Research Involving Children

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Introduction

The history of research with human subjects includes medical experimentation on children. That history has greatly influenced the research that is now permitted to include children. This module presents an overview of the historical involvement of children in biomedical research, as well as the development of 45 CFR 46, Subpart D. A discussion of the permitted research, with examples, provides a detailed review for biomedical researchers who are, or will be, conducting research with children. Additionally, National Institutes of Health (NIH) guidelines, as well as U.S. Food and Drug Administration (FDA) guidance and regulation are included.

Learning Objectives

By the end of this module, you should be able to:

- Describe the major historical events that influenced how research with children as subjects is currently conducted.
- Identify the types of research with children permitted under 45 CFR 46, Subpart D.
- Discuss the assent and informed consent requirements on different types of studies involving children.
- Recognize the current efforts by the FDA to ensure the inclusion of children in studies on the safety and efficacy of new drugs.

Historical Events That Have Influenced Research on Children

Early Medical Experiments

Research Involving Children

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 were convenient or in close proximity to the researcher. Edward Jenner tested his theory that prior cowpox infection would protect against smallpox by inoculating an 8-year-old boy with matter from a cowpox lesion, then subsequently deliberately exposing him to smallpox. Early American pediatrician Benjamin Waterhouse tested an initial shipment of vaccine by vaccinating his own children, then exposing three of them to smallpox patients. He subsequently commissioned a controlled trial in which 19 vaccinated and two unvaccinated boys were exposed to smallpox, in order to determine the vaccine's efficacy.

The 19th century saw growth in a wide range of organizations for children (such as, orphanages, foundling homes, and hospitals), reflecting growing public concern for the welfare of children. As these organizations became more common, the health needs of institutionalized children encouraged pediatric experimentation, and these organizations 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
- Pertussis, mumps, and varicella immunizations
- Nutritional deficiencies

Hess (1914, 913-6) insisted, "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, in 1893-4 Louis Pasteur conducted large-scale tests of new diphtheria 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.

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 movement also opposed medical experimentation in charity hospitals, and especially in the use of children as research subjects. The Antivivisectionist press exposed the Rockefeller Institute's studies of lutein for the diagnosis of syphilis in 1912. Control subjects for these trials included 46 normal children between two and eight 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 were performed to determine etiology of rickets. When the details of these studies became public, journalist and social reformer Konrad Bercovici (quoted in AHRP 2016) 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.

National Research Act (1974)

Research excesses (including research on hepatitis using children with intellectual and developmental disabilities at Willowbrook in the 1950s and 1960s) culminating in the exposé of the U.S. Public Health Service (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 (The National Commission). Among the charges of the National Commission was to "identify the requirements for informed consent to participation in biomedical or behavioral research by children" (National Research Act 1974). The National Commission's report on research involving children was published in 1977, and largely translated into the regulations at 45 CFR 46, Subpart D - Additional Protections for Children as Research Subjects.

National Commission Report and Federal Regulations

The National Commission's 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 research's risk-benefit relationship became less favorable, additional protections were to be imposed. These categories were translated into 45 CFR 46.404-7. Research involving minors must fit into one of these categories to be approvable by the Institutional Review Board (IRB).

Review a summary of *National Commission's Analysis of Problematic Issues Involving Children as Research Subjects*.

Regulations and Guidance

Definition of Children

Children are "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" (Protection of Human Subjects 2009).

Assent and Permission in the Federal Regulations and Guidance

For a child to participate in research, permission of one or both parents is required, and in most cases, the child's assent 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 or alteration 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, because these studies involve no more than minimal risk to the subjects.

Categories of Allowable Research

Research Involving No Greater Than Minimal Risk

To be approvable under 45 CFR 46.404 (Protection of Human Subjects 2009), research must present no more than minimal risk to the subject. 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

Examples of Minimal Risk Procedures

- 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.

Note: While a procedure may be minimal risk, it may not necessarily be approvable by the IRB via expedited procedure. Conversely, it should not be assumed that a procedure listed in the expedited categories is automatically minimal risk.

Examples of Research Projects Potentially Approvable Under 45 CFR 46.404

- 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.

Research Involving Greater Than Minimal Risk But Presenting the Prospect of Direct Benefit

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.

Example of A Research Project Potentially Approvable Under 45 CFR 46.405

An example 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 45 CFR 46.405.

Research Involving Greater Than Minimal Risk and No Prospect for Direct Benefit

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 (1977, 139-40), "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 (1977, 9):

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 its effects.

- The research must be likely to yield knowledge of vital importance about the child's disease or condition.

Example of A Research Project Potentially Approvable Under 45 CFR 46.406

An example 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 45 CFR 46.406.

Research Otherwise Not Approvable

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 under 45 CFR 46.407. A panel of experts appointed by the Secretary of HHS must review the research. The research must be conducted in accordance with sound ethical principles.

Inclusions of Wards

Remembering the exploitation of orphans as medical research subjects, the National Commission (1977) 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" (The National Commission 1977, 139-40). Further, they found 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 National Commission (1977, 20) 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 (Protection of Human Subjects 2009), 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 45 CFR 46.406); or
- Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (research approvable under 45 CFR 46.407).

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, organizations, 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, researchers, or guardian organization. It is important to note that it is the IRB's responsibility to appoint the guardian and not the researcher.

Who Provides Permission?
(Per 45 CFR 46.408 [Protection of Human Subjects 2009])

Category	Parental Permission
45 CFR 46.404	At least one parent*
45 CFR 46.405	At least one parent*
45 CFR 46.406	Both parents**
45 CFR 46.407	Both parents**

* The IRB may find that permission of one parent is sufficient.

** Research falling under 46.406-7 requires permission to be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Note: The IRB shall determine that adequate provisions are made for soliciting the child's assent, when in the IRB's judgment the child is capable of providing assent. The child's assent is not a necessary condition for proceeding with the research if the IRB determines that:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child (45 CFR 46.405 [Protection of Human Subjects 2009]) and is available only in the context of the research.

Vulnerable Subjects - Research Involving Children

Dr. Berry, an internist, and Dr. Smith, a sports medicine specialist, are developing a research plan in which children 8 to 12 years of age with mild asthma are asked to walk on a treadmill at an easy pace while wearing a loose-fitting mask to measure oxygen consumption. The premise is that this test might help predict which children with "mild asthma" are at risk for exacerbation of their symptoms during exercise.

At the IRB meeting, the pediatrician says, "This research involves minimal risk because normal children walk, and the risks of wearing the mask are no more than those encountered in daily life of a normal child." The pulmonologist states, "This is greater than minimal risk because no normal child wears a mask, but there is benefit because the child's oxygen consumption is being measured." The social worker argues, "it is a bit more than minimal risk and there is no direct benefit, although the research will provide vital information about the child's asthma status." Helen, a fourth year medical student, is curious about the IRB and observing the meeting.

- What information would help Helen better understand the IRB members' discussion about the risk involved in this research?

Helen could refer to the federal regulations, which state "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" (Protection of Human Subjects 2009). For further reading, she could consult the Secretary's Advisory Committee on Human Research Protections (SACHRP 2005) recommendation of using the concept of equivalence of risk. The report states:

> Research procedures involving children can be approved as minimal risk if the probability and magnitude of harm are equivalent to risks of daily life or routine examinations with respect to duration, cumulative characteristics, and reversibility of harm.

After considering this information, Helen may also come to the conclusion that this research involves minimal risk, because normal children walk, and the mask's risks are no more than those encountered in a normal child's daily life.

- The IRB determines that the research involves no greater than minimal risk. Now Helen wonders who must give consent for the child to participate - the child, the parent, or both?

Both. The parent must give permission and the child must provide assent.

Parents do not give consent; they give permission. Permission means the parents' agreement to the participation of their child in research. As allowed by the federal regulations, research posing no more than minimal risk to the child requires the permission of one parent; however, the IRB may require both parents to give permission if it believes that this additional requirement will provide meaningful additional protection for the child. The federal regulations dictate that other types of research involving more than minimal risk and no prospect of direct benefit to the child require the permission of both parents.

Children do not give consent; they give assent. Assent means a child's affirmative agreement to participate in research. Merely failing to object should not be construed as assent. Researchers must obtain assent from all children; however, there are limited circumstances when assent from a child, or all the children, is not necessary. Assent is not required if the capability of some or all of the children is so limited that they cannot reasonably be consulted (for example, infants or developmentally delayed children). Assent is also not needed if the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. The requirement for assent is not based on the research's risk level.

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

NIH Guidelines

Although the adoption of 45 CFR 46, 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 (AAP) agreed that children capable of providing assent have the right to refuse research participation. However, the AAP 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 percent 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 (NIH 1998). Possible justifications for the exclusion of children from NIH-funded studies include:

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

In addition, the NIH (1998) guidelines state, "inclusion of children must be in compliance with all applicable subparts of 45 CFR 46." In October 2015, the NIH (2015) published an update to the definition of the age of children from under 21 to 18 years old.

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). In 2013, the FDA issued a **final rule** formally amending its regulations. It should be noted that while the FDA regulations are largely equivalent to 45 CFR 46, Subpart D, some differences exist with respect to the waiver of consent. Specifically, the FDA regulation does not allow waiver of parental permission except in emergency research in keeping with 21 CFR 50.23 and 50.24. However, FDA (2017) issued guidance that states it will not object when IRBs approve a waiver or alteration of consent for clinical investigations involving no more than minimal risk to subjects if certain criteria are met and documented. The FDA also stated that they plan to revise the regulation to include the waiver and alteration of informed consent for no more than minimal risk research in the future.

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.

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 regulations. The National Research Act established the National Commission. The National Commission's 1977 report on research involving children 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 include:

- Research involving no greater than minimal risk requires the permission of one parent and the child's assent.
- Research involving greater than minimal risk but presenting the prospect of direct benefit requires:
    - The benefit must balance or outweigh the risks of harm.
    - The risk-benefit relationship must be at least as favorable as that seen with standard care.
    - Permission of one parent and assent of the child.
    - Assent of the child, unless the research holds out a prospect of direct benefit to the child, which is not available outside the research.
- Research involving greater than minimal risk and no prospect for direct benefit requires:
    - The risk is only a minor increase over minimal risk.
    - The risks of harm are commensurate.
    - The research will likely yield knowledge of vital importance.
    - Permission of both parents (unless the exceptions noted apply)
    - Assent of the child.

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Additional Resources

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