

Presidential Commission for the Study of Bioethical Issues

**Ethical Considerations in Anthrax
Vaccine Trials Involving Children**

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Ethical Issues in Research Involving Children

Children are Unique

- **Diseases**
- **Development**
- **Growth**
- **Metabolism**
- **Toxicity**

Ethical Issues in Research Involving Children

Is it ethical to do research involving children?

- **Paul Ramsey(1970)—Protestant theologian:**
only if the research furthers the medical interests of the child
- **Richard McCormick(1974)—Catholic theologian:**
parents may consent even if there is no therapeutic benefit

Ethical Issues in Research Involving Children

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978)

- **The Belmont Report**
- **Research Involving Children**
- **Institutional Review Boards**
- **Research Involving those
Institutionalized as Mentally Infirm**

Ethical Issues in Research Involving Children

National Commission – Research Involving Children

“The Commission acknowledged that exceptional circumstances may arise in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk...”

Ethical Issues in Research Involving Children

National Commission – Research Involving Children

“In exceptional circumstances, dangers to children or the community resulting from a failure to involve children in research might exceed whatever risk is presented by that research. For instance the threat of an epidemic that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable....”

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§46.407)**

“Ethical Conduct of Clinical Research Involving Children”
Institute of Medicine of the National Academies -- 2004

Minimal risk:

- **Interpret minimal risk in relation to the normal experiences of average, healthy, normal children**
- **Minimal risk may vary with age but not social status, illness, or circumstances**
- **Focus on “equivalence of risk” in daily lives or experiences in routine physical or psychological exams or tests**
- **Minimize risks even when risks are minimal**

“Ethical Conduct of Clinical Research Involving Children”
Institute of Medicine of the National Academies -- 2004

Prospect of direct benefit:

- **Tangible positive outcome (e.g. cure or prevention of disease, relief of pain, increased mobility)**
- **Level of risk may be greater than minimal but balanced by the compensating benefit**
- **Collateral or indirect benefits are not considered prospect of direct benefit**
- **Gifts, payments, compensation are not considered prospect of direct benefit**

“Ethical Conduct of Clinical Research Involving Children”
Institute of Medicine of the National Academies -- 2004

Minor increase over minimal risk:

- **Slight increase beyond minimal risk (as defined in relation to normal children)**
- **Assess duration, probability, and magnitude**
- **Commensurability—reasonably comparable to known past or future experiences**
- **“Condition” refers to a set of physical, psychological, neurodevelopmental, or social characteristics that has been shown to affect health, well-being or risk of future health problem**

§45CFR 46.407 and §21CFR 50.54: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

- (a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children; and**
- (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:**
 - (1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:**
 - (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;**
 - (ii) the research will be conducted in accordance with sound ethical principles;**
 - (iii) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408**

Federal Policy for the Protection of Human Subjects

§45CFR 46.407 and §21CFR 50.54

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children:

- **“IRB finds ...”**
 - **A scientifically sound protocol**
 - » **Valid questions that can be answered**
 - » **Power calculations**
 - » **Assess level of risk**
 - **Clear consent and assent forms and procedures**
 - **Wish to approve the protocol but may not under §404, §405, or §406 because of level of risk without compensating prospect of direct benefit.**

Federal Policy for the Protection of Human Subjects

45CFR 46.407 and 21CFR 50.54

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children:

- **Reasonable opportunity to further understanding, prevention, or alleviation of a serious problem...**
 - “Vital importance” (Section 406) vs.
 - “A reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children” (Section 407)
- **“Ethical Conduct of Clinical Research Involving Children”
Institute of Medicine of the National Academies -- 2004
Should adopt the more stringent standard of “vital importance”**

Federal Policy for the Protection of Human Subjects

45CFR 46.407 and 21CFR 50.54

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children:

- **Research will be conducted in accordance with sound ethical principles...**
 - **Appropriate level of risk—minimize risk**
 - **Justice concerns--recruitment populations and strategies**
 - **Prior adult studies, then assenting adolescents, then assenting young children, then toddlers, and finally infants**
 - **Public review and comment**
 - **Prospectively create both pre and post-event research studies**

Federal Policy for the Protection of Human Subjects

45CFR 46.407 and 21CFR 50.54

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children:

- **Adequate provisions for assent of children and permission of parents....**
 - **Careful review of consent forms and process – community engagement to assure honesty and transparency with clear delineation of risks and lack of likely benefit**
 - **Assent process that is:**
 - » **developmentally appropriate**
 - » **informs the child about the study from the perspective of the child's experience, and**
 - » **clearly elicits willingness to participate while respecting reluctance or refusal**

Presidential Commission for the Study of Bioethical Issues

Ethical Considerations in Anthrax Vaccine Trials Involving Children

Conclusions for your consideration:

- Need for scientifically strong protocol of “vital importance” to health and welfare of future children**
- IRB review and wish to approve but may not based on level of risk**
- Determination that level of risk to subjects is just a bit more than minor increase over minimal and there is no likelihood of compensating benefit**
- Reasonable recruitment populations and strategies**
- Clear informed consent documents and processes**
- Appropriate assent documents and processes**
- Stratified study with older children completing study before embarking on study of younger children**
- Public review and comment**
- Prospectively create both the pre-event and post-event studies to measure the outcome of widespread use of the vaccine in the chaotic atmosphere of a bioterrorist attack**