Research Involving Minors

1 Introduction

For as long as people have been doing medical research with human subjects, children have been involved in one context or another. Only recently has either the medical community or society in general raised concerns regarding the rights and welfare of children as subjects in biomedical research.

By the end of this module you will be able to:

- Describe the major historical events that influenced how research with children as subjects is currently conducted.
- Identify problems with research involving children that may violate ethical standards.
- Understand the assent and informed consent requirements on different types of studies involving children.
- Understand the current efforts by the FDA to ensure the inclusion of children in studies on the safety and efficacy of new drugs.

2 Historical Events that have Influenced Research on Children

2.1 Early Medical Experiments

In the 18th century, a number of early "medical experiments" involved the immunization of children. They were deemed good subjects because they had no prior experience with the disease and they were convenient or in close proximity to the investigator. Edward Jenner tested the first smallpox vaccine on his own son, and then on 48 children in an almshouse. The orphans were then infected with smallpox to determine efficacy. Early American pediatrician Benjamin Waterhouse tested an initial shipment of vaccine by vaccinating his own children, then exposing 3 of them to smallpox patients.

The nineteenth century saw growth in a wide range of institutions for children (orphanages, foundling homes, hospitals), reflecting growing public concern for the welfare of children. As these institutions became more common, the health needs of institutionalized children encouraged pediatric experimentation, and these institutions provided ideal conditions for these experiments. Alfred Hess, the medical director of Hebrew Infant Asylum in New York, used his charges to conduct seminal experiments on the anatomy and physiology of digestion, on

pertussis, mumps, and varicella immunizations, and on nutritional deficiencies. He insisted that "conducting experiments in an asylum is ideal because it approximated the conditions insisted on in studying experimental infection in animals but which could rarely be controlled in a study of infection in man."

Some of these experiments were of benefit to the children involved. For example, Louis Pasteur conducted large scale tests of new diphtheria antitoxin in 1893-4 in children in Paris orphanages. Others were less beneficial or dangerous to children. Karl von Ruck tested a “TB vaccine” on 262 children in a Baptist orphanage in North Carolina. Experiments in guinea pigs (performed after the large scale human tests) subsequently showed that the “vaccine” increased the risk of developing TB.

2.2 Growing Concern

The latter half of the 19th century saw the rise of the Anti-vivisection movement. Primarily opposed to use of live animals for medical research, the movements also opposed medical experimentation in charity hospitals, and especially in the use of children as research subjects. The Antivivisectionist press exposed the Rockefeller Institute studies of lutein for the diagnosis of syphilis in 1912. Control subjects for these trials included 46 normal children between 2 and 8 years of age.

Between 1914 and 1920 Alfred Hess and Mildred Fish conducted studies on etiology of scurvy during which they withheld orange juice from institutionalized infants until they developed hemorrhages associated with scurvy. Similar studies performed to determine etiology of rickets. When the details of these studies became public, journalist and social reformer Konrad Bercovici wrote "no devotion to science, no thought of greater good to the greater number, can for an instant justify the experimenting on helpless infants, children pathetically abandoned by fate and entrusted to the community for their safeguarding. Voluntary consent by adults should, of course, be the *sine qua non* of scientific experimentation

2.3 National Research Act (1974)

Research excesses (including research on hepatitis using mentally retarded children at Willowbrook in the 1950s and 1960s) culminating in the exposé of the PHS syphilis experiments, led to the passage of the National Research Act in 1974.

The Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Among the charges of the commission was to "identify the requirements for informed consent to participation in biomedical or behavioral research by children." The Commission report on Research Involving Children was published in 1977, and largely

translated into regulations as 45 CFR 46 (subpart D), "Additional Protections for Children as Research Subjects."

2.4 National Commission Report and Federal Regulations

The National Commission report described a "sliding scale" for research involving children. Research was to be classified according to the risk and the direct benefit to the child. As the risk-benefit relationship of the research became less favorable, additional protections were to be imposed. These categories were translated into sections 45 CFR 46.404, 405, 406 and 407 of subpart D of the DHHS Regulations. Research involving minors must fit into one of these categories to be approvable by the IRB.

See Appendix for summary of National Commission's Analysis of Problematic Issues Involving Children as Research Subjects.

2.5 Assent and Permission in the Federal Regulations

For a child to participate in research, permission of one or both parents is required, and in most cases, assent of the child is also needed. "Assent" means a child's agreement to participate in research. Mere failure to object should not be construed as assent. However, not all children are capable of assent, due to their age, maturity, and psychological state. IRBs are responsible for making the decision when assent is an absolute requirement.

Waiver of consent or assent is also allowed, as per the requirements of 45 CFR 46.116(d). This only applies to studies approvable under 45 CFR 46.404, as will be seen below, since these studies involve no more than minimal risk to the subjects.

3 Categories of Allowable Research

3.1 Research involving no greater than minimal risk (46.404)

To be approvable under 45 CFR 46.404, research must present no more than minimal risk to the subject. Minimal risk is defined as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or routine medical or psychological examination, of healthy children." Note that minimal risk is weighed against a standard of the life of a healthy child.

3.1.1 Minimal risk procedures might include:

- Venipuncture, bagged urine collection.
- Chest radiograph.
- Psychological tests.
- Classroom observation.

No direct benefit to the child is needed for research to be approvable under 45 CFR 46.404. The permission of one parent and the assent of child are required.

4 Examples of research projects potentially approvable under 46.404 include:

- A study to determine the relationship between maternal age and head circumference at birth. Measurement of head circumference is part of the normal newborn examination, and is therefore minimal risk.

- A study to determine the incidence of asymptomatic proteinuria in school age children. The research involves the analysis of a voided urine collection, which is minimal risk.

4.1 Research involving greater than minimal risk but presenting the prospect of direct benefit (46.405)

Research that presents greater than minimal risk to the subject may be approvable under 45 CFR 46.405 if it holds the potential for direct personal benefit to the child. The benefit must balance or outweigh the risks, and the risk-benefit relationship must be at least as favorable as that seen with standard care. As in the previous section, the permission of one parent and the assent of the child are usually required. However, if the research holds out a prospect of direct benefit to the child which is not available outside the research, the consent of the parent is sufficient; that is, assent of the child, though desirable, is not an absolute requirement.

4.1.1 An example of a research project potentially approvable under 46.405 is:

A pilot study of a shorter duration of antibiotic treatment for uncomplicated otitis media. The potential benefit associated with the shorter duration of treatment is reduced cost, increased compliance, and a reduced rate of antibiotic related diarrhea. The risk associated with the shorter duration of therapy is a higher likelihood of treatment failure.

The risks associated with this research appear to be greater than minimal, but there is the prospect of direct benefit to the child (reduced cost, increased compliance, and a reduced rate of antibiotic related diarrhea). If the IRB decides that the potential benefits balance or outweigh the risks, and the risk-benefit relationship is as favorable as that seen with standard care, this research would be approvable under 46.405.

4.2 Research involving greater than minimal risk and no prospect for direct benefit (46.406)

Research involving greater than minimal risk and no prospect for direct benefit to the subject may be approvable under 45 CFR 46.406. Under this section, the risks associated with the research must satisfy certain specific criteria:

- The risks must be no more than a “minor increase” over minimal risk. No definition of “minor increase is provided in the Federal Regulations. According to the National Commission "…while [minor increase] goes beyond the boundaries of minimal risk, it poses no significant threat to the child’s health or well being." Interventions that might constitute a minor increase include:
    - Catheterized urine collection
    - Skin biopsy or bone marrow biopsy
    - MRI scan with sedation
    - Sensitive survey
- Risks must be commensurate with those inherent in the subject’s actual medical situation. According to the National Commission, "the requirement of commensurability of experience should assist children who can assent to make a knowledgeable decision about their participation in research, based on some familiarity with the procedure and it’s effects.. "
- The research must be likely to yield knowledge of vital importance about the child’s disease or condition.

To participate, the permission of both parents and the assent of the child are required.

4.2.1 An example of a research project potentially approvable under 46.406 is:

A study to determine the clinical relevance of a new technique to quantitate minimal residual disease (MRD) during therapy for acute lymphoblastic leukemia in children. The study requires one additional bone marrow aspirate be performed during the course of treatment. Therapy for the subject will not be altered based on the results of the assay. However, if it can be shown that the presence of MRD predicts poor outcome, in the future, patients with MRD can receive more intensive treatment and increase their chance of cure.

It can be argued that the risk of a bone marrow aspirate in a normal child is only a minor increase over minimal risk. Further, the risk appears commensurate with risks inherent in the subject’s actual medical situation, and the research may yield knowledge of vital importance about the child’s disease (leukemia). Therefore, this research may be approvable under 46.406.

4.3 Research otherwise not approvable (46.407)

Research not approvable under any of the previous sections, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children, may still be approvable. The research must be reviewed by a panel of experts appointed by the Secretary of DHHS. The research must be conducted in accordance with sound ethical principles. The assent of subjects and permission of parents must be obtained.

4.4 Inclusions of Wards (e.g., Foster Children)

Remembering the exploitation of orphans as subjects of medical research, the National Commission also specifically addressed the inclusion of wards of the state. They noted that it is important to "learn about the effects of the settings in which children who are wards of the state may be placed … in order to improve the care that is provided for such children." Further, they thought it important to avoid embarrassing these children by excluding them from research in which their peers in a school, camp or other group setting might be participating. To these ends, the commission notes that the IRB should "evaluate the reasons for including wards of the state as research subjects and assure that such children are not the sole participants in a research project unless the research is related to their status as orphans, abandoned children, and the like."

45 CFR 46.409, reflecting the National Commission report, restricts the involvement of wards in research that is greater than minimal risk and without direct subject benefit (research approvable under 46.406). Wards may only be enrolled in such research if the research is related to their status as wards, or is conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. Further, the regulations require that each child have an advocate appointed who has the background and experience to act in, and agrees to act in, the best interests of the child, and who is not associated in any way with the research, the investigators, or the guardian organization. It is important to note that the IRB has the responsibility to appoint the guardian and not the investigator.

5 Other Guidelines on the Inclusion of Children in Research Involving Human Subjects

5.1 NIH Guidelines

Although the adoption of subpart D marked a high point in the protection of children, there were concerns that children would also be denied the potential benefits of medical research. In 1977 the American Academy of Pediatrics agreed that children capable of providing assent have the right to refuse research participation. However, the Academy also pointed out that exclusion of children

from drug studies was more unethical than clinical testing, and could lead to devastating results.

The antibiotic chloramphenicol was released in the 1950s without adequate testing in infants and children. As use of the drug became more common, reports of a serious and often fatal reaction called the Grey Baby Syndrome surfaced. This reaction was related to slow clearance of the drug in infants as compared to adults, due to deficiency in hepatic glucuronyl transferase in infants. Similarly, though less devastating, widespread use of tetracycline in children was subsequently shown to be associated with dental dysplasia.

Nonetheless, children continued to be excluded from drug testing. A survey of the 1991 Physician's Desk Reference showed that 81% of listed drugs contained language disclaiming use in children or restricting use to certain age groups.

In March 1998, the NIH published Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, to answer some of these concerns. The guidelines state "... children must be included in all human subjects research conducted or supported by the NIH unless there are scientific or ethical reasons not to include them". Possible justifications for the exclusion of children from NIH Funded studies include:

- The research topic is irrelevant to children.
- Knowledge sought is already available in children or will be obtained from another ongoing study.
- A separate age-specific study is warranted and preferable, or
- Insufficient data are available in adults to determine potential risks in children.

In addition, the NIH Guidelines state that "inclusion of children must be in compliance with all applicable subparts of 45 CFR 46"

For more details see NIH Policy and Guidelines on the Inclusion of Children as Participant in Research involving Human Subjects

5.2 FDA Guidance and Regulation

In 2001, in response to the Children's Health Act of 2000, the FDA adopted Additional Protections for Children in Clinical Investigations (21 CFR 50 subpart D). These regulations are largely equivalent to the HHS regulations at 45 CFR 46 subpart D.

The FDA has also attempted to answer concerns regarding the exclusion of children, by taking a “carrot and stick” approach. The Best Pharmaceuticals for Children Act (2002) extends marketing exclusivity for pharmaceutical companies

who test new drugs in children. The Pediatric Research Equity Act (2004) enables FDA to require testing of drugs for pediatric use.

6 Summary

Early medical experiments involving children, especially institutionalized children, lacked sound ethical research practices. Growing public concern over the exploitation of children led to movements aimed at protecting the rights of children and resulted in the establishment of ethical standards and federal regulation. The National Research Act for the Protection of Human Subjects in Biomedical and Behavioral Research established the National Commission. The National Commission Report provides a “sliding scale” classifying research according to the risk and the direct benefit to the child, and provides the requirements for assent and informed consent for participation in research involving children. Specific requirements are:

6.1 Research involving no greater than minimal risk (46.404) requires the permission of one parent and the assent of the child

6.2 Research involving greater than minimal risk but presenting the prospect of direct benefit (46.405) requires:

- The benefit must balance or outweigh the risks.
- The risk-benefit relationship must be at least as favorable as that seen with standard care.
- Permission of one parent.
- Assent of the child, unless the research holds out a prospect of direct benefit to the child which is not available outside the research.

6.3 Research involving greater than minimal risk and no prospect for direct benefit (46.406) requires:

- The risk is only a minor increase over minimal risk.
- The risks are commensurate.
- The research will likely yield knowledge of vital importance.
- Permission of both parents.
- Assent of the child.