Ethical Considerations for Pediatric Studies in Rare Diseases

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Disclosure

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration, or the Department of Health and Human Services
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Topics Covered

- Basic Ethical Framework in Pediatrics
- “Low Risk” and “Higher Risk” Pathways for Pediatric Product Development
- Component Analysis
- Choice of Controls, including Placebo
- Considerations for Studies in Rare Diseases
- Conclusion

Introduction

- Over time, we have evolved from a view that we must protect children from research to a view that we must protect children through research
- We have an obligation 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 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
  - 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

Principle of Scientific Necessity

- Practical application: determine the type and timing of clinical studies required for establishing "safe and effective" pediatric use of FDA-regulated products
  - Using extrapolation of efficacy if appropriate from adults to children
  - Studies may be initiated in children if an appropriate adult population does not exist
- “A more targeted generation of evidence should help to ensure that children only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children and address the requirements for regulatory decision-making”

(EMA Reflection Paper on Use of Extrapolation (9 October 2017)

Pediatric Extrapolation

- The use of extrapolation was first introduced in the 1994 Pediatric Labeling Rule
- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] 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…"
- "A study may not be needed in each pediatric subpopulation if data from one subpopulation can be extrapolated to another…."
- Efficacy can be extrapolated, but dosing and safety cannot be extrapolated

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 assent by children must be solicited (21 CFR 50.55)

Additional Safeguards for Children 21 CFR 50 Subpart D

- Not involving greater than minimal risk (21 CFR 50.51)
- Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (21 CFR 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 (21 CFR 50.53)
- Not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (21 CFR 50.54)†
- Requirements for permission by parents or guardians and for assent by children (21 CFR 50.55)

† Requires review by federal panel

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

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

Prospect of Direct Benefit (PDB)†

- 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

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

Minor Increase over Minimal Risk†

- “Minimal risk” is 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”
- Are limited to children with a “disorder or condition” (absent federal review and approval)
  - May include children “at risk” for a disorder
- Must contribute to generalizable knowledge about the child’s disorder or condition

† 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 of components to consider include: “research only” procedures such as muscle biopsies, MRI’s with procedural sedation, assessing risk of placebos, especially “invasive” ones

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 delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures
  - 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

Council for International Organizations of Medical Sciences (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
- No treatment (nonblinded) as a concurrent control
- Dose-ranging as a concurrent control
  - Using differences in dose response, if no difference seen, trial may be uninterpretable
- Historical (or retrospective) control
  - Requires adequate natural history data

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

Placebo Controls in Pediatrics

- Examples of placebo arms that exceed a minor increase over minimal risk and alternative approaches
  - Multiple lumbar punctures over the course of a trial for administration of placebo
    - Consider sham injections instead, may involve superficial skin puncture if necessary to maintain the blind
  - Indwelling central catheters to provide placebo in a blinded trial
    - Consider use of a midline catheter instead for frequent infusions over a short period of time
    - A totally implantable venous access catheter (TICVAD) has been approved by a federal panel under 21 CFR 50.54 when considered in the context of a specific protocol*

*FDA Determination Memo
https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM560819.pdf

Non-therapeutic Procedural Sedation

- The Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) met in in March 2015 to discuss the use of procedural sedation for non-therapeutic research interventions
- The PES/PAC was unable to reach consensus on whether one or more approaches to procedural sedation should be considered a minor increase over minimal risk (YES: 7; NO 9)
- The committee did agree upon recommendations that should be included in a protocol to consider if the protocol is approvable under 21 CFR 50.53 or if review under 21 CFR 50.54 is required†

†http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM510177.pdf.

Considerations for Studies in Rare Diseases

- If the disease exists in adults and efficacy can be extrapolated, data should be collected in adults first to reduce the burden on children from participation in pediatric trials
  - Data in pediatric patients are needed to support safety and dosing
- Studies may be initiated in children when the disease is dissimilar in adults or if there are no adults with disease
  - Examples include inborn errors of metabolism or infantile forms of disease that are fatal in childhood, for targeted therapies where intervention in childhood is critical, such as the replacement of a defective enzyme, or gene transfer
  - When there are limited or no other treatment options

Considerations for Studies in Rare Diseases

- If there are no adults with disease, data from studies in healthy adult volunteers or adults using the product for other indications may be informative
  - Testing in adults may provide some evidence of activity
  - Pharmacokinetic (PK) properties of the product may be understood and help inform pediatric dosing
  - Human safety data may be supportive even if for a different indication
- These data should be used, if available, to inform the pediatric program

Considerations for Studies in Rare Diseases

- If there are no adults with disease and testing in adults will not be informative
  - Proof of concept and starting dose may be derived from animal disease models to support PDB
  - If no animal model exists, other mechanistic in vivo or in vitro data can be substituted, particularly if the therapy is targeted
  - Safety information may be limited to nonclinical toxicology models
    - Nonclinical studies to evaluate maximum tolerated doses
    - Juvenile animal studies to support the pediatric age groups
    - Study duration sufficient to support chronic dosing for chronic conditions

Considerations for Studies in Rare Diseases

- Administration of an experimental intervention in a pediatric study of a rare disease is unlikely to be considered as a minor increase over minimal risk and thus must offer a PDB to children
  - Single dose PK studies do not generally offer PDB to pediatric patients
  - The initial dose used in a pediatric study should have some expectation of being effective to offer a PDB
  - Multidose studies must be of sufficient duration to offer benefit
  - Adaptive study designs†, (e.g. prospectively planned dose ranging or dose titration) with continued dosing once a dose is established, should be considered to offer PDB and reduce the need to conduct multiple studies in children

†Adaptive Designs for Clinical Trials of Drugs and Biologics (September 2018)
https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf

Conclusion

- Unique ethical considerations impact the design of clinical studies intended for children with rare diseases
- 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
- When extrapolation is appropriate, data from adults should be used to support studies in children so that children are not exposed to unnecessary or overly burdensome clinical trials
- If sufficient PDB is established to justify risks, studies in rare diseases may be initiated in children for diseases that occur primarily or only in children and for which there are limited or no other options
- Adaptive pediatric study designs should be considered to minimize the number of studies needed to be conducted in children

Thank you!

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