

## MODULE ONE: The History and Ethics of the Protection of Human Participants in Research

The current system for the protection of the human participants in research dates from the work of The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, established in 1974 in response to the revelation of researcher misconduct in such trials as the [Public Health Service Study of Untreated Syphilis in Black Males conducted at the Tuskegee Institute](#). The charge to the National Commission was to identify the basic ethical principles that underlie the conduct of human research and to develop guidelines to assure that human research is conducted in accordance with those principles.

Meeting monthly for four years, the National Commission produced several reports, two of which are of particular interest to pediatric researchers. [The Belmont Report](#) (1979), named after the conference center at which the Commission deliberated, outlined the ethical principles which serve as the moral foundation for our system of protections for human research participants. The Report and [Recommendations: Research Involving Children](#), published in 1977, established the important concepts of minimal risk, parental permission and child assent that are central to the additional protections afforded children who participate in research. Before we consider the moral framework established by the National Commission, it is so important to understand some of the historical background leading up to the Commission's establishment.

In December of 1946, 23 leading [German physicians and administrators](#) were put on trial for their willing participation in the systematic killing of those deemed "unworthy of life" and the performance of crippling and deadly medical experiments on thousands of concentration camp prisoners. After an eight-month trial, 16 of the 23 physicians were found guilty and the other 7 were sentenced to death and subsequently executed. Many of the German physicians argued in their defense that the experiments were morally justified since the participants were going to die anyway and through their sacrifice would provide scientific knowledge benefiting many. Concerned about this argument, Dr. Leo Alexander drafted a memorandum to the judge which outlined six points as criteria for legitimate research. The judge's verdict in August 1947 included a section called "Permissible Medical Experiments" which adapted and expanded Dr. Alexander's memorandum into the 10 points that became known as the ["Nuremberg Code."](#) The first principle states that "a voluntary consent of the human subject is absolutely essential." The Code further established that animal experimentation should precede human experimentation; all unnecessary physical and mental suffering and injury should be avoided; the degree of risk to the participants should never exceed the "humanitarian importance of the problem" and should be minimized through "proper preparations"; and that the participants should always be at liberty to withdraw from the experiments. Although never adopted into either American or German law, the Nuremberg Code informed and continues to inform numerous international ethics statements. In effect, the Nuremberg Code serves as the first systematic statement of the professional ethic of medical researchers.

The [World Medical Association](#) adapted the Nuremberg Code to the needs of the biomedical community, producing the first version of the [Declaration of Helsinki](#) in 1964. The major change in the initial version was to allow for surrogate consent when informed consent could not be obtained, either because of physical or mental incapacity, or in the case of a minor child. The Declaration of Helsinki has been revised four additional times, most recently in 1996. Included among the 31 principles is a requirement for the experimental protocol to be reviewed by a "specially-appointed committee independent of the investigator and the sponsor." The Declaration also makes a distinction between research "in which the aim is essentially diagnostic or therapeutic for a

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patient" and research "which is purely scientific." In medical research which is either diagnostic or therapeutic, "every patient - including those of the control group, if any - should be assured of the best proven diagnostic and therapeutic method." This stipulation has been controversial. Some interpreters believe that a placebo should never be used whenever effective therapy is available, regardless of the seriousness of the condition being studied. Others use this stipulation to argue that international trials should be conducted with a uniform standard of medical care, effectively excluding a placebo-controlled trial of low-dose AZT for the prevention of perinatally-transmitted HIV infection. In research which does not offer the prospect of direct benefit to the participant, the Declaration of Helsinki restricts such research to volunteers who are either healthy or "for whom the experimental design is not related to the patient illness." In addition, the "life and health of that person" should take precedence over the successful completion of the research. The Declaration also advocates that research which was not performed "in accordance with [these] principles... should not be accepted for publication."

The World Medical Association is currently [revising the Declaration of Helsinki](#) for a fifth time, since much research that is considered acceptable (such as the use of placebo controls in trials of nonserious conditions, and basic research which offers no benefit yet poses minimal risk) is inconsistent with the current Declaration. Nevertheless, the Declaration of Helsinki is the international standard for the conduct of clinical research. Investigators are increasingly being asked to sign a document that affirms compliance with the ["Good Clinical Practice" standards](#), as developed by the [International Conference on Harmonization](#) and adopted as a guidance for clinical research in Japan, the United States and the European Union. These standards specifically states that the research will be conducted in a manner consistent with the ethical principles of the Declaration of Helsinki. The standards for "Good Clinical Practice" are discussed in the fourth module of this training program.

An article published by [Henry K. Beecher](#) in 1966 in the *New England Journal of Medicine* shattered the perception that unethical research was not happening in the United States. Examples included: a placebo-controlled trial of the use of penicillin in treating streptococcal infections (in spite of known evidence of the effectiveness of penicillin); a double-blind study to further define the known hematologic toxicity of chloramphenicol, comparing two grams versus six grams of chloramphenicol per day in randomly chosen patients; and the induction of cardiac arrhythmias using carbon dioxide while under cyclopropane anesthesia. In addition to the inappropriate risk exposure and questionable scientific design, there was no documentation of consent. In 1971, a randomized, placebo-controlled crossover study to determine the side effects of oral contraceptives was performed in a number of Mexican-American women who came to a Texas clinic looking for contraception. The women were not told that they were involved in the study, nor that they were at risk for receiving a placebo. Eleven women in the control group became pregnant, versus 1 in the study group. Perhaps the most notorious example of a study involving the deception of a targeted vulnerable group is the long-term study of untreated syphilis in Negro males conducted [at Tuskegee by the United States Public Health Service](#). Started in 1932 as a study of the natural history of untreated syphilis, the study continued until 1970, in spite of the wide availability of penicillin after 1951 and review by a local ethics committee after 1966. The men involved thought that they were receiving treatment for "bad blood" and were not warned of the risk of ongoing sexual activity. Hardly conducted in secret, the results were published widely in the medical literature over several decades, and included 28 deaths, 100 cases of disability, and 19 cases of congenital syphilis. Among the

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ethical problems identified were the absence of informed consent, deception (such as being told that nontherapeutic spinal taps were "treatment"), promising a "burial benefit" to assure continued participation, withholding effective treatment, the lack of effective oversight, and targeting a vulnerable population. The public outrage when this study became widely publicized led directly to the formation of the National Commission (June 1974) and the initial publication of 45 Code of Federal Regulations 46 by the Department Of Health Education and Welfare (May 1974). The regulations continue in revised form to govern the review and performance of clinical research supported by the Department Of Health and Human Services.

Children, especially institutionalized children with mental retardation, were not exempt from possible exploitation. In a series of studies carried out at the [Willowbrook State School](#) in New York from 1955 through the early 1970s, newly-admitted mentally retarded children were deliberately infected with hepatitis in order to study the natural history of the disease under controlled circumstances. The research was justified, according to the investigators, since the children would eventually contract hepatitis anyway given the crowded and unsanitary conditions, and only children whose parents consented were included. However, parents consented when they received a letter offering admission to the special study unit shortly after receiving notification of being placed on a waiting list because of the crowded conditions. Other criticisms included the failure to enlist adult staff in the research in spite of a similar risk of hepatitis, the withholding of other treatments such as gammaglobulin, and the failure to advocate for other infection control measures within the general population. In a report published in 1995, the [Advisory Committee on Human Radiation Experiments \(ACHRE\)](#) examined 21 nontherapeutic studies using radioisotopes administered to children either conducted or funded by the federal government during the 30 years prior to 1974. Two such studies were performed in 1946 and again between 1950 and 1953 at the [Walter E. Fernald School](#) located outside Boston. The first study exposed 17 children to radioactive iron, the second exposed 57 children to radioactive calcium in a series of related experiments. Letters addressed to parents dated November 1949 and May 1953 failed to mention any risks associated with the research, nor the use of radioactive isotopes. Both letters implied that the research was intended for the child's benefit - an assertion which is false. The children who were enrolled "voluntarily" into the studies were members of a so-called science club, who were provided with special privileges in exchange for their participation. The ACHRE report concluded that, regardless of limited risk exposure, the children at Fernald were wronged by inadequate attention to parental permission and the lack of meaningful assent by the children - both made possible by their vulnerability and lack of social privilege.

[The Belmont Report](#), published in 1979, continues to serve as the ethical foundation for the practice and regulation of clinical research. The report first distinguishes between medical practice and research in order to "know what activities ought to undergo review for the protection of human subjects of research." This distinction is difficult to make at times, given that research often includes medical treatment and innovative "departures from standard practice" are often called "experimental." The Commission points out that therapeutic interventions are intended to benefit an individual patient with a reasonable hope of success, while research seeks to develop "generalizable knowledge" through the systematic collection of information according to a formal protocol. Although innovative medical or surgical practice is not necessarily research, the Commission recommended that such innovations should "be made the object of formal research at an early stage in order to determine whether they are safe and effective." The distinction between medical practice

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and research, however difficult to make, establishes the responsibility of the clinical investigator to submit research activity for review by the Institutional Review Board (discussed in Module two). Reflecting the discussion by the National Commission, current regulations define research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" ([45CFR46.102\(d\)](#)). Various criteria have been proposed to distinguish medical practice from research, such as the intent to publish or the use of research techniques such as randomization. The judgment as to whether a given activity constitutes research is often complex and contextual, and may require consultation with the Institutional Review Board. The National Commission then went on to discuss the three ethical principles that should "guide the resolution of ethical problems arising from research involving human subjects"; that is, respect for persons, beneficence and justice.

The principle of "respect for persons" includes the moral conviction "that individuals should be treated as autonomous agents" and "that persons with diminished autonomy are entitled to protection." We show respect for others by giving weight to their "considered opinions and choices," allowing them the freedom to act on these "considered judgments" and providing them with the information necessary to make these judgments. Clearly, respect for persons requires seeking the informed consent of an individual to participate in research. Although the detailed requirements for informed consent will be discussed in Module two, the National Commission identified three elements to informed consent; that is, sufficient information for the "reasonable volunteer" to evaluate the research, the presentation of this information so that the potential volunteer can comprehend and make an informed choice, and conditions that are "free of coercion and undue influence." The Belmont Report incorporates under the principle of "respect for persons" the requirement to protect those persons with "diminished autonomy." As a result, there are special protections in the federal regulations for the involvement of prisoners ([Subpart C of 45 CFR 46](#)) and children ([Subpart D of 45 CFR 46](#)) in research. Anticipating the specific requirements for research involving children (discussed in Module two), The Belmont Report argues that respect for children (and others with limited capacity) requires "giving them the opportunity to choose to the extent they are able," honoring their dissent unless the research provides an otherwise unavailable therapy, and seeking parental permission "in order to protect the subjects from harm." As in the clinical setting, the parents and/or legal guardian should "act in that person's best interest." Thus, the principle of "respect for persons" serves as the moral foundation for the procedural requirements of informed consent, assent and permission.

The principle of "beneficence" is understood as an obligation to act in accordance with the participant's "well-being" through avoiding harm, maximizing "possible benefits" and minimizing "possible harms." The Belmont Report recognizes that learning what may benefit patients through research may require exposing other persons to risks. "Avoiding harm requires learning what is harmful." Thus, the obligation to the beneficence requires both the "maximization of benefits and the reduction of risk." The application of the principle of beneficence includes proper research design, evaluating the competence of investigators to minimize risk, and determining that the research provides a favorable balance of risk and benefit. An assessment of risks and benefits includes both the probability and the severity of the possible harm and anticipated benefits. The National Commission recognized that this assessment includes psychological, physical, legal, social, and economic harm and the corresponding benefits. Also, "risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at

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large." Thus, the principle of beneficence requires both the "determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk." Although the clear disclosure of possible harm and anticipated benefits of participating in the research is a necessary condition, it is not sufficient to establish that the research should proceed. A favorable assessment of the risk and benefit of the research is also required, especially when the research either involves "significant risk of serious impairment" or "vulnerable populations."

The principle of "justice," in the sense of "fairness in distribution" or "what is deserved," requires us to ask about who receives the benefits of research and bears its burdens. It is inappropriate to select certain research participants "simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied." The principle of justice is thus reflected in the regulations that require research using prisoners to be directed either toward their "health or well-being" or to "conditions particularly affecting prisoners as a class" [45 CFR 46.306 (a)(2)]. Similarly, for research involving children that presents greater than minimal risk and does not offer the prospect of direct benefit, the risk can only be a "minor increase over minimal risk" and the research should be "likely to yield generalizable knowledge about the subject's disorder which is of vital importance" [45 CFR 46.406 (c)]. The principle of justice also requires that a person not be denied a benefit to which they are otherwise entitled without good reason. The National Commission recognized that the benefits of publicly-funded research should be available to all. Nearly two decades later, the National Institutes Of Health now requires grant applications to address the appropriate inclusion of both women and children in publicly-funded research as a condition of receiving grant support.

The three ethical principles of respect for persons, beneficence and justice thus serve as the moral foundation for the review and conduct of clinical research involving human participants. Beneficence requires an examination of the experimental design, and evaluation of the risk and benefit of the research, minimization of the risks of research participation, and the qualifications of the principal investigator. Justice requires attention to participant recruitment, the equitable distribution of the burdens and benefits of research, and the inclusion and exclusion criteria for selecting participants. Respect for persons requires attention to informed consent (information, comprehension, and voluntariness), surrogate permission, assent, maximization of choice, protection of privacy and confidentiality, and the protection of vulnerable populations. Finally, an Institutional Review Board must determine whether or not a clinical trial is justified based on whether there is genuine uncertainty among the expert medical community about the comparative therapeutic merits of each arm of a clinical trial. This condition has been called a state of "clinical equipoise." Although there is debate about the necessity of "clinical equipoise" as an ethical condition for all clinical research, there is general agreement that it is necessary when the possible outcomes include either serious disability or death, or when there is no readily available "rescue" from an adverse outcome.

In the report on Research Involving Children, the National Commission discussed the controversial question of whether parents could choose to enroll their child in research that did not offer any direct benefit for the child. Recognizing that parental discretion properly operates to balance the risks and benefits of everyday life, the National Commission sought to create a research environment which resembles this everyday context and to specify, through the definition of "minimal risk," the limits of parental authority in permitting the child to

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participate in nonbeneficial research. The National Commission defined "minimal risk" as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children." The category of minimal risk thus plays a central role in the ethical justification of research involving children that does not offer the prospect of direct benefit (45 CFR 46.404 and 406). The definition of minimal risk found in 45 CFR 46 omits the phrase "of healthy children" and thus creates an ambiguity as to whether minimal risk should be indexed to a healthy child or to the life of the particular child being considered for research participation. Either interpretation is consistent with existing federal regulations, although many argue on ethical grounds that minimal risk should be indexed to healthy children. Largely on pragmatic grounds, the National Commission decided to permit nonbeneficial research involving greater than minimal risk if the research investigated the child's "disorder or condition" and the research involved only a "minor increase" over minimal risk (45 CFR 46.406). Finally, the National Commission adopted the language of parental permission, rather than consent, and of the child's assent or dissent, as part of the informed consent process leading up to a child's participation in research. The concepts of permission and assent apply the principle of respect for persons to children. Together, the provisions for parental permission and child assent show "respect for the general prerogatives of parents in protecting the health and safety of their children and respect for the maturing autonomy of the child."

Before proceeding with the rest of the training modules, we should ask "why are we here?" The Belmont Report was written in 1979, and the current regulations governing research were in place in the early 1980s. Willowbrook and the Public Health Service study at Tuskegee are well behind us. However, a number of recent events suggest a need to refocus our attention on the protection of the human participants and the proper conduct of research. A few illustrations will suffice. On March 31st, 1996, a 19-year-old Asian-American undergraduate student at the University of Rochester agreed to participate in a bronchoscopy procedure whose purpose was to harvest alveolar macrophages for basic science research. The procedure was difficult and the participant required numerous doses of topical lidocaine to tolerate the procedure. Understanding the importance of informed consent, the investigators repeatedly asked her if she wanted to continue, and she nodded yes. The procedure was finally completed and the participant sent home only to return in cardiac arrest several hours later. She was found to have a highly toxic blood level of lidocaine. She died on April 2, 1996. An investigation performed by New York State and the Office for Protection from Research Risks (now the Office for Human Research Protections or OHRP) found that the protocol did not limit the lidocaine dose, the lidocaine dose was not documented, there was no period of observation after bronchoscopy, and the lidocaine concentrations were increased without IRB approval.

Informed consent is not a substitute for the responsibility of an investigator to protect a research participant by stopping the study if the research procedures are not tolerated. An article published in *Plastic and Reconstructive Surgery* in 1998 reported the results of a prospective study comparing a deep and superficial approach to the performance of face-lift surgery. To resolve a disagreement about the merits of two accepted surgical techniques, the surgeons decided to perform a face lift using one approach on one side and the other approach on the opposite side of the same patient's face. The patients were simply told that two surgeons would be performing the procedure. The surgeons did not seek IRB review, believing it was not necessary since both procedures were widely accepted. Finally, in remarks to the

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Association of American Medical Colleges on May 11, 2000, [Dr. Jane Henney, Commissioner, U.S. Food and Drug Administration](#), stated:

"What we have witnessed-esoteric or complex standards have not been the issue, but rather the most basic elements of what it takes to properly conduct clinical studies. Enrollment of patients who did not meet the eligibility criteria for the study; Failure to report adverse events as required; Failure to ensure that a protocol was followed; Inadequate training for study staff; Investigators changing protocols without proper notice to the IRB and to FDA; Failure to incorporate agreed-upon protocol changes; Failure to revise informed consent forms as requested by FDA; Inadequate record keeping and informed consent documentation; Failure to notify FDA of animal deaths that suggest an increased risk to humans; and Conflict of interest issues for both investigators and institutions. I would underscore, these are not isolated incidents occurring on the fringes of science or by physicians with no academic credentials. We have found these problems in some of the most renowned research centers in the country and these unacceptable practices by leaders in their fields of study."

The ability to conduct research using human participants is a privilege granted to us by society for the advancement of knowledge and the bettering of the human condition. This privilege is predicated upon trust - a trust which is threatened by reports of unethical and/or thoughtless research practices. Our commitment should be to the highest ethical and procedural standards of professional research conduct, and to earning and maintaining the trust of those who participate in research.