent with ICH E-10 and 2013 Declaration of Helsinki.
- What is an “acceptable” placebo risk? 1 IM injection? 50 IM injections? PIV lines? PIC catheters? Sham surgery?

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Parental Permission

- Parental permission is defined as an agreement to the participation of child in a clinical investigation.
 - Permission must be obtained in compliance with 21 CFR §50.20-27 (see 21 CFR §50.3(r))
- Waiver of parental permission?
 - 21 CFR 50.55 does not include waiver of parental permission found under 45 CFR 46.408(c)
 - Only a waiver for emergency research under 21 CFR §50.24
- Subpart D may[†] not apply to minors who have the legal right to consent to treatment (e.g., STIs in many states) with the interventions or procedures included in the clinical investigation (21 CFR §50.3(o))

† depends on interpretation by responsible legal counsel of local jurisdiction

Child Assent

- affirmative agreement to participate in research
 - Mere failure to object may not be construed as assent
- adequate provisions for soliciting a child's assent
 - when a child is capable of providing assent
 - age, maturity, and psychological state
- Assent may be waived if...
 - capability so limited that cannot be consulted, or
 - prospect of direct benefit important to child's health or well-being available only in research, or
 - minimal risk research that otherwise is not feasible

Permission of Both Parents?

- For clinical investigations under 21 CFR 50.53, permission is to be obtained from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available.
 - Thus permission of both parents would be required for all blinded randomized placebo controlled clinical investigations, perhaps delaying timely enrollment in such trials
- Solution: interpret “reasonably available” with some flexibility, focusing on the ability to obtain a timely signature
 - For example, speak to other parent on telephone and obtain verbal permission (i.e., ethical intent of requirement) but consider parent “not reasonably available” if unable to procure timely signature (e.g., no fax machine, unable to print and scan email attachments)

Expand Role for Parent/Child Perspective

- Are the research objectives sufficiently important to place children at risk?
- What outcomes provide a clinically meaningful benefit to children?
- Are any “research only” tests included in the protocol really necessary? What will be the children’s experience?
- What harms would be tolerable? What probability of harm would not be acceptable? How much uncertainty can one tolerate given the disease and any alternate treatments?
- How will the risks of non-treatment be minimized?

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FDA Obligation

- FDA has a moral and legal obligation to ensure that all research involving children regulated by FDA is in compliance with 21 CFR 50, subpart D.
- One of the most important mechanisms for ensuring such compliance is the judicious use of a “clinical hold” to compel the re-design of a pediatric protocol so that it is in compliance with 21 CFR 50, subpart D.

21 CFR 312.42 Clinical holds.

- Clinical hold of a Phase 1 study under an IND.
 - Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;
 - Clinical investigators named in IND are not qualified by reason of their scientific training and experience to conduct the described investigation;
 - The investigator brochure is misleading, erroneous, or materially incomplete; or
 - The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies.
- Clinical hold of a Phase 2 or 3 study under an IND.
 - Any of the above conditions apply; or
 - The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

Use of Clinical Holds in Pediatrics

- The additional protections (21 CFR 50 subpart D) for children in research set standards for “reasonable” risk exposure that differ depending on whether an intervention does or does not offer an enrolled child a prospect of direct benefit.
- If the risks of an intervention fall outside of these standards, the intervention exposes the enrolled child to an “unreasonable and significant risk of illness or injury.”
- Thus, failure to be in compliance with 21 CFR 50 subpart D is sufficient grounds for imposing a clinical hold on a proposed or on-going pediatric clinical trial.

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Thank you.

