Selected Ethical and Legal Issues in Pediatric Clinical Research

This roundtable discussion is sponsored by the Children’s Hospital Affinity Group of the In-House Counsel (In-House) and Teaching Hospitals and Academic Medical Centers (TH/AMC) Practice Groups and the Life Sciences (LS) Practice Group.

February 10, 2014 · 3:30-4:45 pm Eastern

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Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
  - Prospect of Direct Benefit
  - Component Analysis
- “Low Risk” Pathway for Pediatric Product Development
  - Minimal Risk and a Minor Increase over Minimal Risk
- “Higher Risk” Pathway for Pediatric Product Development
  - Sufficient Prospect of Direct Benefit to Justify Risks
  - Case Study on the Use of Component Analysis
- Parental Permission and Child Assent
  - Adolescent Consent and Permission from Both Parents
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.
- Clinicians and regulators 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.
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.
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 protections for children enrolled in FDA-regulated clinical investigations in that there is a limit to the risk that knowledge can justify.
Additional Protections for Children
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, 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
Additional Safeguards
21 CFR 50, Subpart D

- Not involving greater than minimal risk (§50.51)
- Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (§50.52)
- Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subjects’ disorder or condition (§50.53)
- Not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (§50.54)†
- Requirements for permission by parents or guardians and for assent by children (§50.55)

† Requires review by federal panel
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.
  - Practical application: determine the type and timing of clinical studies required for establishing "safe and effective" pediatric use of drugs, biologics and devices (e.g., use of extrapolation)

- 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).

Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]
Linking Science and Ethics

Ethical challenge is to establish sufficient scientific data using either preclinical animal models or adult human clinical trials† to conclude that:

- **“Low Risk” Pathway**: Absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably “low” risk, 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 (PDB)

- A “benefit” is “direct” if it:
  - Accrues to individual subject enrolled in clinical trial;
  - Results from research intervention being studied (and not from other clinical interventions included in protocol)

- PDB is based on “structure” of an intervention (i.e., dose, duration, method of administration, etc.).
  - Direct benefit is an attribute of the intervention or procedure and not of the overall research protocol and/or objective(s).

- Level of evidence needed to support PDB (“proof of concept”) lower than that required to establish efficacy.
  - “Proof of concept” may be based on animal or adult human data, using a “clinical” endpoint or a “surrogate” (e.g., disease pathophysiology).
Questions to ask re. PDB

- What empiric data (either from adult humans or animal models) is available about this intervention/product?
- Does this data make us reasonably comfortable that children might benefit from this intervention/product?
  - Similar to judgments about using an intervention/product in clinical practice
- Is dose/duration of treatment adequate to provide 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

- 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.

- 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).

- 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).
Simplification

- Procedures that present no more than minimal risk may or may not offer a prospect of direct benefit.
  - For example, a venipuncture for diagnostic blood work.

- Such procedures may be finessed when doing a “component” analysis of a protocol based on the presence or absence of a prospect of direct benefit.
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).
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What is Minimal Risk?

- The US National Commission defined “minimal risk” as those risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.”
- Although the phrase “of healthy children” was deleted from the current definition, most ethicists and US federal panels (e.g., SACHRP, IOM) agree with this limitation.
- Administration of experimental drug/biological products 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.

- 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" 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.

Pediatric PK Studies

- The administration of a single dose of an investigational product (e.g., PK study) generally does not offer a prospect of direct benefit to the individual child enrolled in the study.

- Administration of a single dose of an investigational product presents more than minimal risk, but the risks of a single dose of some products (existing data) may be no more than a minor increase over minimal risk. Children enrolled in such a PK study must have a condition (21 CFR 50.53).

- Alternatively, a PK study of a drug that presents greater than a minor increase over minimal risk could be performed as part of a clinical trial that offers a prospect of direct benefit (21 CFR 50.52). In this case, the risks of the PK study do not include the drug administration.
Example: OTC† Cough & Cold Products

■ Single-dose PK studies of OTC cough & cold products are necessary to establish the correct dose for use 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)
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- **“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
“First-in-Children” under 21 CFR 50.52

- Any clinical investigation [presenting] more than minimal risk to children… by an intervention [with] the prospect of direct benefit… may involve children as subjects only if:
  - risk justified by anticipated benefit to subjects;
  - relation of anticipated benefit to risk as favorable to subjects as… available alternative approaches.

- 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?
Proposal: Sliding Threshold

- Data (whether animal or human adult) necessary 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.

- **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”)


Examples: 21 CFR 50.52

“Subretinally administered vectors restored retinal function in 23 of 26 eyes.”

Long-Term Restoration of Rod and Cone Vision by Single Dose rAAV-Mediated Gene Transfer to the Retina in a Canine Model of Childhood Blindness

Gregory M. Acland, Artur V. Cideciyan, Jean-Yves Leveille, Albert M. Maguire, Krzysztof P. Flament, and David A.C. Robinson

The short- and long-term effects of gene therapy using AAV-mediated RPE65 transfer to canine retinal pigment epithelium were investigated in dogs affected with disease caused by RPE65 deficiency. Results with AAV 2/2, 2/5, and 2/5 vector pseudotypes, human or canine RPE65 cDNA, and constitutive or tissue-specific promoters were similar. Subretinally administered vectors restored retinal function in 23 of 26 eyes, but intravitreal injections consistently did not. Photoreceptor and postreceptoral function in both rod and cone systems improved with therapy. In dogs followed electoretinographically for 3 years, responses remained stable. Biochemical analysis of retinal retinoids indicates that mutant dogs have no detectable 11-cis-retinal, but markedly elevated retinyl esters. Subretinal AAV-RPE65 treatment resulted in detectable 11-cis-retinal expression, limited to treated areas. RPE65 protein expression was limited to retinal pigment epithelium of treated areas. Subretinal AAV-RPE65 vector is well tolerated and does not elicit high antibody levels to the vector or the protein in ocular fluids or serum. In long-term studies, wild-type cDNA is expressed only in target cells. Successful, stable restoration of rod and cone photoreceptor function in these dogs has important implications for treatment of human patients affected with Leber congenital amaurosis caused by RPE65 mutations.
Leber congenital amaurosis
progressive blindness in childhood caused by mutation in RPE65 gene (encodes protein in retinal pigment epithelium)

X-linked adrenoleukodystrophy lethal neurologic disease of children with progressive cerebral demyelination and adrenal insufficiency caused by mutations in gene for peroxisomal membrane protein (ALDP)

Examples: 21 CFR 50.52

“The deficiency of ALDP in mice does not duplicate the clinical and pathological abnormalities of the human ALD.”

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, and conversion of NOAELs to a human equivalent dose with the application of a safety factor.
- Risk/potential benefit for NOAEL “safe starting dose” may not be equivalent to MRSD dose associated with greatest efficacy in animal studies.
- A NOAEL dose may not offer sufficient PDB to justify “first-in-children” clinical trial, and the MRSD may present greater risks.
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 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 to support 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.

IND 13028/6: MRK Ad5 HIV Vaccine (NIH released RMN from confidentiality restrictions)
Placebo Controls in Pediatrics

- 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 must be no greater than a minor increase over minimal risk
- This approach is consistent with ICH E-10 and the 2008 Declaration of Helsinki.
- What is an “acceptable” placebo risk? 1 IM injection? 50 IM injections? PIV lines? PIC catheters? Sham surgery?
Case Study: Background

- 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.
- FDA Pediatric Ethicist called by a concerned IRB Chair about proposal to use a peripherally inserted central catheter (PICC) to facilitate infusion.
- Upon review, the protocol and supporting documents provided by the sponsor to the FDA review division never mentioned PICC use.
FDA Assessment

- The insertion and use of a PICC for administration of the investigational product presented more than a minor increase over minimal risk.
- PICC use was justified in children receiving active product due to the prospect of direct benefit from the infusion.
- Children receiving the placebo via PICC were offered no direct benefit from the infusion, but exposed to greater than a minor increase over minimal risk.
- Thus, PICC insertion and use in the placebo group was not in compliance with 21 CFR 50, subpart D.

Further details and discussion of this case can be found in the slides posted at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM331657.pdf
Use of Clinical Holds in Pediatrics

- Criterion for a clinical hold under 21 CFR 312.42: Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.
- 21 CFR 50 subpart D sets the standards for “reasonable” risk exposure in pediatric clinical trials.
- 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.
Corrective Actions

- Clinical trial had been suspended by the sponsor due to lack of product efficacy, so no future pediatric subjects were at imminent risk.
- FDA advised the sponsor that PICC utilization was not allowed for future pediatric subjects, and requested information from the participating IRBs.
- IRBs were asked whether PICCs had been used at each site, and if so, how PICC insertion was justified in the IRBs’ assessment of the study.
- FDA provided a written analysis of the information and comments obtained from the IRBs, explaining the application of component analysis and the risks that are allowable under 21 CFR 50.53.
- The letter (signed by the responsible division director) was sent to the sponsor, with instructions to disseminate it to all IRBs that participated in studies of the investigational product.
“The general consensus of the [FDA Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, meeting in June 2008] was that the placebo arm of a trial cannot be considered to confer the prospect of direct benefit under §50.52… In general, the PES advised that the so-called “inclusion” benefit is not a “direct” benefit, and that children enrolled in the placebo arm of a trial should be exposed to no more than minimal risk or a minor increase over minimal risk.”

78 Federal Register 12937-12951 (February 26, 2013)
“FDA agrees with [the Pediatric Ethics Subcommittee’s] position. Because we do not consider the administration of a placebo to offer a prospect of direct benefit, part 50, subpart D, therefore requires that the placebo arm must present no more than minimal risk (§ 50.51) or a minor increase over minimal risk (§ 50.53), unless the clinical investigation is referred for review under 21 CFR 50.54.”
“A placebo-controlled study of an investigational drug or biologic may involve the withholding of known effective treatment (section 2.1.3, ICH E 10). In such situations, however, the risks of such withholding of known effective treatment in the placebo control group should present no more than minimal risk or a minor increase over minimal risk, i.e., the placebo control arm of such a clinical trial must be approvable under either § 50.51 or § 50.53. The arm that receives the investigational product often would be approvable under § 50.52.”
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When does Subpart D apply?

- 21 CFR 50.3(o) defines children as 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. (also 45 CFR 46.402(a))

- 21 CFR 50.55 does not include waiver of parental permission found under 45 CFR 46.408(c)

- However, 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
Parental Permission

- Agreement… to participation of child… in clinical investigation. Permission must be obtained in compliance with 21 CFR 50.20-27 (IC regulation) [21 CFR 50.3(r)]
- Waiver? Only EFIC for emergency research [21 CFR 50.24]
- Under 21 CFR 50.53, both parents must give permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal… custody of the child.
  - The appropriate use of component analysis to evaluate the appropriate level of risk exposure for non-beneficial interventions or procedures should not present an obstacle to the conduct of controlled clinical trials.
  - One parent could be available by telephone for the parental permission process, but not reasonably available for the purpose of signing the document (i.e., no access to facsimile, scanner for emailing PDF).
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

- The interpretation of child assent should be grounded on the (moral/social) role of parental permission.
- The protective function of voluntary and informed consent attaches to parental permission, not child assent.
- Child assent remains important but under limited circumstances (e.g., no direct benefit, capable).
  - Capacity? Sufficient to agree or disagree to intervention
- This relationship explains why a waiver of parental permission is controversial and potentially hazardous to child.
Thank you.
INFORMATION DISCLOSURE: SPECIAL CHALLENGES IN PEDIATRIC RESEARCH

Incidental Findings

Background

Definition
“Incidental research findings” = unexpected findings discovered in course of research but beyond study aims

Can have varying degrees of clarity and clinical significance

Can be differences among researchers, parents, minor subjects about who should be told

IRB’s evaluation of incidental findings disclosure plan will depend on risks, potential benefits of disclosing or not disclosing
Incidental Findings with Clear and Proximate Clinical Significance

Important variables: age of child, nature of the information, family context

For research involving infants, very young children, approach should be same as in research with adult subjects

For research involving adolescents, parent’s or child’s preference for nondisclosure to the other, and timing/order of disclosures may be challenging
Relaying sensitive information –

In clinical context, adolescents offered statutory confidentiality regarding specified sensitive health care; in Part D, adolescents may participate in research without parental permission when study concerns a “condition or population for which parental permission is not reasonable to protect the child” – but focus is on permission for enrollment, not incidental research findings.

In research context, pragmatic problems to keep some incidental findings information confidential (ie, not disclose to parent)
Suggestions:

In consent process, both adolescent and parent are informed that clear, clinically important information will be disclosed to both.

In assent process, researcher explains possible incidental findings (e.g., results of pregnancy or drug tests for screening), that results will be disclosed to parent, and that adolescent is entitled to decline participation in the study.
Relaying serious information

Suggestions:

Disclosing to parent first may help parent collaborate with researcher on best way to disclose to child, process the information emotionally
Incidental Findings Without Clear and Proximate Clinical Significance

Arguments for disclosure:
- Reciprocity and respect – Subjects contribute their time and bodies in exchange for information about themselves
- “Significance” of the information is subjective

Argument against disclosure: Risks not balanced by sufficient benefits
- Psychosocial risks
- Physical risks if the information results in erroneous clinical decisions
- “Open futures” argument – disclosure deprives child of later decision as to whether to receive this information as an adult; and some adult children would want to keep this information private

Case Study:
- Identification of misattributed paternity
Recommendations:

In designing study, investigators develop plan regarding incidental findings that includes:

- Identifying incidental findings that may result
- Categorizing incidental findings with and without clear and proximate clinical significance
- Plan for disclosure to child and/or parent
  - Default plan = disclose to both parent and child incidental findings with clear and proximate clinical significance
  - For incidental findings without clear and proximate clinical significance, communicate with IRB regarding potential clinical value, risks of disclosure and nondisclosure, maximizing benefits and minimizing risks

Communicate plan to subjects and families