



# Ethical Pathways for Pediatric Product Development

Robert „Skip“ Nelson, MD PhD  
Deputy Director & Senior Pediatric Ethicist

Office of Pediatric Therapeutics, Office of the Commissioner  
Food and Drug Administration, Silver Spring MD  
<[Robert.Nelson@fda.hhs.gov](mailto:Robert.Nelson@fda.hhs.gov)>

October 10, 2012

# Topics

- **Basic Ethical Framework in Pediatrics**
- **Two Key Concepts**
  - Prospect of Direct Benefit; Component Analysis
- **“Low Risk” and “Higher Risk” Pathways**
- **Parental Permission and Child Assent**
- **Assuring Compliance (21 CFR 50 subpart D)**

# 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.
- 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.

# 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.

# General Justification of Research Risk (Adult and Pediatric)

- 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 either "minimal" or a "minor increase over minimal" risk absent a potential for direct benefit to the 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*

# The Principle of Permission

## Basic Ethical Principle

- 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) who may consent on behalf of the vulnerable subject.

## Additional Safeguard

- Requirements for permission by parents or guardians and for assent by children (21 CFR 50.55)

# 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)<sup>†</sup>
- Requirements for permission by parents or guardians and for assent by children ( 50.55)

<sup>†</sup> Requires review by federal panel



# Principle of Scientific Necessity

- 1) 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
- 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).

# Linking Science and Ethics

- Ethical challenge is to establish sufficient scientific data using either preclinical animal models or adult human clinical trials<sup>†</sup> to conclude that:
  - 2) *“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)
  - 3) *“Higher Risk” Pathway*: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify “higher” risks.
    - 21 CFR 50.52

<sup>†</sup> Data also may come from post-marketing pediatric (i.e., “off label”) and/or adult data

# Different Strategies for Pediatric Licensure

- Product being developed for pediatric and adult indication (*prima facie* goal: concurrent licensure).
  - Sequential Development (linear or staggered)
    - The results (efficacy and/or safety) of adult studies are necessary to inform pediatric development.
  - Parallel Development
    - Pediatric and adult development may proceed together, based on data supporting the initiation of pediatric clinical trials.
- Product being developed for pediatric indication alone (i.e., no adult indication exists).
  - Challenge: developing sufficient preclinical data<sup>†</sup> to support the initiation of pediatric clinical trials.

<sup>†</sup> Safety data from adult studies/post-marketing use for another indication may exist.

# Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
  - Prospect of Direct Benefit; Component Analysis
- “Low Risk” and “Higher Risk” Pathways
- Parental Permission and Child Assent
- Assuring Compliance (21 CFR 50 subpart D)

# 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: PDB

- What empiric data (either from adult humans or animal models) is available about this product?
- Does this data make us reasonably comfortable that children might benefit if given this product?
- Is the dose/duration of treatment adequate to provide benefit?

# 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).



# Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
- “Low Risk” Pathway
  - Level of allowable risk; disorder or condition
- “Higher Risk” Pathway
- Parental Permission and Child Assent
- Assuring Compliance (21 CFR 50 subpart D)

# 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.
- 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<sup>†</sup> 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)

# “Low Risk” Pathway

- “Low risk” pathway may have applicability, depending on the product
  - Must be able to generate an accurate risk estimate given adult testing experience
- Used for “low risk” procedures; may be used for drugs, *if* ample data exists to establish that the risk of use is “low” (e.g. PK/PD studies of well-characterized drugs)

# Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
- “Low Risk” Pathway
- “Higher Risk” Pathway
  - Role of Human Adult Data Indication
  - Choice of Control Group
- Parental Permission and Child Assent
- Assuring Compliance (21 CFR 50 subpart D)



# Additional Protections for Children

## 21 CFR 50 subpart D

- Research involving children either
  - must be restricted to either "minimal" or a "minor increase over minimal" risk absent a potential for direct benefit to the 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*

# Prospect of Direct Benefit (PDB)

- 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.

# Choice of Control Group

- Placebo Control
- Active Treatment Control
  - Non-inferiority design based on previous trials
  - Superiority design (also with placebo control)
- Other possible alternatives
  - Dose-response
  - Randomized withdrawal
- External Controls
  - Historical (or retrospective) control

# 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?

# Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
  - Prospect of Direct Benefit; Component Analysis
- “Low Risk” and “Higher Risk” Pathways
- Parental Permission and Child Assent
- Assuring Compliance (21 CFR 50 subpart D)

# 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<sup>†</sup> 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
- Children = persons who have not attained legal age for consent to treatments or procedures involved in clinical investigations, under applicable law of jurisdiction [i.e., local study site].
  - 21 CFR 50.3(o)

# 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

# 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.

# Topics

- Basic Ethical Framework in Pediatrics
- Two Key Concepts
- “Low Risk” Pathway
- “Higher Risk” Pathway
- Parental Permission and Child Assent
- **Assuring Compliance (21 CFR 50 subpart D)**

# Public Law 106-310 (October 17, 2000)

- "Notwithstanding any other provision of law, not later than 6 months after the date of the enactment of this Act, the Secretary of Health and Human Services shall require that all research involving children that is conducted, supported, or regulated by the Department of Health and Human Services be in compliance with subpart D of part 46 of title 45, Code of Federal Regulations."
  - SEC. 2701. REQUIREMENT FOR ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED IN RESEARCH.
- 21 CFR 50, Subpart D was promulgated as an Interim Final Rule on April 24, 2001.

# 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.

# “Unreasonable and significant risk of illness or injury”

- The latitude afforded sponsors by omission of the criterion of being “clearly deficient in design” from the Phase 1 clinical hold criteria does not set a different standard for the use of clinical holds based on safety concerns.
- The risks in question are those to the individual human subject, and thus do not vary by the size of the trial.
- There is no discussion of the interpretation of “unreasonable” and “significant” in the preamble to the Final Rule 21 CFR 312, published on March 19, 1987 (nor in any subsequent amendments).



# 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.



# Thank you.

