

21 CFR 50, Subpart D

Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products

Robert M. Nelson, MD PhD
Pediatric Ethicist, Office of Pediatric
Therapeutics, Food and Drug
Administration



Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, June 9, 2008

“Nested” Protections

Scientific Necessity

Parental Permission



Child Assent

Appropriate Balance of Risk and Benefit



Principle of Scientific Necessity

- Children should not be enrolled in a clinical investigation unless absolutely necessary to answer an important scientific question about the health and welfare of children.
 - Study design capable of answering question (e.g., sample size, control group, blinding, etc.)
 - Practical application: “extrapolation”
 - Objective: “public health benefit” for children



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

21 CFR 56: Criteria for IRB Approval of Research

- Minimize Risks [21 CFR 56.111(a)(1)]
 - Eliminate any research procedures (as unnecessary) that do not contribute to scientific objective
- Equitable selection [21 CFR 56.111(b)]
 - 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).



4

EMA - Scientific Necessity

- Children should not be included in clinical trials when the research can be done in adults capable of informed consent.
 - Proof of concept should first be obtained in relevant animal models and/or in adults whenever possible.
- If research with children necessary...
 - least vulnerable usually included (i.e. older children)
 - pediatric population based on target population for tested medicine, possibility of extrapolation, and scientific validity of such an approach.



EMA, Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, 2008

5

Justice and “Fair” Subject Selection

- “These groups [i.e., legally incompetent, physically or mentally incapable of giving consent or a legally incompetent minor] should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.”

Declaration of Helsinki, Paragraph 24



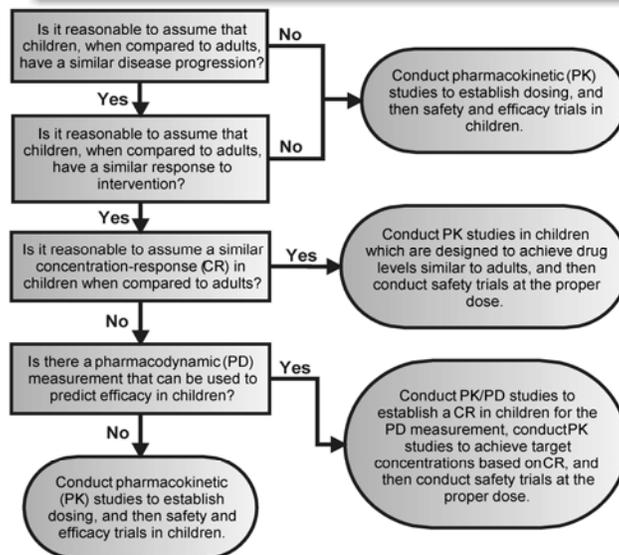
6

Extrapolation

- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that 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."
- "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group."



FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation (under BPCA or PREA)



Extrapolation

- The selection of an appropriate dose (i.e., drug exposure) and the assessment of pediatric-specific safety should never 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).



“Nested” Protections

Scientific Necessity

Parental Permission



Child Assent

Appropriate Balance of Risk and Benefit



Appropriate Balance of Risk and Benefit

Adults (21 CFR 56.111)

- Risks are reasonable in relation to anticipated benefits, if any, to subjects and importance of knowledge that may reasonably be expected to result

21CFR 56.111

“Subpart D” (children)

- For research not offering the prospect of direct benefit, restricts allowable risk exposure (minimal risk, minor increase over minimal risk; ICH E6 GCP §4.8.14 “low”)
- For research that offers prospect of direct benefit, restricts justification of risk exposure

21CFR 50.51 & 50.53

21CFR 50.52



11

Additional Protections for Children

	Direct Benefit	No Direct Benefit
Minimal Risk	21 CFR 50.51	
Greater than Minimal Risk	21 CFR 50.52	21 CFR 50.53 (minor increase)



12

Additional Protections for Children

	Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in <u>daily life</u> or during the performance of <u>routine physical or psychological examinations or tests</u> . <small style="float: right;">21 CFR 56.102(i)</small>	
Minimal Risk		
Greater than Minimal Risk	21 CFR 50.52	21 CFR 50.53 (minor increase)



Additional Protections for Children

Criteria for approval: 1) only a <u>minor (or slight) increase</u> over minimal risk ✓ Requires known estimate of risk based on data 2) experiences reasonably commensurate with actual or expected situation 3) yield generalizable knowledge of vital importance for understanding or amelioration of <u>disorder or condition</u>		
Greater than Minimal Risk	21 CFR 50.52	21 CFR 50.53 (minor increase)



Additional Protections for Children

Minimal Risk	Criteria for Approval: 1) <u>Risk justified by anticipated direct benefit to subjects (within each arm of study)</u> 2) Relation of anticipated direct benefit to risk at least as favorable as available alternative approaches (both inside and outside research)	
Greater than Minimal Risk	21 CFR 50.52	21 CFR 50.53 (minor increase)



FOCUS: 21 CFR 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

- Any clinical investigation ... in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if...:
 - a) The risk is justified by the anticipated benefit to the subjects;
 - b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
 - c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

