



Ethical Considerations in Evaluating Non-Therapeutic Studies in Children

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3rd Annual Pediatric Pharmacogenomics and Personalized Medicine

March 29, 2012

Pediatric Research: A Moral Imperative

↑ “The performance of research studies to evaluate drugs in children is critical for determining the safety and efficacy of medications in children. ...Without proper drug studies in children, children may not benefit from and may even be harmed by drugs that are available to adults. Also, certain disorders affect children primarily, necessitating drug testing on appropriately aged subjects. It is morally imperative, therefore, to formally study drugs in children so that they can enjoy appropriate access to existing and new therapeutic agents.”

↑ Robert E. Shaddy, MD, Scott C. Denne, MD and The Committee on Drugs and Committee on Pediatric Research. PEDIATRICS Vol. 125 No. 4 April 2010, pp. 850-860

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 and biological products in infants, children and adolescents.
- The critical need for pediatric research on drugs and biological products 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.

Topics

- Introduction
 - Who are children?
 - Additional Protections at 21 CFR 50 Subpart D
- Two Key Concepts
 - Component Analysis; Prospect of Direct Benefit
- Non-Therapeutic Studies and the “Low Risk” Pathway
- Recent Advisory Committee Recommendations

Who are “children”?

- Labeling regulations for drugs/biologics:
- 0 to < 17 years [21 CFR 201.57(c)(9)(iv)]
- Pediatric Medical Device Safety Improvement Act: 0 to 21 years [Section 301(E)(i)]
- Additional Protections for Children (subpart D):
“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” [21 CFR 50.3(o)]

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 (Principle of Scientific Necessity).
- 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

- Derived from requirement for 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).
- Practical application: determine type and timing of clinical studies required to establish "safe and effective" pediatric use of FDA-regulated products

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

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 safeguards 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 (i.e., Principle 2), 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 (i.e., Principle 3).
 - *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

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:
 - 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

† Data also may come from post-marketing pediatric (i.e., "off label") and/or adult data

The Role of Prior Data

- We need scientific data using either preclinical animal models or adult human clinical trials to establish *either*...
 - “proof of concept” for sufficient prospect of direct benefit that justifies exposing children to risks of the intervention (21 CFR 50.52), or...
 - sufficient safety data to conclude that risks of the intervention are no more than a minor increase over minimal risk (21 CFR 50.53).
- If appropriate, adults should be enrolled prior to adolescents and younger children to obtain data in support of either judgment.
 - Once *sufficient prior data* exists to make either judgment, pediatric development should proceed without further delay.

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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
- "Fallacy of the Package Deal"
 - Research protocols may combine non-therapeutic interventions with other interventions that either: (1) offer (as a research intervention) a prospect of direct benefit to the enrolled child, or (2) would be considered part of necessary health care for that child.
 - The risks of "research only" interventions (i.e., no prospect of direct benefit) should not be justified by other "bundled" interventions that offer a prospect of direct benefit.

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).

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)
 - Word “benefit” often modified by “clinical” to indicate that “direct benefit” relates to health of enrolled subject.
- PDB is based on “structure” of an intervention (i.e., dose, duration, method of administration, etc.), and not the investigator’s “intent” or protocol objective(s).
 - Direct benefit is an attribute of the intervention or procedure and not of the overall research protocol and/or objective(s).

Prospect of Direct Benefit (PDB)

- The necessary level of evidence to support PDB (“proof of concept”) is less than the level of evidence required to establish efficacy.
- Whether experimental intervention offers PDB is separate from whether that PDB is 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”

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Exploratory IND Studies

- No therapeutic or diagnostic intent (i.e., no PDB)
- Involves very limited human exposure
 - Limited drug exposure (dose, duration); small number of human subjects.
- Conducted early in phase 1
 - prior to traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program
 - pediatric phase 1 studies may occur later in overall adult drug development program

Applicability to Pediatrics?

- “Because exploratory IND studies involve administering either sub-pharmacologic doses of a product, or doses expected to produce a pharmacologic, but not a toxic, effect, the potential risk to human subjects is less than for a traditional phase 1 study that, for example, seeks to establish a maximally tolerated dose. ***Because exploratory IND studies present fewer potential risks than do traditional phase 1 studies that look for dose-limiting toxicities, such limited exploratory IND investigations in humans can be initiated with less, or different, preclinical support than is required for traditional IND studies.***”⁶

⁶ “Generally, these types of studies would not be carried out in pediatric patients or in pregnant or lactating women.”

PK Studies in Children

- Usually no therapeutic or diagnostic intent (i.e., no PDB) unless monitoring drug levels is necessary for therapeutic purposes (e.g. lithium)
- Involves moderate human exposure
 - Near-therapeutic dose, limited duration
- Intent: characterize ADME; define pediatric dose
 - Generally occurs after PK/preliminary safety characterized in the adult population
 - Modeling and simulation helpful to define starting dose

Applying 21 CFR 50 subpart D

- 21 CFR 50 subpart D applies to a clinical trial regardless of whether 1 child or 100 children are exposed to experimental drug (i.e., risk is not limited by reducing number of exposed subjects).
- The risks of drug exposure remain the same for each child enrolled in a clinical investigation.
- Given the lack of PDB, what are the conditions under which a non-therapeutic pediatric study could proceed using the “low risk” pathway?

“Low Risk” Pathway

- Absent a prospect of direct benefit, studies or procedures must either be:
 - “Minimal Risk” (21 CFR 50.51)
 - “Minor increase over Minimal Risk (21 CFR 50.53)
 - Studies that do not fit these criteria must be referred for Federal panel review (21 CFR 50.54)
- Application of the “low risk” pathway depends on our ability to generate an accurate risk estimate based on previous human data (absence of risk data is *not* evidence of absence of risk!)

“Normal” or “routine” risks?

- 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.”
- The phrase “of healthy children” was deleted from the current definition, yet most ethicists and US federal panels (e.g., SACHRP, IOM) agree with reinstating this phrase.
- Administration of experimental drug products is neither “normal” or “routine” and thus is not “minimal” risk.
- Acknowledging this restrictive definition of minimal risk, the National Commission added a category for research presenting a “minor increase over minimal risk.”

Minor Increase over Minimal Risk

- “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.”
 - National Commission - Report on Research Involving Children, pages 139-40 (1977)

- Research under the “minor increase” category 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
 - (21 CFR 50.53)

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.

† IOM, Ethical Conduct of Clinical Research Involving Children (2004)

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.

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.

Defining Acceptable Risks

- Multiple factors are relevant to the moral evaluation of risk, including the harmfulness of the event, the type of harm it represents, its probability of occurrence, the distribution of a risk, whether it is voluntarily assumed or involuntarily imposed, the context of the activity in which the risk is encountered, and other factors.
- Pluralism in risk assessment may thus be a practical, theoretical and moral necessity.

Minimizing Risks of Non-Therapeutic Studies

- When possible, “piggyback” onto treatment studies or routine clinical care
 - Minimizes nontherapeutic drug exposure
 - Use existing indwelling lines, time under anesthesia, residual “opportunistic” samples
- Routine peripheral venipuncture considered “low” risk, unless done frequently or volume of blood is excessive
- Exclude children with difficult venous access

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Pediatric Ethics Subcommittee

May 11, 2011

- Exploratory IND studies of drugs otherwise considered under the “higher risk pathway” may be approvable when administered in sub-therapeutic doses as a minor increase over minimal risk.
- Caveats
 - Sufficient prior animal and adult human data
 - Adequate data about dose-dependent and non-dose-dependent toxicities

Pediatric Ethics Subcommittee

May 11, 2011

For products presenting a minor increase over minimal risk when administered in therapeutic doses (e.g., OTC cough and cold products), the PES was hesitant to identify circumstances where the use of a sub-therapeutic dose of such a product would reduce the risk to no more than minimal risk (thereby allowing an exploratory IND study in children without the relevant disorder or condition to proceed under 21 CFR 50.51).

Pediatric Microdosing Study?

- To approve administration of a radiolabeled drug microdose with repeated blood sampling, the following must be true:
 - Combined risks of the drug + radiation exposure + phlebotomy + blood volume loss must be no greater than a minor (slight) increase over minimal risk
 - Study must provide information of “vital importance” for the understanding or amelioration of the child’s disorder or condition
 - Parental permission and (if applicable) child assent must be obtained

Clinical Pharmacology AC

March 14, 2012

- Committee voted 7 to 6 in favor of the routine use of PBPK in pediatric drug development.
- An estimate of clearance and volume of distribution with a precision representing a standard error of approximately 20% or less is not a reasonable standard.
- Adult PK data can be used to determine the appropriate dose for studies in adolescents without the need for a separate PK study.



Thank You



IND Exempt?

ALL of the following must apply:

- Investigation not intended to support a new indication or change in *labeling* or *advertising* of the product;
- Investigation does not involve a route of administration or dosage level or use in a patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for IRB review and informed consent.
- The studies will not be used to promote unapproved indications, in compliance with §312.7.

IND Application for Exploratory Programs

- Information on a clinical development plan
- Chemistry, manufacturing, and controls information
- Pharmacology and toxicology information
- Previous human experience with the investigational candidate or related compounds, if any

Objectives for Exploratory IND Study

- Determine whether a mechanism of action defined in experimental systems can also be observed in humans (e.g., a binding property or inhibition of an enzyme)
- Provide important information on PK
- Select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target in humans, based on PK or PD properties
- Explore a product's biodistribution characteristics using various imaging technologies