Children in Research: Ethical and Practical Challenges

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Learning Objectives for Today

- Discuss the ethical considerations and IRB review process and pediatric regulations
- Recognize the special considerations that apply to minors in clinical research
- Practice applying the regulatory approval for IRB approval in sample scenarios involving minors

Children in Research

- Ethical Considerations/IRB Review
- Special Considerations
- Case Studies

CRITERIA
for IRB approval

The Belmont Report, 1978

Basic Ethical Principles:

The Belmont Report, 1978

Basic Ethical Principles:

- Respect for persons

The Belmont Report, 1978

Basic Ethical Principles:

- Respect for persons
- Beneficence

The Belmont Report, 1978

Basic Ethical Principles:

- Respect for persons
- Beneficence
- Justice

The Belmont Report, 1978

Applications:

- Respect for persons
  - Informed Consent
- Beneficence

- Justice

The Belmont Report, 1978

Applications:

- Respect for persons
  - Informed Consent
- Beneficence
  - Assessment of Risks and Benefits
- Justice

The Belmont Report, 1978

Applications:

- Respect for persons
  - Informed Consent
- Beneficence
  - Assessment of Risks and Benefits
- Justice
  - Selection of Subjects

45CFR46* (1979, 1991, 2009)

Code of Federal Regulations
TITLE 45
PUBLIC WELFARE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PART 46
PROTECTION OF HUMAN SUBJECTS

aka *The Common Rule

§ 46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

§ 46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

§ 46.111 Criteria for IRB approval of research.

(1) Risks to subjects are minimized:

(i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

§ 46.111 Criteria for IRB approval of research.

(1) Risks to subjects are minimized:

(ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

§ 46.111 Criteria for IRB approval of research.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

§ 46.111 Criteria for IRB approval of research.

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

§ 46.111 Criteria for IRB approval of research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

§ 46.111 Criteria for IRB approval of research.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

§ 46.111 Criteria for IRB approval of research.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116.

§ 46.111 Criteria for IRB approval of research.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.

§ 46.111 Criteria for IRB approval of research.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

§ 46.111 Criteria for IRB approval of research.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

§ 46.111 Criteria for IRB approval of research.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as **children**, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Subpart D

pediatric regulations

45CFR46, Final Rule, 1983 version

Subpart D…

- § 46.404 – Research not involving greater than minimal risk
- § 46.405…
- § 46.406…
- § 46.407…

45CFR46, Final Rule, 1983 version

Subpart D…

- § 46.404 …
- § 46.405 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- § 46.406…
- § 46.407…

45CFR46, Final Rule, 1983 version

Subpart D…

- § 46.404…
- § 46.405…
- § 46.406 - Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects disorder or condition
- § 46.407…

45CFR46, Final Rule, 1983 version

Subpart D…

- § 46.404…
- § 46.405…
- § 46.406…
- § 46.407- Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

§ 46.404

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that 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.

§ 46.405

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

§ 46.405

(a) The risk is justified by the anticipated benefit to the subjects;

(b) 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

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.406

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

§ 46.406

(a) The risk represents a minor increase over minimal risk;

(b) 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;

§ 46.406

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407

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 or welfare of children; and

§ 46.407

…(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,

§ 46.407

…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 …

Case Study #1: Interventional Trial in Pediatric Cardiovascular Surgery

Infants/newborns with complex congenital heart disease randomized to one two types of modifications to a palliative cardiac surgery.

Details:

- All eligible infants were scheduled to undergo the palliative (lifesaving) surgery.
- The randomization concerned modifying one part of the surgery.

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

- Diagnosis is fatal in the newborn period without surgical intervention
- Limited surgical interventions available:
  - Staged palliation
  - Heart transplant
- Mortality and morbidity still significant with staged surgical palliation: ~30% in first year of life

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

- First staged surgery has highest mortality
- New modification of surgery being done at some surgical centers with increased success
- True equipoise regarding superiority of new modification compared to standard procedure
  - Stage 1 Norwood with modified Blalock-Taussig shunt (MBTS)
  - Stage 1 Norwood with right ventricle to pulmonary artery shunt (RVPAS)

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

Additional details of study:

- Neurodevelopmental evaluation at 14 months of age, important for these subjects
- Genetic evaluation post first surgery and again at 14 months of age
- Collection of medical data up to 14 months of age; important for generalized knowledge

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

What are the benefits to the subject?

- Although one shunt may offer direct benefit, it is unknown
- What if some surgeons/clinical team are better at caring for subjects after one type of surgery compared to the other?
- Neurodevelopmental evaluation at 14 months of age: not all subjects will receive this benefit given high mortality in first year of life

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

How would you categorize this study?

- Greater than minimal risk?
- Greater than minimal risk but presenting prospect of direct benefit?
- Greater than minimal risk with no prospect for direct benefit, but likely to yield generalizable knowledge

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

Greater than minimal and no direct benefit:

- Minor increase over minimal risk?
- Intervention/procedure reasonably commensurate with actual or expected medical situation?
- Likely to yield generalized knowledge which is of vital importance to understanding condition?

Interventional Surgical Trial in Pediatric Cardiovascular Surgery

How would you approve this study?

- How are the risks minimized?
- Are the risk reasonable in relation to anticipated benefits and importance of knowledge?
  - What are the risks related only to research and not the underlying condition or procedure?

Case Study #2: Drug Trial Infants post Cardiovascular Surgery

Infants with complex congenital heart disease were randomized to receive drug or placebo up to 14 months of age.

- Subjects experience stunted somatic growth in first year of life
- Study drug thought to reduce work of the heart, reduce energy expenditure and promote somatic growth

Drug Trial in Infants post Cardiovascular Surgery

- Needed approval of cardiologist and surgeon prior to enrolling and randomizing
- Study drug clinically used in this patient population, but not standard of care
- Neonates/Infants enrolled and randomized within days of first palliative surgery
- Clinicians and parents blinded to randomization

Drug Trial in Infants post Cardiovascular Surgery

- Greater than minimal risk with potential for direct benefit
  - Benefit:
    - improved somatic growth and associated benefits
    - Neurodevelopment evaluation at 14 months of age
  - Risks:
    - safety labs required needle sticks
    - placebo group missing potential benefits of drug
    - Side effects of drug: hypotension, abnormal labs

Drug Trial in Infants post Cardiovascular Surgery

Patient/family considerations:

- Enrolling subjects in the newborn period post complex cardiac surgery
- Subjects experienced multiple adverse events related to cardiac surgery, cardiac diagnosis and potentially related to study drug
- Competition with other studies enrolling subjects

Case Study #3: Drug Trial in Subjects with Progressive Cardiac Disease

Children < 18 years of age with connective tissue disease were randomized to one of two drugs

Purpose: determine which drug better prevents progression of disease

- First arm: drug commonly used clinically
- Second arm: new drug with potential for better prevention of disease progression
- Subjects on study drug for 3 years

Drug Trial in Pediatric Subjects with Progressive Cardiac Disease

Greater than minimal risk with potential benefit

Other considerations:

- Subjects on drug for 3 years
- Some subjects reached 18 years during study and had to be consented
- Transfer of clinical care from local clinician to center conducting study

Case Study #4: Drug Trial in Pediatric Subjects during Cardiovascular Surgery

Children 18 months to 3 years of age undergoing palliative cardiac surgery were randomized to 1 of three treatment arms during and immediately after surgery:

- Patient population more vulnerable than others with congenital heart disease
- Drug under study may provide better protection of heart and kidneys during surgery

Drug Trial in Pediatric Subjects during Cardiovascular Surgery

Treatment arms:

- #1: commonly-used pediatric post-operative drug but no proof of efficacy in this patient population and potential for harm
- #2: new drug with potential to protect heart and kidneys during surgery, may be especially helpful to population under study
- #3: placebo

Drug Trial in Pediatric Subjects during Cardiovascular Surgery

Other considerations:

- fragile population
- Standard of care is not so standard
- Clinicians blinded to treatment assignment; challenges to bedside clinical care
- Placebo considerations

Questions?

Thank you!

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