The Analysis of Risk and Benefit in Early Phase Research Involving Children

Historical and Ethical Considerations

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Kefauver-Harris Amendments (1962) to the Food, Drug, and Cosmetic Act (1938)

- Thalidomide controversy precursor:
  - FDA requested more data on human effects of thalidomide in response to NDA filing in 1960, but birth defects reported in Germany and NDA withdrawn in 1961
- Drug testing and approval process:
  - Codified the process by which drug testing is to be done primarily in adults and results extrapolated to children
- Law of unintended consequences:
  - Therefore, 75% of licensed drugs have never been tested in children

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Mandated by the National Research Act of 1974 (Public Law 93-348)

Research Involving Children, September 6, 1977

1) Involvement of children in research raises ethical concern because of reduced autonomy and incompetency to give informed consent.
2) Such concerns should not be answered by restricting participation in research to persons who are competent to consent, for the conduct of research involving children is necessary to develop new treatment or prevention for conditions that jeopardize the health of children.

Letter to the President from the National Commission Chair (1977)

The commission sought to answer two questions:

1. Under what conditions is participation of children in research ethically acceptable?

2. Under what conditions may such participation be authorized by the subjects and their parents?

Is it ethical to do research involving children?

- Paul Ramsey—Protestant theologian:

  only if the research furthers the medical interests of the child

- Richard McCormick—Catholic theologian:

  parents may consent even if there is no therapeutic benefit

National Commission's Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

Beneficence:

- *"effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children"*

- *"research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices…that may turn out to be dangerous"*

Belmont Report (cont'd)

Respect for Persons:

- Individuals with capacity… treated as autonomous
- Persons with diminished autonomy…entitled to protection
- An ethical imperative to obtain assent from children in research and to inform them of risks

Belmont Report (cont'd)

Justice:

- *"Historically the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients."*

- Children should be exposed to the benefit of research as well as adults

HHS Policy for the Protection of Human Subjects (45 CFR 46)

- Subpart A: Basic Policies
  Institutional Review Boards
  Informed consent

- Subpart B: Pregnant women, fetuses, and neonates [1975]

- Subpart C: Prisoners

- Subpart D: Children [1983]

HHS Policy for the Protection of Human Subjects, Subpart D*

- Categories of 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)
  - Not within scope of above categories, but reasonable opportunity to further understand, prevent or treat a serious problem (Secretary HHS review) (§46.407)

* FDA has comparable regulatory provisions for clinical investigations of FDA-regulated products involving children, including an FDA Commissioner review process.

Definition of Minimal Risk

45 CFR 46.102 (Part A)

[Risk is a product of ***two vectors***]

*(i) 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 daily life or during the performance of routine physical or psychological examinations or tests.*

45 CFR 46.404 – Research not involving greater than minimal risk

Provided that:

- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

45 CFR 46.405 – Research involving greater than minimal risk but with the prospect of direct benefit

- 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
- Adequate provisions are made for soliciting the assent of the children and permission of the parent or guardians

Prospect of direct benefit

IOM Report -- *Ethical Conduct of Clinical Research Involving Children* (2004)

- Tangible positive outcome (e.g. cure 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

National Commission (1977)

- "The expectation of success should be scientifically sound to justify undertaking whatever risk is involved."

Example of a Study Not Approvable under 46.405 SACHRP (2005)

- A phase 1 pediatric cancer protocol will give a dosage with no probability of ameliorating the subject's disease or disease management.
  - It could be approvable under 406 if it entailed a minor increase over minimal risk, of vital importance to the subjects' disease, commensurate with actual or expected experience, and parental permission and assent obtained.

Phase I Trials in Children

- **Council for International Organizations of Medical Sciences (2002)**
  - Phase I research with children may be appropriate because the disease to be treated does not occur in adults or is manifested differently in children

Recent FDA Draft Guidance

- ***Exploratory IND Studies*** **(April 2005)**
  - A early phase I clinical trial without therapeutic intent involving screening or microdose studies
  - Conducted prior to traditional dose escalation studies and safety studies
  - Duration of dosing limited, e.g. 7 days
  - Footnote 6: "Generally, these types of studies would not be carried out in pediatric patients . . ."

- ***How to Comply with the Pediatric Research Equity Act*** **(Sept 2005)**
  - Pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available may begin earlier in development than might occur for less serious diseases… as early as phase 1 or phase 2, when the initial safety data in adults become available.

45 CFR 46.406 – Minor increase over minimal risk and no prospect of direct benefit

- Experiences of subjects commensurate with actual or expected medical situations
- Likely to yield generalizable knowledge of vital importance about subject's disorder or condition
- Assent of child and permission of parents

IOM Report – *Ethical Conduct of Clinical Research Involving Children*

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

45 CFR 46.406 – Assessing Degree of Risk

National Commission's Four Perspectives:

1. Common sense estimation of risk
2. Investigators' experience with similar interventions/procedures
3. Available statistical information regarding risk of interventions/procedures
4. Situation of the proposed subjects

Component Analysis

"To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively…."

National Commission: Research Involving Children, 1977

Component Analysis

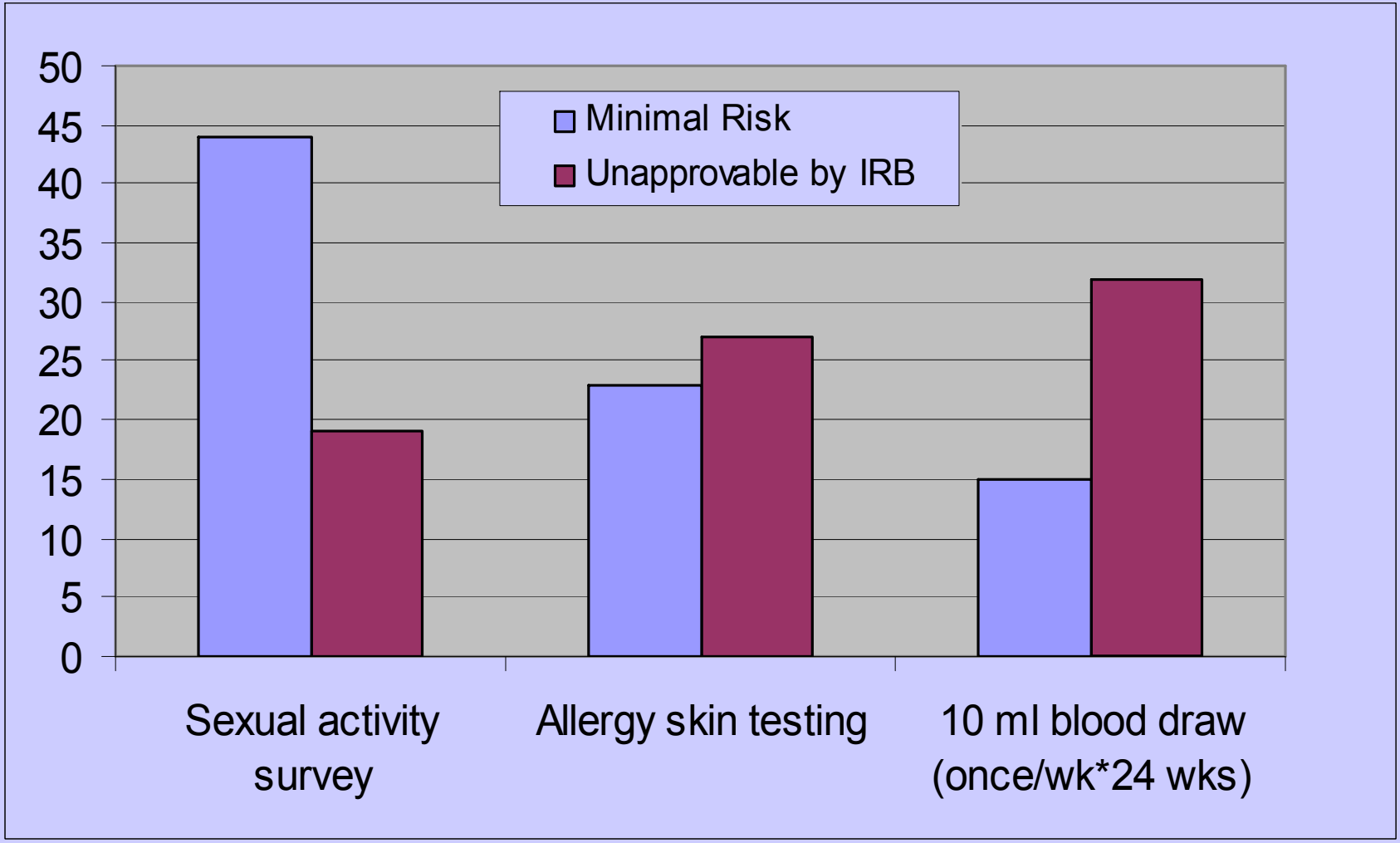
- Each research procedure in a treatment study must be evaluated independently in terms of potential benefits and risks to subjects.

- Different procedures in a single trial may be approved or disapproved under different Subpart D criteria.

45 CFR 46.407– Research found by IRB not to be approvable under sections 404, 405, or 406

- Requires approval by Secretary DHHS following review by expert panel and period of public comment
- Research presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children

Variability in Risk Assessment by 188 IRB Chairs Shah et al., JAMA, 2004



Quantifying Risks in Daily Life

- No comprehensive empirical assessment exists of the range of risks healthy children ordinarily encounter in daily life.
- Death in car crash: 1 in 250,000 car trips (ages 15-19)
- Risk of injury playing football: ~ 1 per 250 games

Wendler et al., JAMA 2005

"In America, sooner or later, everything ends up in court," [or no good deed goes unpunished.]

Alexis de Tocqueville,
Democracy in America, 1830

"There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents."

Committee on Drugs, American Academy of Pediatrics

Pediatrics, 95, 1995

Best Pharmaceuticals for Children Act

- Signed January 4, 2002
- Established a process for studying "*on-patent*" as well as "*off-patent*" drugs
- FDA/NIH collaboration to improve pediatric therapeutics
- Mandated IOM report on review of Federal regulations governing children in research

Pediatric Research Equity Act, 2003

- Passed unanimously by both houses of Congress
- Provides legislative authority for FDA to require companies to do pediatric testing for drugs and biologics
- Medicines to be used by children should undergo pediatric testing and not rely on adult testing

What have we learned?

- Drug metabolism in children differs from adults
- Adverse events in children may not always be predicted from the adult experience
- Ethical issues require continued careful assessment in pediatric patients