

Additional Safeguards for Children in Clinical Investigations 21 CFR 50 Subpart D

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Topics Covered

- Basic Ethical Framework in Pediatrics
- “Low risk” and “higher risk” pathways for pediatric product development
- Choice of Controls in Pediatric Research
- Considerations for Studies in Achondroplasia

Basic Ethical Framework in Pediatrics

1. Children should only be enrolled if scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally
2. Absent a prospect of direct clinical benefit, the risks to which children are exposed must be “low”
3. Children should not be placed at a disadvantage by being enrolled in a clinical trial
4. Vulnerable populations unable to consent (including children) should have a suitable proxy to consent for them

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 FDA-regulated products
 - Study design capable of answering question (e.g., sample size, control group, blinding, etc.)
 - Objective: "public health benefit" for children

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

Principle of Scientific Necessity

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

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 Safeguards 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;45 CFR 46.404/406
 - 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;45 CFR 46.405
- Permission by parents or guardians and for assent by children must be solicited (§50.55)



Additional Safeguards for Children

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- 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)

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.)
 - Dose and duration of treatment must be adequate to provide a prospect of direct benefit
- The necessary level of evidence to support PDB (“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

Minor Increase over Minimal Risk[†]

- “Minimal risk” was originally defined as those risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children”
- "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 no more than a minor increase over minimal risk, and be limited to children with a “disorder or condition” (absent federal review and approval)

[†] National Commission - Report on Research Involving Children (1977)

Component Analysis

A clinical investigation may include more than one intervention or procedure

Each intervention/procedure must be evaluated separately to determine whether it does/does not hold out the prospect of direct benefit to the enrolled child

This approach is consistent with recommendations of the National Commission and the resulting regulations

Interventions or procedures that hold out the prospect of direct benefit should[†] be considered under 21 CFR 50.52

Interventions or procedures that do not hold out the prospect of direct benefit should[†] be considered under 21 CFR 50.51 or 50.53 (but not 50.52)

[†] Can be considered under 21 CFR 50.54 (thus "should" and not "must")

Component Analysis

- 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)
- Examples include
 - Central lines in a placebo study arm
 - Liver or kidney biopsies for research purposes

Substantial Evidence of Effectiveness

- “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved” [1962]
Section 505(d), Food, Drug & Cosmetic Act
 - “Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness”

- “FDA has been flexible..., broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing”
 - In 1997, “Congress amended section 505(d)... to make it clear that [FDA] may consider ‘data from one adequate and well-controlled clinical investigation and confirmatory evidence’ to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness”
 - In doing so, “Congress confirmed FDA’s interpretation of the statutory requirements for approval”
 - This flexibility has been used to approve drugs for rare diseases

Choice of Control Group

- “As a general rule, research subjects in the control group of a [clinical] trial... should receive an established effective intervention”
- However, placebo [or no treatment] may be used:
 - “When there is no established effective intervention”
 - “When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms”
 - “When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects”

CIOMS, Guideline 11, 2002

ICH E-10 Choice of Control Group, May 2001

Choice of Control Group

- Placebo Control
- Active Treatment Control if treatment available
 - Provide evidence to justify a “non-inferiority margin” based on previous clinical trials; or,
 - Superiority design
- External Controls
 - Historical (or retrospective) control
 - Is there adequate natural history data?
 - Variant: Change from Baseline
 - For any changes involving growth, defining a meaningful change may be difficult

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
 - Duration of placebo/sham injections may impact the risk determination
- The approach to defining risk with placebo use is consistent with ICH E-10 and the 2013 Declaration of Helsinki

Considerations for Studies in Achondroplasia

- Population under study must have some PDB to participate in the trial
 - Age of child most likely to benefit may be dependent on the outcome of interest
 - Dose must have some expectation of being effective
- Duration of the study must be adequate to support a PDB
 - How long is too long to constitute a “minor increase over minimal risk” especially if placebo injections are required

