# Finding a Path Forward: The Ethics of Pediatric Product Development in Rare Diseases

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# 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

# Topics

- Introduction
  - Basic Ethical Framework (4 principles)
  - Paths to Licensure: Linking Science and Ethics
- Two Key Concepts
- “Low Risk” Pathway
- “Higher Risk” Pathway

# 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.

# Basic Ethical Framework

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)†
- Requirements for permission by parents or guardians and for assent by children (§50.55)



† 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

- 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)]

# Different Pathways to Pediatric Licensure

- Product is being developed for both a pediatric and adult indication (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 is being developed for a pediatric indication alone (i.e., no adult indication exists).
  - Challenge: developing sufficient preclinical data† to support the initiation of pediatric clinical trials.

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

# 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

# Topics

- Introduction
- Two Key Concepts
  - Prospect of Direct Benefit
  - Component Analysis
- “Low Risk” Pathway
- “Higher Risk” Pathway

# 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 lower than the level of evidence required to establish efficacy.
  - "Proof of concept" may be based on animal or adult human data, using a "clinical" endpoint or a "surrogate" based, for example, on disease pathophysiology.
- 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"

# Three Key Questions for PDB

1. Does the intervention have the potential to ameliorate the condition under investigation?
2. Does the health benefit accrue to each individual participant?
3. Is the potential benefit sufficient to justify the (known or unknown) potential risks?

# 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 do or do 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

- Introduction
- Two Key Concepts
- “Low Risk” Pathway
  - Minimal Risk
  - Minor Increase over Minimal Risk
- “Higher Risk” Pathway

# What is "Low" Risk?

- 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 may be referred for Federal panel review under 21 CFR 50.54

# 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.
- Interventions/procedures that do not present a prospect of direct benefit must present a “low” (e.g., minor increase over minimal) risk, and thus must be limited to children with a “disorder or condition” (absent a federal exception).

National Commission - Introduction, Report on Research Involving Children (1978)

# 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).

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

# 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)

# Enrolling "Healthy" Children?

- The word "healthy" is not used in 21 CFR 50 & 56, and can be misleading.
- A child can be healthy and "at risk" (i.e., have a "condition"); a child with a condition may not have the condition related to the research (and thus be "healthy").
- A more accurate designation is:
  - Children with the disorder (disease) or "at risk" condition which is the object of the research.
  - Children without the disorder (disease) or "at risk" condition which is the object of the research.

# 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)

# "Low Risk" Pathway

- "Low risk" pathway may have limited applicability in product development for rare pediatric diseases.
  - Unable to generate an accurate risk estimate given limited (to no) adult testing experience.
- E.g., used for "low risk" procedures; limited single-dose PK testing (with adequate adult database to establish known risk).

# Topics

- Introduction
- Two Key Concepts
- “Low Risk” Pathway
- “Higher Risk” Pathway
  - Role of Human Adult Data in support of an Orphan Pediatric Disease
    - Establishing Prospect of Direct Benefit
    - Extrapolation and “Substantial Evidence”
  - Small Clinical Trials (i.e., no human adult data)

# 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.

# Extrapolation

- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, …pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as PK studies."

Pediatric Research Equity Act of 2007 (Title IV FDA Amendments Act 2007)

# Extrapolation

- The selection of an appropriate dose (i.e., drug exposure) and the assessment of pediatric-specific safety should not be extrapolated.
- The extrapolation of efficacy requires an understanding of disease pathophysiology and the mechanism of therapeutic response to the investigational product. In addition, “bridging studies” may be required to support extrapolation (e.g., humoral or cellular immune response).

# Extrapolation in JIA/JRA

- Disease Classification (JIA subsets)
  - Pauci-articular
  - Poly-articular
    - Similar clinical course; response to treatment (cf. adult RA)
  - Systemic-onset
  - Oligoarthritis (HLA-B27)
- Timing of Pediatric Studies
  - "Testing may begin in children, however, when the anticipated benefits based on existing knowledge justify the anticipated risk." (similar to 21 CFR 50.52)

# Choice of Control Group

- Active Treatment Control
  - Provide evidence to justify a “non-inferiority margin” based on previous clinical trials; or,
  - Superiority design (also with placebo control)
- Other possible alternatives
  - Dose-response
  - Randomized withdrawal

# Use of Placebo Controls in Pediatrics

- Placebo administration does not offer a prospect of direct benefit (setting aside any alleged “placebo effect”).
- Risk of placebo itself is “minimal” (if appropriately chosen).
- Risks to placebo control group is related to the risk of harm from not receiving “proven” or “effective” treatment.
- Thus, risks to which placebo group is exposed by withholding proven effective treatment must be restricted to no more than a “minor increase over minimal risk.” (21 CFR 50.53)
- This approach is consistent with ICH E-10 and the 2008 Declaration of Helsinki.

# "Substantial Evidence"

- Data from adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved
  - Usually interpreted to mean two clinical trials, each with a $p < 0.05$
  - Use of only one clinical trial may require a $p < 0.025$
- Data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) may be sufficient to establish effectiveness.
  - Issue: degree of "tolerable" uncertainty about product efficacy.

21 USC 355(d)

# Topics

- Introduction
- Two Key Concepts
- “Low Risk” Pathway
- “Higher Risk” Pathway
  - Role of Human Adult Data
  - Small Clinical Trials
    - Plan: “Proof of Concept” (direct benefit; surrogates)
    - Tolerable Level of Uncertainty

# Small Clinical Trials

- "Properly designed trials with small sample sizes can contribute to substantial evidence of efficacy."
- Planning (e.g., prospect of direct benefit; surrogates)
  - "Because of the design and analysis constraints of small-sample-size trials and because of their inherent uncertainties, they require at least as much--and probably more--thought and planning than traditional large clinical trials."
- Degree of Tolerable Uncertainty?
  - "There is nothing very different about small clinical trials relative to larger clinical trials other than greater uncertainty about the inferences made from results of the trials."

Institute of Medicine. Small Clinical Trials: Issues and Challenges (2001)

# A Refinement: "The Role of Adult Human or Animal Data"

- To enroll children in clinical investigations, 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 or animal models should be studied prior to adolescents and younger children to obtain data in support of this judgment.
- Once *sufficient adult or animal data* exist to make this judgment, pediatric development should proceed without further delay.

# 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")

# Starting Dose for "first-in-human" clinical trials

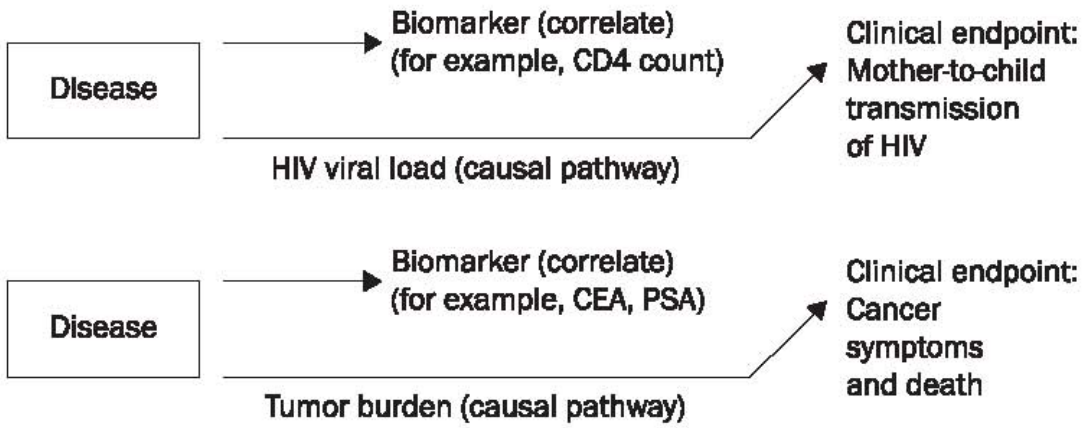
- Maximum recommended starting dose (MRSD) frequently based on "no observed adverse effect levels" (NOAEL) in the tested animal species, and conversion of NOAEL to a human equivalent dose with the application of a safety factor.
- Risk/potential benefit for NOAEL "safe starting dose" may not be equivalent to MRSD dose associated with greatest efficacy in animal studies.
- Challenge: NOAEL dose may not offer sufficient PDB to justify "first-in-children" clinical trial, and the MRSD may present greater risks.

# Establishing Useful Surrogates

## Animal modeling; Early IND Studies ("phase 0")

**EXHIBIT 1**

**A Reason For The Unreliability Of A Proposed Surrogate Endpoint: The Proposed Surrogate Is Not In The Causal Pathway Of The Disease Process**




**SOURCE:** T.R. Fleming and D.L. DeMets, "Surrogate End Points In Clinical Trials: Are We Being Misled?" *Annals of Internal Medicine* 125, no. 7 (1996): 605–613.

**NOTES:** Correlates are useful for disease diagnosis or for assessing prognosis. Valid surrogates are useful for replacement endpoints. See discussion in text. CEA is carcinoembryonic antigen. PSA is prostate-specific antigen.

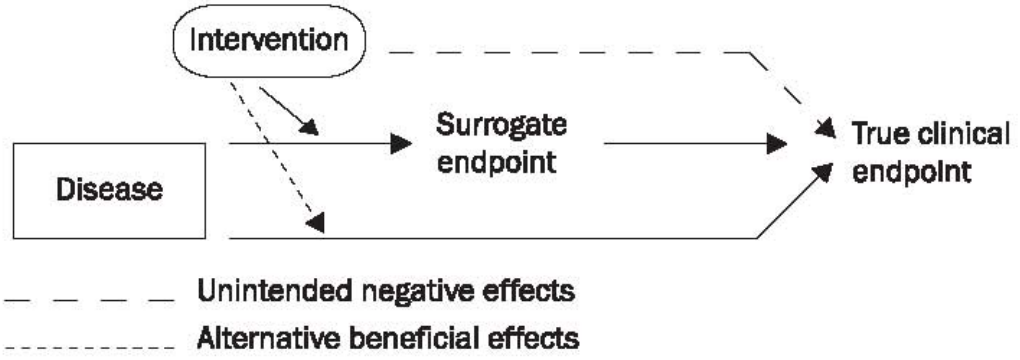
Fleming TR. Health Affairs 24(1):2005;67-78.

# Unreliability of Proposed Surrogates

## Hazard of "Accelerated Pathway"

**EXHIBIT 2**

**Additional Reasons For The Unreliability Of Proposed Surrogates: Disease Processes Having Multiple Causal Pathways And Interventions Having Mechanisms Of Action Independent Of The Disease Process**

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Fleming TR. Health Affairs 24(1):2005;67-78.

# Selected Problems in Drug Development for Rare Diseases

- Lack of natural history studies to characterize the disease process, including variability in disease severity, symptom stability, and outcomes.
- Poor use of early-phase safety and dosing studies to inform phase III or pivotal studies.
- Inadequate trial design, including lack of formal protocols, poorly defined questions, inadequate control groups, and lack of validated biomarkers and appropriate surrogate measures.

Pariser (2010) as quoted in IOM Report on Rare Diseases and Orphan Products (2010)

# Alternate Types of Control Groups

- Concurrent Controls
  - Placebo (blinded) or no treatment
  - Active treatment (superiority or non-inferiority)
  - Dose comparison
- External Controls
  - Historical (or retrospective) control
  - Variant: Change from Baseline

# alglucosidase alfa (Myozyme)

- Approved for treatment of Pompe Disease based largely on randomized (two doses), open-label, historically controlled study in 18 infantile-onset patients.
- 83% ventilator-free survival at 18 months in treated infants (vs. 2% overall survival in 61 age-matched historical controls).

http://www.myozyme.com/~/media/Files/MyozymeUS/Documents/mz_pi.pdf

# Linking Science and Ethics

- Discussed two ethical pathways for establishing sufficient scientific data to conclude that:
  - ✓ *"Low Risk" Pathway*: Absent direct benefit, product administration presents an acceptably "low" risk, or…
    - ✓ 21 CFR 50.51/50.53 (cf. ICH E-6 §4.8.14)
  - ✓ *"Higher Risk" Pathway*: Product administration presents a sufficient prospect of direct benefit to justify "higher" risks, compared to available alternatives.
    - 21 CFR 50.52
- Each pathway presents different ethical and scientific challenges that can be negotiated with sufficient planning and focused effort.

# Thank you.