Ethical Principles Guiding FDA-Regulated Pediatric Clinical Trials, with a Focus on Devices

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Disclaimer

The views expressed in this presentation are those of the speaker and do not necessarily represent the policy of either the Food and Drug Administration or the Department of Health and Human Services.
Who are “children”?

Persons who have not attained legal age for consent to treatments or procedures involved in a given clinical investigation, under applicable law of the jurisdiction [in which the research is being conducted.]

– 21 CFR §50.3(o)
When do Pediatric Protections Apply?

• When research subjects are children as defined previously in 21 CFR §50.3(o)
• Special protections (Subpart D) may† not apply to minors who have the legal right to consent to treatment with the interventions or procedures included in the clinical investigation.

† depends on interpretation by responsible legal counsel of local jurisdiction
Additional Protections for Children

Scientific Necessity

Parental Permission

Child Assent

Appropriate Balance of Risk and Benefit
Topics Covered

• Scientific Necessity
• Equitable Selection
• Appropriate Balance of Risk and Benefit
• Assent/Parental Permission
Principle of Scientific Necessity

Children should not be enrolled in a clinical investigation unless absolutely necessary to answer an important scientific question about the health and welfare of children.
Corollary

Children should not be enrolled in studies that are duplicative or unlikely to yield valuable generalizable knowledge related to the product or condition under investigation.
Importance of Study Design and Conduct

• Scientific question addresses an important public health need in children

• Study design capable of answering question
  – Appropriate endpoints (are surrogates validated?)
  – Sufficient power
  – Adequately controlled
  – Sufficient sample size to obtain useful data

• Appropriately conducted to ensure data quality
Topics Covered

• Scientific Necessity
• Equitable Selection
• Appropriate Balance of Risk and Benefit
• Assent/Parental Permission
Equitable Selection

“...take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations ...”

-Criteria for IRB Approval of Research, at 21 CFR 56.111(a)(3)
When Possible, Study the Least Vulnerable Subjects First

Adults \rightarrow Older Children

Infants \leftrightarrow Younger Children
Topics Covered

• Scientific Necessity
• Equitable Selection
• Appropriate Balance of Risk and Benefit
• Assent/Parental Permission
Minimization of Risks

“…using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk…”

-Criteria for IRB Approval of Research, at 21 CFR 56.111(a)(1) of Subpart C

“…consider only those risks and benefits that may result from the research…”

-21 CFR 56.111(a)(2) of Subpart C
Practical Points

• Use the least invasive procedure possible
• Minimize the number of invasive or uncomfortable procedures, or the length of exposure to experimental intervention
• “Piggyback” whenever possible onto clinically indicated care (e.g. surgery)
Basic Ethical Framework

• An intervention that does not offer a prospect of direct benefit to the enrolled child must be no more than “low” risk.

• If the risk of an intervention is not “low”, two conditions must be met:
  1. The intervention offers a sufficient prospect of direct benefit to justify the risk, and
  2. the balance of risk and potential benefit must be comparable to available alternatives.
## FDA’s Regulatory Framework

<table>
<thead>
<tr>
<th>Minimal Risk</th>
<th>Direct Benefit</th>
<th>No Direct Benefit</th>
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## Potential Case Examples

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<td>Cardiac Stent or Closure Devices</td>
<td>Some Single-Dose PK Studies</td>
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## Minor Increase, No Direct Benefit

**Criteria for approval:**
1) only a **minor (or slight) increase** over minimal risk
   - Requires known estimate of risk based on data
2) experiences reasonably commensurate with actual or expected situation
3) yield generalizable knowledge of vital importance for understanding or amelioration of **disorder or condition**

| Greater than Minimal Risk | 21 CFR 50.52 | 21 CFR 50.53 (minor increase) |
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.”
Disorder or Condition

- No authoritative definition
- 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.”

IOM Recommendation 4.3 (2004)
Being “at Risk”

• A child may be “at risk” for vancomycin resistant organism (VP shunt infection)
• A child who is “at risk” may be enrolled in greater than minimal risk research about antibiotic treatment of shunt infections, but not about some other condition for which they are not known to be “at risk”
• No good consensus on what it means to be “at risk”, and the likelihood of at-risk individuals actually becoming ill varies between studies
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### Greater Than Minimal Risk

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<td>Non-therapeutic Biopsy (21 CFR 50.54)</td>
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More than a Minor Increase Over Minimal Risk

If the experimental intervention is more than a minor increase over minimal risk, *either* (1) the intervention must offer a prospect of direct benefit (21 CFR 50.52) or (2) the IRB must refer the protocol for federal review under 21 CFR 50.54. Otherwise, the clinical investigation is not approvable under Subpart D.
Criteria for Approval:
1) **Risk justified by anticipated direct benefit** to subjects (within each arm of study)
2) Relation of anticipated direct benefit to risk **at least as favorable** as available alternative approaches (both inside and outside research)

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Prospect of Direct Benefit (PDB)

• Evidence supporting PDB is "weaker" than evidence supporting "efficacy"
  – Otherwise, one would need to know the answer to the research question prior to doing the research!
• May be based on a surrogate endpoint (e.g., immune response) if sufficient evidence exists linking surrogate to clinical efficacy
• Absent an adult disease correlate, may be possible to establish "proof of concept" for PDB in animal model
Justification of Risk?

• Need *empirical* evidence of sufficient “prospect of direct benefit” to justify exposure to risks

• Justification of risk by PDB can include:
  – Importance of “direct benefit” to subject
  – Possibility of avoiding greater harm from disease
  – Justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments
First-in-Human Pediatric Studies

- Scientific necessity of the study
- Solid pre-clinical animal data establishing sufficient prospect of *benefit* to offset the risks of the trial
- Aggressively minimize risks
- If possible, start in older children first (must still establish prospect of direct benefit!)
"Fallacy of the Package Deal"

- The risks of an experimental intervention must be offset by the prospect of direct benefit from that specific intervention, and not by other therapeutic interventions included in the protocol. This mistake is often called the "fallacy of the package deal."
- **Corollary:** The potential direct benefit of one intervention does not justify the risks of another intervention lacking direct benefit (i.e., research only). This is often called "component analysis."
Additional Protections for Children

- Scientific Necessity
- Parental Permission
- Child Assent
- Appropriate Balance of Risk and Benefit
Parental Permission

Agreement… to participation of child… in clinical investigation. Permission must be obtained in compliance with 21 CFR §50.20-27 (Informed Consent regulation)

– 21 CFR §50.3(r)
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

21 CFR 50.3(n); 50.55
Implications for Assent & Permission

• Should ground the interpretation of child assent on the (moral/social) role of parental permission
  – Subpart D constrains parental authority to enroll children in research given “normative” parental role
• Efficacy (i.e., protective function) of voluntary and informed consent attaches to parental permission
• Child assent remains important but under limited circumstances (e.g., no direct benefit, capable)
  – Capacity? Sufficient to agree or disagree to intervention
• Explains why waiver of parental permission is controversial and potentially hazardous to child
  – Parental disqualification, rather than child capacity
Thank you.