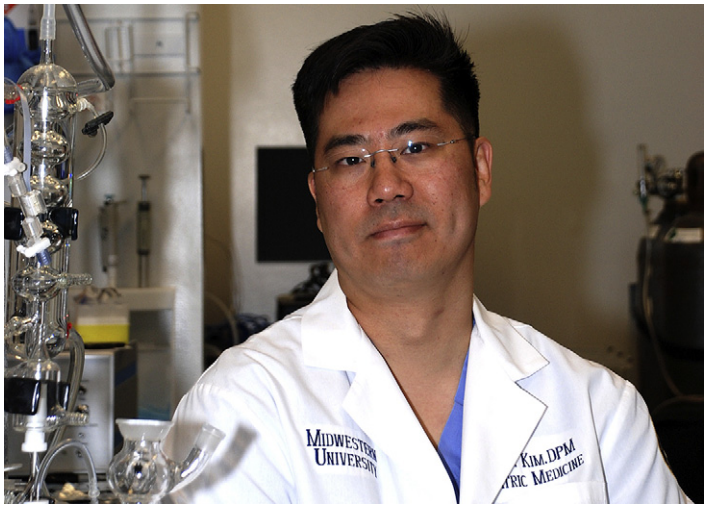
Editorial

Human Subject Protection: Overkill?



Conducting clinical research can be an arduous and complicated process. The investigator is under constraints of budget, time, and other pressures that can delay the process involved in its execution and completion. This is especially true in clinical trials owing to safety concerns regarding the use of human subjects. For example, it takes an estimated $1 billion and more than 7 years to bring a new drug to market (1). Human subject protection can play a major role in the increase in costs and delay in time in performing clinical research.

There are multiple safeguards built into the clinical research system that protect human subjects. Paul Lietman, MD, PhD says, "As long as you promise not to learn anything from what you are doing, you don't have to go through the IRB" (2). This revealing quote reflects the frustration from the clinical research community regarding these safeguards that often add to the overwhelming complexity involved in conducting research. These safeguards include components such as institutional review boards (IRBs), data safety monitoring committees, individual institutional policies, and government rules and regulations. The clinical researcher is tasked to precisely navigate through this maze to conduct his or her clinical research. Is this often-cumbersome process really necessary? To answer this question, we need to look back into the sordid history of research in medicine and the pivotal events that shaped our current clinical research system.

Celsus wrote in the first century, "It is not cruel to inflict on a few criminals sufferings for which may benefit multitudes of innocent people through all centuries" (3). This attitude was pervasive through much of ancient medicine and research where unwanted members of society were used for medical experimentation. Substantive changes began in the early 1800s with the adoption of a more paternalistic attitude of "do no harm." Claude Bernard (1813–1878) wrote, "The principle for medical and surgical morality…consists in never performing on man an experiment which might be harmful to him to any extent, even though the results might be highly advantageous to science, i.e., to the health of others" (4). Despite the changing attitudes, the respect for personal rights for subjects in experimentation was not fully adopted. In fact, in 1847 the American Medical Association (AMA) code of ethics included the statement, "The obedience of a patient to the prescriptions of his physicians should be prompt and implicit. He should never permit his own crude opinions as to their fitness to influence his attention to them" (5). This statement reflects the sentiment of the time that rights of the patient are solely under the discretion of the physician. In other words, the doctor knows best and it is only his or her judgment that matters.

During the early 20th century, clinical research focused on the safety and efficacy of pharmaceuticals. This included the passing of the Pure Food and Drug Act (1906); Food, Drug, and Cosmetic Act (1938); and the formation of the Food and Drug Administration (1906) and the National Institutes of Health (1930) (3). Although patient safety was becoming more fully acknowledged, the rights of subjects in clinical research still had a long and tumultuous road to travel.

There are many pivotal moments in the evolution of bioethics in clinical research. Our discussion focuses on a few key events that changed how we conduct clinical research today. We begin our discussion with the Tuskegee Study (1932) where poor, uneducated, African American males were enrolled in a study of syphilis by the US Public Health Service (6, 7). The researchers wanted to study the natural course of the disease and did not provide any information regarding the study to the subjects or their families. Even though penicillin was established to be curative in 1943, the subjects were not treated with this medication and hence 100 subjects died directly from the disease and countless others from complications of the disease. The experiment was finally halted in 1972 after public outcry following a *New York Times* front-page story (8). Further, the US government did not formally apologize until 1997.

The atrocities committed by the Nazi regime were exemplified by their medical "experiments" conducted on "undesirables." This included experimentation with poisons and exposure to environmental extremes (9). At the conclusion of the war, 23 Nazi defendants (20 physicians) were tried in the case of *The United States of America v Karl Bradt et al*, widely known as the Nuremberg Trials (10). Fifteen of the 23 defendants were found to be guilty, and 7 of these participants were sentenced to death. Debate among bioethicists continues today regarding whether the data collected should be used despite the manner in which it was gained. Regardless of this debate, one positive outcome was the establishment of the Nuremberg Code (11). This was the first document to systematically outline a code of ethics regarding human experimentation. The following 10 points were outlined: (1) informed consent of volunteers must be obtained without coercion in any form, (2) the experiment should yield fruitful results for the good of society, (3) the experiment should be based on animal experimentation and the anticipated scientific results should justify the performance of the experiment, (4) the experiment should avoid all unnecessary physical and mental suffering, (5) no experiment should be conducted if there is reasonable belief that death or disabling injury may occur, (6) the degree of risk should never exceed the humanitarian importance of the problem to be solved by the experiment, (7) proper preparations should be made to protect subjects from harm, (8) the experiment should be conducted by scientifically qualified persons, (9)

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human subjects should be free to end an experiment at any time, and (10) the scientist in charge must be prepared to end an experiment at any stage. This code set the foundation for further guidelines involving human subject experimentation.

In 1964, the World Medical Association further promoted ethical clinical research by adopting a 32-point statement of ethical principles that "defined rules for therapeutic and non-therapeutic research" in the Declaration of Helsinki document (12). However, further examples of suspect clinical research persisted beyond Nuremberg and Helsinki. One of the more troubling was the research (1962–1966) conducted at the Willowbrook State School, which was an institution that housed mentally retarded children (7, 13). Children were admitted only if their parents agreed to have them participate in experimentation. The parents were told that a "vaccine" was being investigated. In fact, these children were infected with a mild strain of hepatitis to evaluate the natural course of this disease. There are numerous other misguided cases of suspect clinical research during the second half of the 20th century. Henry Beecher, MD (1904–1976), was an important figure in exposing this sort of experimentation (14, 15). He publicized these cases in articles published in the *New England Journal of Medicine,* the *New York Times,* and the *Wall Street Journal* describing 22 "ethically problematic" research protocols. As the result of the public outcry, the US government responded with new rules and regulations concerning the protection of human subjects in research.

The National Research Act of 1974 created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which set regulations for protection of human subjects. This included a requirement for informed consent and IRB review. The direct result was the publication of the Belmont Report in 1979 (16). The Belmont Report laid down 3 overriding principles in human subject research: (1) respect for persons: the protection of autonomy (informed consent); (2) beneficence: the principle of maximizing benefits and minimizing harm; and (3) justice: promotion of fairness in subject selection and the protection of vulnerable groups.

As we thoughtfully consider the history of human subject research, it becomes clear that prior ethical violations have set the stage for the current layers of human subject protection. Bioethical considerations must be of paramount importance to the clinical researcher. Because the public's perception of research changes and is based both on historical events and current social attitudes, we should not sit in judgment of past indignities, but rather learn from these experiences and come to respect the current clinical research environment. Public perception drives policy makers in adopting new rules and regulations. Therefore, the clinical researcher should be mindful that ethical violations have future implications in conducting clinical research.

As physicians, we are bound by a code of ethics that always places the needs of the patient first. This supersedes any desire for publications, pressure to receive funding, other financial incentives, or professional accolades. Although some of the examples provided here seem obvious in their ethical violations, it is not always so black and white. More often it is a case of deciding between one good intention and another. Therefore, a set of rules, regulations, and guidelines *assists* and does not encumber the clinical researcher in the facilitation of human subject research.

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