Children as Human Research Subjects

Subpart D

A Presentation for IRB Members
Additional Protections Included in 45 CFR 46

**Subpart B** - Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Pregnant Women, Fetuses, and Neonates (non-viable and those of uncertain viability)

**Subpart C** - Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

**Subpart D** - Additional DHHS Protections for Children Involved as Subjects in Research (adopted in 1983)
• **Authority:**
  - Federal Food, Drug, and Cosmetic Act (1962)

• **Regulations:**
  - IRB: 21 CFR 56
  - Informed Consent: 21 CFR 50
    - [Adopted Sub Part D](#) --- April 2001
  - Investigational Drugs: 21 CFR 312
  - Investigational Devices: 21 CFR 812
Inclusion of Children

• All ethical standards and regulatory requirements that apply to adults (DHHS and FDA) are required for the conduct of research involving children

• Subpart D contains additional safeguards that the IRB must consider for research involving children

• NIH Guidelines expand inclusion requirements
  – (Individuals of all ages must be included in human subject research, conducted or supported by NIH unless scientific or ethical reasons exclude them.)
Categories of Allowable Research Involving Children

• Research not involving greater than Minimal Risk

• Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

• Research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

• Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
Research not Involving Greater than Minimal Risk

Requirements:
✓ Parental Permission - the IRB may find that the permission of one parent is sufficient for research

✓ Child’s Assent
  ▪ the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.
  ▪ In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved.
Definition of Minimal Risk

• Federal regulations define minimal risk as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

• As written, the definition of minimal risk in federal regulations (45 CFR 46.102(i); 21 CFR 56.102(i)) provides an inconclusive standard by which risks involved in a research study are compared to those encountered in daily life. The uncertainty lies with whether the definition applies to those risks found in the daily lives of healthy individuals or in the daily lives of the potential research participants.
Some IRBs have interpreted “daily life” as referring to the daily life of a normal healthy person, a so-called “absolute standard,” while others have interpreted “daily lives” as experiences of the “research subject.” This is a much lower risk threshold and is referred to as a “relative standard of minimal risk.” The relative standard allows ill research participants to be exposed to greater risk than normal healthy participants.

Based on the most recent advisory report (released in 2001) from the National Bioethics Advisory Commission (NBAC). The NBAC report recommends using a minimal risk standard related to the risks of daily life that are familiar to the general population.

Common risks would include, for example:

- driving to work
- riding a bike
- crossing the street
- getting a blood test
- answering questions over the telephone
• UCI’s IRB wanting to afford greater protection to human research participants has adopted an absolute standard of minimal risk.

• Per UCI IRB policy, minimal risk is defined as the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily lives of the general population or during the performance of routine physical or psychological examinations or tests.

• The IRB may consider the daily lives of the general population matched on age of the proposed subject population. For example, if the protocol calls for the enrollment of junior high students the IRB should consider minimal risk in the context of the daily lives of the general population of 12-13 year olds.
Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

Regulations: 45 CFR 46.405 & 21 CFR 50.52

Requirements:
- the risk is justified by the anticipated benefit to the subjects;
- 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
- Parental permission as described in 45 CFR Part 46.408 and 21 CFR Part 50.55
- Minor Assent as described in 45 CFR Part 46.408 and 21 CFR Part 50.55
Research involving a **minor increase over minimal risk** and **no prospect of direct benefit** to individual subjects, but likely to yield generalizable knowledge about the **subject's disorder or condition**

Regulations: 45 CFR 46.406 & 21 CFR 50.53

Requirements:

- the risk represents no more than a **minor (i.e., slight) increase** over minimal risk;
- the intervention or procedure presents experiences to subjects that are **reasonably commensurate** with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- the intervention or procedure is likely to yield generalizable knowledge about the **subject's disorder or condition** which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- adequate provisions are made for soliciting assent of each child and permission of both parents or guardians, as set forth in 45 CFR 46.408 and 21 CFR Part 50.55.

* “disorder or condition” refers to specific (or set of specific) physical, psychological, developmental or social characteristic(s) that have been shown to negatively affect children’s health and well-being or to increase their risk of developing a problem in the future.
Research **not otherwise approvable** which presents an opportunity to understand, prevent, or alleviate a **serious problem** affecting the health or welfare of children

Regulations:
- 45 CFR 46.407
- 21 CFR 50.54

Requirements:
- the IRB finds that the research presents a **reasonable opportunity** to further the understanding, prevention, or alleviation of a **serious problem affecting the health or welfare of children**; and
- OHRP/FDA consultation with a **panel of experts**
- Opportunity for **public review and comment**
Component Analysis of Pediatric Trials

• **Different components** of a clinical investigation involving children may carry different levels of risks and may or may not hold out the prospect of direct benefit to subjects => analyze each component.

• In 2013, FDA indicated that it does “not consider the administration of a placebo to offer a prospect of direct benefit.” FDA conclusion: the placebo arm of a study can carry either no greater than minimal or a minor increase over minimal risk.

• Study arms receiving investigational products could have direct benefit.

Component Analysis - Case study

- Multinational, placebo-controlled, study of an investigational product in children ≥ 7 years old, Product (or placebo) administered by IV infusion using use a peripherally inserted central catheter (PICC)
- Documents provided to the FDA by the sponsor DID NOT mention PICC
- The insertion and use of a PICC for administration of the investigational product determined by the FDA to be more than a minor increase over minimal risk.
- PICC use was justified in children receiving the active product due to the prospect of direct benefit from the infusion.
- Children receiving the placebo via PICC were offered no direct benefit from the infusion, but exposed to greater than a minor increase over minimal risk - not in compliance with 21 CFR 50, subpart D.
NIH Policy and Guidelines on the Inclusion of Children as Participants in Research

It is expected that children will be included in all NIH supported research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

- The research topic to be studied is irrelevant to children.
- There are laws or regulations barring the inclusion of children in the research.
- The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. Documentation of other studies justifying the exclusions should be provided.

(continued on the next slide)
A separate, age-specific study in children is warranted and preferable.

Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

Study designs aimed at collecting additional data on pre-enrolled adult study participants (e.g., longitudinal follow-up studies that did not include data on children).
Questions?

Please contact:

➢ Your HRP Staff colleagues!

This presentation was adapted from:

• *Institutional Review Board: Management and Function*, Amdur and Bankert, 2002 and
• *Component Analysis 2012 Presentation* to the Secretary’s Advisory Committee on Human Research Protections by Robert Nelson, MD PhD, Senior Pediatric Ethicist/Lead Medical Officer, FDA