U.S. FOOD & DRUG ADMINISTRATION

Pediatric Clinical Investigations: Ethical Considerations

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Developing Therapies for Primary Mitochondrial Diseases: Bridging the Gaps
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Purpose

- To describe the FDA's human subject protection regulations that govern clinical investigations involving children
  - The Additional Safeguards for Children in Clinical Investigations (21 CFR 50 Subpart D)
- To provide practical considerations for developing a pediatric clinical trial that complies with the 21 CFR 50 Subpart D regulations

Justification of Research Risk

- For adults, Institutional Review Board (IRB) approval of research is generally justified by the following criterion:
  - 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))
- For children, this criterion is modified in that there is a limit to the risk that knowledge alone can justify

Additional Safeguards for Children in Clinical Investigations

21 CFR 50 Subpart D

- 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 (21 CFR 50.51/3), *OR*
  - must present risks that are justified by the "**prospect of direct benefit**" to the child; the balance of which is at least as favorable as any available alternatives (21 CFR 50.52)
- **Permission** by parents or guardians and **assent** by children must be solicited (21 CFR 50.55)

Additional Safeguards for Children in Clinical Investigations

21 CFR 50 Subpart D

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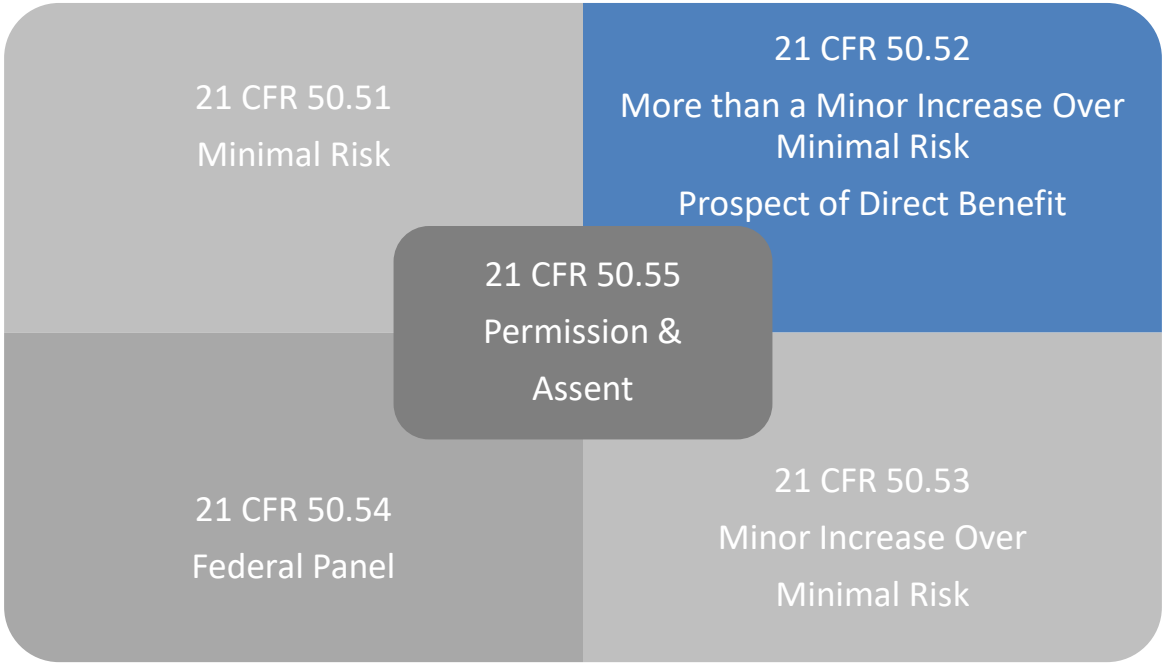

Prospect of Direct Benefit (PDB)

- A benefit is “direct” if it:
  - Accrues to individual subject enrolled in the clinical trial
  - Results from the research intervention being studied (and not from other clinical interventions included in the protocol)
  - Word “benefit” often modified by “clinical” to indicate that “direct benefit” relates to health of enrolled subject

- PDB is based on evidence to support the proof of concept and on the “structure” of the intervention (e.g., dose, duration, etc. as specified in the protocol)

Practical Implications of PDB

- Adult data to support the proof of concept may not be needed to initiate studies in pediatric patients
  - Nonclinical data may be sufficient, especially for diseases that are primarily pediatric
- A minimally effective dose must be tested to provide a PDB
  - Although a lower dose may be "safer," if there is no benefit, then testing in pediatric patients is not justified; dose escalation for individual participants may be needed
- The clinical investigation must be of a sufficient duration to provide a PDB
  - Treatment should be long enough to impact a relevant clinical outcome or an accepted surrogate outcome measure

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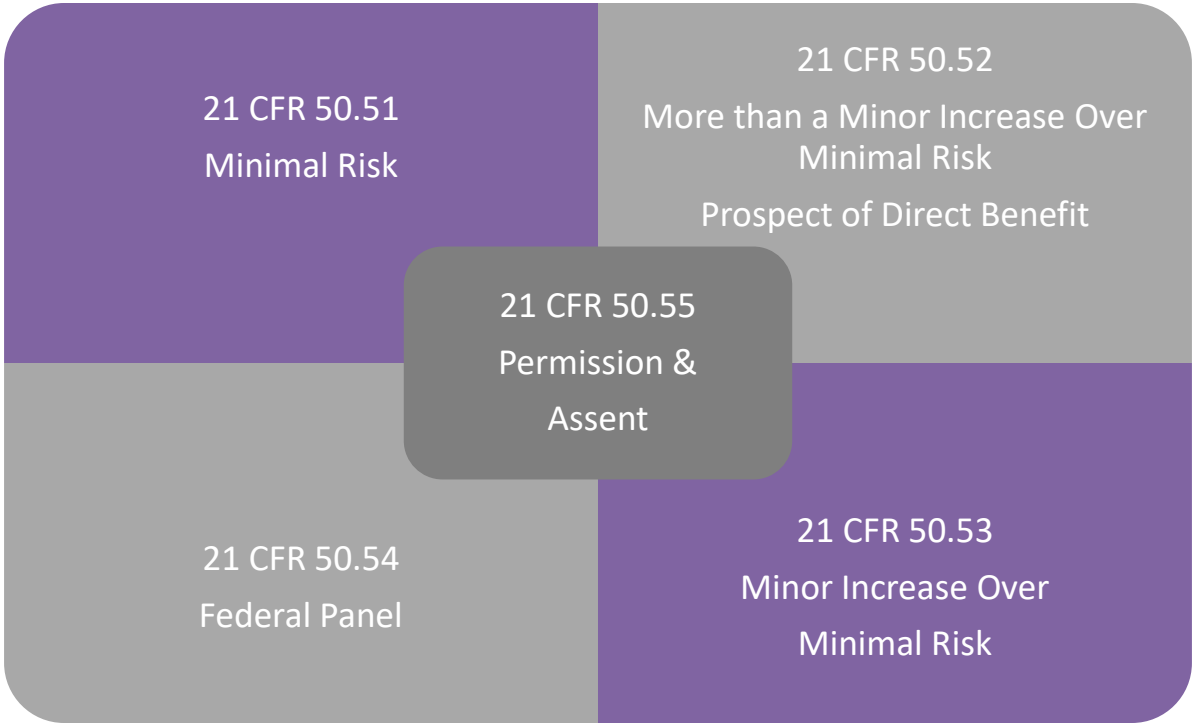

"Low" Risk

- "**Minimal risk**" is defined as those risks "normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children"

- "**Minor increase**" over minimal risk "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" and must contribute to generalizable knowledge about the child's disorder or condition

National Commission Report on Research Involving Children (1978)

Component Analysis

- A clinical investigation may include more than one intervention or procedure
- Evaluate each intervention or procedure separately to determine whether it holds out the prospect of direct benefit to the enrolled child
- 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)

Practical Implications of "Low" Risk

- Interventions or procedures within a study that might be considered minimal risk:
  - Single blood draw, questionnaires, physical exams, electrocardiograms (EKGs)
- Interventions or procedures within a study that might be considered a minor increase over minimal risk:
  - Multiple blood draws, X-ray(s), single computed tomography (CT) scan without contrast

Interventions/Procedures Requiring Special Consideration

- Biopsies
  - Skin or muscle biopsies
  - Large organ biopsies (e.g., liver or kidney)*
- Placebo
  - Risks of placebo include the risk of placebo itself (e.g., invasive administration such as a lumbar puncture) and the risk of withholding an established effective treatment
- Diagnostic imaging studies
  - Total radiation exposure and type/use of contrast
- Non-therapeutic procedural sedation
  - May be allowable in certain circumstances
  - Pediatric Ethics Subcommittee Meeting March 23, 2015

*Large organ biopsies done for research purposes offer no prospect of direct benefit and present more than a minor increase over minimal risk, so FDA considers these biopsies not allowable under 21 CFR 50 Subpart D, unless reviewed by a federal panel per 21 CFR 50.54

Clinical Hold

- FDA has obligations to ensure that children are only enrolled in clinical investigations that are in compliance with 21 CFR 50 Subpart D
- Failure to comply with 21 CFR 50 Subpart D is sufficient grounds for imposing a clinical hold on a proposed or ongoing pediatric clinical trial
- This requirement is consistent with criteria established for the placement of a clinical hold under 21 CFR 312.42

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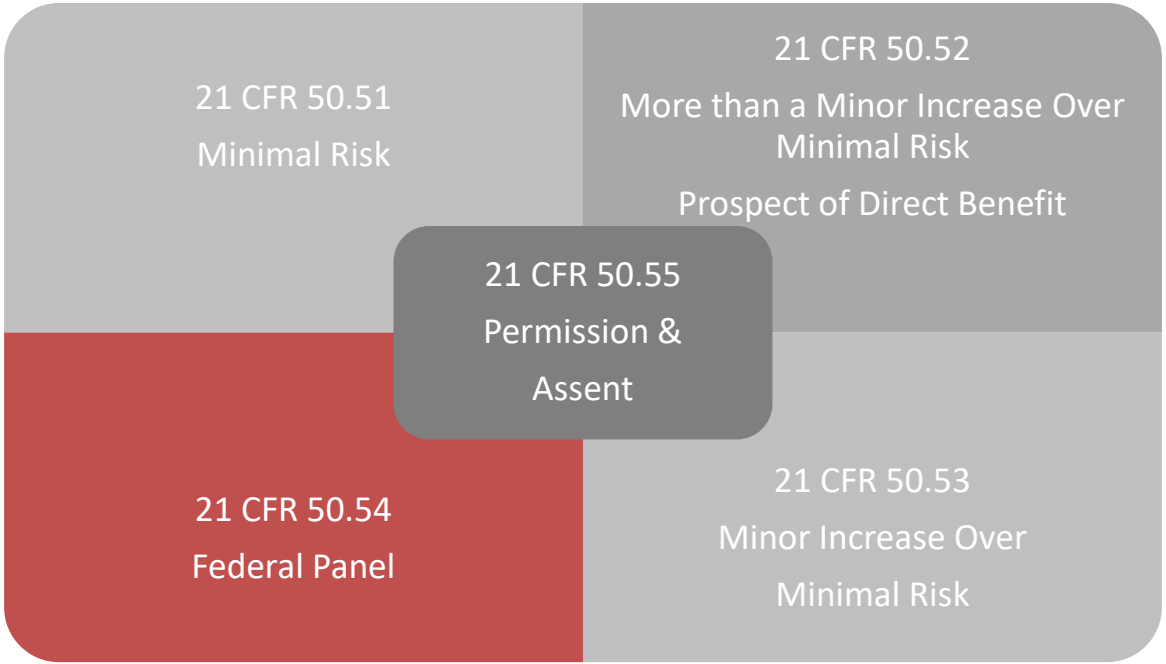

Summary

- Children are a vulnerable population, so there are additional regulatory protections for children involved in research
- Research involving children must be either “low” risk (defined as “**minimal**” or a “**minor increase over minimal**” risk) OR, if the risks are “high,” then they need to be balanced by the **prospect of direct benefit**, unless reviewed by a **federal panel**
- Failure to comply with 21 CFR 50 Subpart D is grounds for a Clinical Hold


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