Current Ethical and Regulatory Framework for Pediatric Product Development

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Introduction

- Over the past 15 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 an 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 underscores our shared responsibility to ensure that children are only enrolled in scientifically necessary and ethically sound research.
- Children are widely considered to be vulnerable persons who, as research participants, require additional protections beyond those afforded to competent adult persons.

Topics

- Basic Ethical Framework in Pediatrics
  - Principle of Scientific Necessity;
  - "Low Risk" and "Higher Risk" Pathways
- Four Key Concepts (with examples)
  - Prospect of Direct Benefit; Extrapolation
    - Enrollment of Adolescents in HIV Vaccine Trial
  - Component Analysis
    - Use of Central Venous Catheter
  - Disorder or Condition
    - "Over the Counter" (OTC) Cough & Cold Products
- Federal Public Panel Review

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.

Principle of Scientific Necessity

1) Children should only be enrolled in a clinical trial
   - ➢ to answer an important scientific and/or public health question about the health and welfare of children, and
   - ➢ the question cannot be answered through enrolling other subjects (e.g., competent adults, non-human primates)
- Equitable selection (*prima facie* obligation)
  - Enroll subjects capable of consent (i.e., adults) before children
  - Do not enroll children unless essential (i.e., no other option)
- Practical Applications
  - Use of Extrapolation of efficacy from adults to children (see below)
  - Use of FDA "Animal Efficacy Rule" (21 CFR 314.610)
    - Levofloxacin approved for treating pneumonic plague on April 27, 2012

Additional Protections for Children

- ✓ Need sufficient scientific data from animal models or adult human clinical trials to conclude that:

  2) *"Low Risk" Pathway*: Absent sufficient prospect of direct benefit to the child, administration of investigational product presents an acceptably "low" risk, or…
     - 21 CFR 50.51 ("minimal risk")/50.53 ("minor increase over minimal risk")

  3) *"Higher Risk" Pathway*: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify "higher" risks, and the balance of risk and potential benefit is at least as favorable as any available alternatives.
     - 21 CFR 50.52 ("greater than minimal risk")

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Prospect of Direct Benefit (PDB)

- A “benefit” is “direct” if it accrues to the enrolled child; and results from the research intervention being studied.
- PDB is based on the “structure” of an intervention (i.e., dose, duration, method of administration, etc.)
- The level of evidence needed to support PDB (“proof of concept”) lower than that required to establish efficacy.
- Whether PDB sufficient to justify risks, given the clinical context, is a complex judgment similar to clinical practice
- Given the intervention, the enrolled child should have “as good a chance for benefit as the clinical alternatives”

Extrapolation of Efficacy

- Conditions for Extrapolation: "If the *course of the disease* and *the effects of the drug* are sufficiently similar…"
  - Requires understanding of disease pathophysiology and mechanism of therapeutic response to the investigational product
  - Confirmatory studies may be used to support extrapolation
- Evidence needed for efficacy:
  - Data from two adequate and well-controlled clinical investigations
  - Data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)
- Typology of Extrapolation:
  - Full: No clinical trials of efficacy required; safety and dosing only.
  - Partial: One "confirmatory" trial required; also safety and dosing.
  - None: Two adequate and well-controlled clinical investigations.

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 (i.e., sufficient prospect of direct benefit to justify risks)
- 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
  - Adjust adolescent sample to improve power to detect a significant safety signal at an incidence of <1-3%
- Extrapolation of efficacy may permit concurrent labeling

IND 13028/6: MRK Ad5 HIV Vaccine (NIH released RMN from confidentiality restrictions)
See Nelson RM, LL Lewis, K Struble and SF Wood. J Acquir Immune Defic Syndr 2010;54:S18-S24.

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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

- Why is component analysis important?
  - Failure to distinguish components of a clinical trial may result in an intervention that does not hold out a prospect of direct benefit exceeding the allowable threshold of a minor increase over minimal risk (absent referral under 21 CFR 50.54).

Research Involving Children: Report and Recommendations. 43 Federal Register 2086 (1978)

Use of Central Venous Catheter

- Multinational, placebo-controlled, double-blind study of an investigational product, in children ≥ 7 years old
- Product (or placebo) administered by IV infusion over 4 hours each day for 14 days
- Insertion and use of central venous catheter (CVL) presented *more than* a minor increase over minimal risk
- CVL was justified in children receiving active product due to prospect of direct benefit from the infusion
- CVL was not justified in children receiving the placebo due to no prospect of direct benefit from the infusion

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"Low Risk" Pathway
Importance of disorder or condition

- Administration of an experimental drug/biological product is not "minimal" risk, and is not approvable under 21 CFR 50.51
- Research under the "minor increase" category (21 CFR 50.53) must be "likely to yield generalizable knowledge about the subjects' *disorder or condition* that is of vital importance for the understanding or amelioration" of the disorder or condition
- Disorder or condition can be defined by "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: Ethical Conduct of Clinical Research Involving Children (2004)
- 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.

† OTC = "over the counter" (i.e., non-prescription)

Developing an "Escape Hatch"

- The National Commission was concerned that the standard categories for IRB approval may exclude important research.
- Key aspects of the discussion
  - "Public review and comment"
    - Should not be an administrative procedure absent oversight by "society"
  - "Sound ethical principles"
    - Should *apply* (**not** suspend) the ethical principles of respect for persons, beneficence and justice to a "new and unanticipated state of affairs"
  - "Serious health problem"
    - Not limit to "national emergency" but restrict to research of "major significance"
- "National Advisory Board" not established until FDA Pediatric Advisory Committee chartered (in 2003) to do these reviews

Required Public Panel Findings

- The clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or
- All of the following conditions are met:
  - The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
  - The clinical investigation will be conducted in accordance with sound ethical principles; and
  - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians

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Thank you.