

**IN THIS ISSUE**

**INTRODUCTION**

Research Involving Human Subjects P.1

**A SHORT HISTORY OF THE FEDERAL  
REGULATIONS PROTECTING HUMAN  
SUBJECTS IN RESEARCH** P.2

**ETHICS IN HUMANRESEARCH  
WHAT IS INFORMED CONSENT?** P.7

**INSTITUTIONAL LAPSES: WHAT  
HAPPENED AND WHY?** P.15

**GOVERNMENT RESTORES DUKE  
UNIVERISTY'S RIGHT TO CONDUCT  
RESEARCH ON HUMANS**  
*Chronicle of Higher Education* P.17

**UNIVERSITY COMMITTEE ON  
RESEARCH INVOLVING HUMAN  
SUBJECTS (UCRIHS): WHAT IS IT, WHO  
NEEDS IT AND WHERE TO GET IT** P.18

**THE "COMMUNITY MEMBER"  
DISCUSSES UCRIHS AND HUMAN  
SUBJECT RESEARCH** P.21

**INTERNET ACCESS** P.23

**USEFUL WEB RESOURCES FOR  
RESEARCH ETHICS INVOLVING  
HUMAN SUBJECTS** P.23

❧ **RESEARCH INTEGRITY** ❧

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❧ **VOLUME IV No. I** ❧  
**RESEARCH INVOLVING  
HUMAN SUBJECTS**

Part I

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**INTRODUCTION**

This issue of *Research Integrity* is part one of a two-part series devoted to issues surrounding research involving human subjects. Included in this issue is an historical summary of federal regulations by Andrea Beach and Dr. David Wright, which provide guidelines and good practices for research involving human subjects (Pg. 2). Also, special attention is given to *Informed Consent*, one of the three important principles that come from the Belmont Report from which all regulations regarding research on human beings flow. Dr. Joyce Tigner (Raritan Valley Community College) provides an informative article which uses the Tuskegee study as a background to discuss the ethical implications of informed consent and the responsibilities and duties of researchers to ensure their subjects are treated with respect (Pg. 7).

The issue of institutional lapses in research involving human subjects is addressed by Dr. Terry May (pg. 15) along with a reprint from *The Chronicle of Higher Education* regarding Duke University and the reinstatement of its right to conduct research on human subjects (Pg. 17).

In addition, there is a section for MSU graduate students and faculty concerning the University Committee on Research Involving Human Subjects (UCRIHS). Specifically, this section explains what is UCRIHS, who needs UCRIHS, where is UCRIHS and how to get important information you need to know if you will be conducting research on human subjects. (Pg. 18)

Finally, the community member of the Institutional Review Board for UCRIHS contributes his thoughts about his experiences and the importance of having an outsider view in this process (Pg.21).



## **A SHORT HISTORY OF REGULATIONS PROTECTING HUMAN SUBJECTS OF RESEARCH**

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The history of regulations protecting human subjects of research in the United States is relatively short but eventful. It involves the huge growth in research spending after World War II, long-held professional assumptions of autonomy among physicians and academics, and growing public awareness of, and investment in, human rights. These three phenomena converged in the space of three decades and culminated in sweeping legislation protecting research subjects' rights and privacy. The regulations are now frequently revised and updated and have become as integral to the research process as the subjects themselves.

### **The Rise in Research on Humans**

Before WWII, research involving human subjects was limited, therapeutic, and intimate. That is, the researchers generally knew their subjects and were experimenting with new treatments for medical conditions unresponsive to standard therapies. They were also experimenting as for example, Jenner's work in 1798 with small pox vaccine, where he tried to confer immunity to a specific patient with his experimental small pox vaccine.<sup>1</sup> This nearly exclusive therapeutic focus is reflected in the law: "There is only one court case involving experimentation in the non-therapeutic setting,

<sup>1</sup> For a thumbnail sketch of research with human subjects before WWII, see A.C. Ivy, "The History and Ethics of the Use of Human Subjects in Medical Experiments," *Science* 108 (2 July 1948), 1-5.

Bonner v. Moran, that reached an appellate court prior to the enunciation of the Nuremberg Code" in 1949 (Annas, Glantz, & Katz, 1977, p. 1).

By 1940, the development of the biomedical sciences and the need to understand and control the diseases that afflicted soldiers made widespread research involving human subjects both possible and desirable. In Germany, Adolph Hitler proclaimed in 1942 that "as a matter of principle, if it is in the interest of the state, human experiments were to be permitted." In the same passage he "someone in a concentration camp or prison to be totally untouched by the war, while German soldiers had to suffer the unbearable, was unacceptable" (Rothman, 1991, p. 75).<sup>2</sup>

In 1945, the scope and horror of the Nazi experiments became apparent. In December of that year, the Governor of the American Zone issued Ordinance No. 7, which established the Military Tribunals to try war criminals. Among these were trials of twenty-three Nazi physicians and administrators charged with experiments including: immersing prisoners in freezing water until they died to study hypothermia; castrating male prisoners after irradiating their genitals; decapitating children of various ages to study neural development; and, "euthanizing" inmates with new Nazi pharmaceuticals (Lifton, 1986; Rothman, 1991).

The first set of ethical codes pertaining specifically to research on humans was drafted in 1947 in Nuremberg in response to the atrocities perpetrated by Nazi doctors in the name of research. The 10 statements of the Nuremberg Code concerned the: necessity for informed voluntary consent of the human subject; prior animal experimentation to lower risks to human subjects; evaluation of risks of experiment; and the right of the human subject to withdraw from the experiment (US v. Karl Brandt et al., 1947).

All the judges presiding at the Nuremberg trials "were required to be American lawyers...The judges were mainly

<sup>2</sup> Rothman's is the best single source on the history or the development of protection for human subjects in the U.S. This short history is substantially indebted to his work.

past or present U.S. judges, and were recruited by the War Department. The prosecutors were predominantly American, and the procedural rules followed were American” (Annas, Glantz, & Katz, 1977). Nevertheless, there was relatively little coverage of the Nuremberg medical trials in the U.S. press. More importantly, the U.S. did not feel bound by treaty to the Nuremberg standards, despite the American authors. As Rothman observes, “well into the 1960s the American research community considered the Nuremberg findings, and the Nuremberg Code, irrelevant to its own work” (1991, p. 31).

In retrospect, this attitude seems as mistaken as it does arrogant. As part of the U.S. war effort, the federal Committee on Medical Research (CMR) funded upward of 600 research protocols at universities, hospitals, and research institutions. Among these were: an experiment that involved injecting high doses of dysentery bacteria into Ohio orphans who experienced average fevers of nearly 105 degrees with severe headache, vomiting, and diarrhea; a protocol wherein to test new therapies, researchers infected psychotic patients at an Illinois State Hospital and prisoners at Joliet state prison with malaria; and an experiment where, to test an influenza vaccine, physicians inoculated patients at a Michigan psychiatric facility (Ypsilanti) and then challenged both them and a control group with influenza. These protocols had in common the exploitation of vulnerable populations for research without informed consent or, in the case of the prisoners, with a consent process that was arguably coercive (Rothman, 1991, p. 32-38).

### **The Rise in Federal Investment in Research**

Prior to World War II, the federal government had relatively little involvement—financially or legislatively—in research. After supporting medical research during World War II, the government slowly but dramatically increased support of academic research. The National Science Foundation was formed in 1950, and The Public Health Service — later called the National Institutes of Health — augmented its intramural research with grants

and contracts to medical schools and universities.

When the Soviet Union launched Sputnik in 1958, the science, space, and research race exploded. The federal government increased spending for basic research from \$179 million dollars annually in 1958 to \$1,251 million in 1968 (Geiger, 1997, p. 282). In addition, funds were made available for buildings and equipment far beyond the level given at the time of the return of GIs in 1945-50. Institutions that had not been able to compete with the established research universities for research dollars 10 years prior now had ample funds available with which to expand their buildings, laboratories, faculties, and graduate programs. Within a decade, the landscape of research universities changed across the country. The Department of Health, Education and Welfare (DHEW) was expanding and the National Institutes of Health, an agency of DHEW, grew to be the largest funding source of academic science (Geiger, 1993, p. 180). The budget for the NIH grew from \$17 million dollars in 1948 to \$803 million in 1967 (Curran, 1969, p. 431). By 1967, the federal government was financing 73 percent of university research (Geiger, 1997, p.284).

This shift in funding profoundly affected the advancement of basic and applied research in the U.S. and around the world. At the same time, it created a huge and unregulated research environment. Experimentation was no longer limited, therapeutic, or intimate. Wide-ranging studies involving large numbers of subjects for myriad basic and applied purposes in the biomedical and social sciences were now underway at hundreds of universities and research institutes.

### **The Rise in Ethical Concern**

In 1961, the Draft Code of Ethics on Human Experimentation by the World Medical Association (ratified at the Declaration of Helsinki in 1964) recommended those conducting research on human subjects obtain peer review and that institutions have a

“procedural document” for consent (Curran, 1969).

A survey of U.S. medical schools was conducted in 1962 to determine to what extent the schools agreed with and complied with these ethical standards. Only 17% of the responding departments claimed to have a procedural document outlining acceptable research practice, no department provided indemnification for injury to human subjects of research conducted in their departments, and only a third of the departments used any kind of special consent form for patients involved in research. The general attitude in the departments surveyed, and indeed in the NIH and FDA at the time, was that decisions regarding research were best left to the individual researcher. Codes, ethical guidelines, and procedures were viewed with skepticism (Curran, 1969). The dominant attitude was that the decisions about ethics were better left to the researcher who followed his/her own ethical code and conscience. Despite this dismissal of the need for a code of ethics, and influenced by the Declaration of Helsinki, the Public Health Service and the Food and Drug Administration began requiring peer review of approved projects in the 1960s (Curran, 1969).

In the social sciences, this “researcher knows best” attitude was strong and entrenched. In 1973, when the American Psychological Association created a set of ethical standards for research with human subjects, many researchers criticized this action (“Ethics of Research,” 1973). They felt the standards would make psychological research difficult or impossible to conduct. This attitude prevailed in the face of numerous instances in which subjects had been treated in a questionable manner (“Ethics of Research,” 1973).

### **The Rise in Public Consciousness**

In the late 1950’s and 1960’s—the time of greatest investment by the federal government into research—the public became increasingly aware of and concerned about research abuses occurring in the United States.

The Drug Amendments Act of 1962 was a direct result of public outrage over Thalidomide, an anti-nauseal drug that, when

taken by pregnant women, caused birth defects in their infants. The drug devastated Western Europe and Canada, where it was widely prescribed. It had not gained FDA approval for use in the United States but was being widely tested in 1959 when the Senate held hearings about use and abuse of new and unapproved drugs. It became apparent that the FDA had no idea how many physicians were testing the drug or how many patients in the U.S. had taken it. The new laws required proof of therapeutic efficacy and safety prior to approval for testing, and held those conducting research to much stricter standards regarding disclosure and consent (Curran, 1969). These were the first set of statutory controls over the research process (Barber, Lally, Makarushka & Sullivan, 1973) that specifically addressed subject consent.

In June 1966, Henry K. Beecher, M.D., Dorr Professor of Anesthesiology at Harvard Medical School, shattered the American medical research establishment’s complacency regarding the ethics of human experimentation with a *New England Journal of Medicine* article, “Ethics in Clinical Research” (Beecher, 1966). (Significantly, Beecher first sent his article to the *Journal of the American Medical Association*, which rejected it (Rothman, p. 73). In his article, Beecher reported twenty-two examples of studies “that risked the health or the life of their subjects” without informing subjects of the risks or obtaining their consent. Beecher’s cases were not the result of investigative reporting, but rather were drawn from the open medical literature from 1945-1964. To focus attention on what he perceived as the widespread abuse of human subjects of research (rather than on individual investigators), Beecher did not name names either of investigators or of the journals in which they published. He pointed out however, that the investigators, their institutions and the journals in which they published were typically leaders in their fields.

Among the cases Beecher reported were these:

- #16: feeding live hepatitis virus to institutionalized retarded persons

- #18 injecting live cancer cells into elderly and senile hospitalized patients
- #20 catheterizing newborns and x-raying their bladders filling and voiding

While Beecher did not name names, he did provide the press with advance notice of his article. Leading newspapers and newsmagazines “reported the experiments in great detail, and reporters, readers, and public officials alike expressed dismay and incredulity as they pondered what had led responsible scientists to commit such acts.” (Rothman, p. 17). Congressmen inquired how NIH proposed to address the problem. NIH’s parent organization, the Public Health Service, responded with the policy that created the Institutional Review Board (“human subject committee”) system for federally sponsored research.

In 1972, the public learned of the Tuskegee Syphilis Project, in which 400 poor black men with the disease were studied without treatment in order that the researchers better understand the progression of the disease. They had been study subjects since 1932, for a total of forty years (See Tigner article P.7 in this newsletter for further discussion). Even after a cure was developed, the men were not treated, and many never knew that they even had syphilis. Over 100 died of the disease (Adair, 1974; Jones, 1981).

Stanley Milgram’s psychology experiments at Yale regarding subjects’ obedience to authority angered the public for their deception and the degree of stress experienced by subjects. Subjects were told they were taking part in an experiment on learning. They had to apply increasing amounts of electroshock to an unseen “learner” when the learner did not answer questions correctly. If a subject protested the increasing shock dosage or the experiment in general, they were told quietly and authoritatively to “continue with the experiment.” The “learners” were actually Milgram’s graduate students and were not being shocked, but many subjects left the experiment deeply troubled (Raven & Rubin,

1976; Thomson, Chodosh, Fried, Goodman, Wax & Wilson, 1981).

The public was bombarded by media accounts of such cases of abuse in research, many involving individuals who were poor, students, minorities, prisoners, and residents in mental institutions. The late 1960’s and 1970’s were a turbulent time, as evidenced by the Civil Rights movement, the feminist movement, growing disillusionment with the war in Vietnam, and student uprisings. People across the United States had a heightened awareness of basic human rights and were far more vocal than in the past about their displeasure with violations of human rights. They were also more aware and critical of the activities of government and of university researchers, and demanded stronger protection from drug testing, abusive or unnecessary research, and the targeting of vulnerable populations for experimentation.

### **The Rise in Regulations**

Between 1973 and 1975, three sets of regulations were adopted that encompassed people’s rights as subjects in biomedical or behavioral research and as patients receiving experimental drugs. The Research Act of 1974 (or Title 45 Code of Federal Regulations, Part 46, Section 491) required creation of institutional review boards (IRBs) to approve all projects utilizing human subjects at any institution that received federal money for such research, and specified standards to which projects would be held “regardless of whether the research is subject to Federal regulation” (Protection of human subjects (Title 45 Code of Federal Regulations, Part 46). 1991, p. 27, emphasis added).

IRBs were charged with examining the sampling process and rationale of research studies, the risk factors to subjects weighed against the potential benefits of the research, and the informed consent plan and documents. They must determine whether the project’s benefit to the current subjects or future society outweighs the risks involved in the research, whether the plan for consent is adequate, and whether the sample of subjects proposed for the study is reasonable and just. Special

attention is paid to protecting children, prisoners, pregnant women, the poor, the uneducated, and those whose diminished mental capacity make informed consent difficult.

The Research Act also created the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and charged it with conducting a thorough examination and recommendation of the ethical standards necessary to protect the rights of human subjects. That group produced the Belmont Report in 1979, which solidified the regulations under which all institutions receiving federal money monitored research, and guided revisions in the Act in 1979, 1985, and 1991.

In 1974, the FDA revised its 1962 regulations to match the stronger peer-review requirements of DHEW grantees. The new laws pertained not only to medical research and drug testing, as had previous regulations, but to any experiment involving humans. The Family Educational Rights and Privacy Act (FERPA) of 1974, also known as the Buckley Amendment, strengthened the rights of citizens by requiring schools, hospitals, and psychologists to allow citizens to see their confidential records. The Act specified that citizens must now give permission before any other professionals or researchers access their files.

All in all, the legislation of the two-year period between 1973 and 1975 caused significant changes in the way biomedical and behavioral research is conducted. The new regulations clearly were a positive step in the protection of research subjects, and have strongly shaped the academic research atmosphere since then. Today, the latest revision of the regulations involves the privacy of medical records and researchers' access to such records without specific consent of patients. The regulations continue to evolve as ethical and moral issues evolve in U.S. society.

## Conclusion

Despite the increase in regulations and federal oversight of research, and the recent suspending of research activity at major medical centers by the Office for the Protection from Research Risk (the federal agency charged with

oversight of human subjects research), the IRB system remains largely an honor system. Institutions are given the responsibility to provide the resources necessary to ensure federal regulations are upheld, but IRBs are autonomous bodies within their institutions. IRBs are staffed mostly with faculty and community members, and all have the latitude to exercise their collective independent judgement to interpret the regulations and set ethical standards for research at their institutions. Investigators, however, are given the ultimate responsibility to ensure that the rights and welfare of their research subjects are protected.



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## **ETHICS IN HUMAN RESEARCH**

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The 1997 film "Miss Evers' Boys" portrays the moral outrages of a study of syphilis conducted from 1932 to 1972 in Alabama. In the study, the U.S. Public Health Service (PHS), with the assistance of the Tuskegee Institute, identified 400 African-American men with syphilis. For many African-Americans in the South, the initial medical exam was their first contact with organized health care. What was offered, however, was not health care but rather a study of the epidemiology of untreated syphilis without informed consent. Even after the introduction of antibiotics in the 1950's, the PHS used its power to ensure that no treatment was provided to study subjects. Subjects later sued the U.S. government, receiving an out-of-court settlement in 1974. John Heller, director of the PHS's Venereal Disease section from 1943 to 1948, later described the study in the following way. "The men's status did not warrant ethical debate. They were subjects, not patients; clinical material, not sick people."<sup>3</sup> The design of the Tuskegee study suggests that it is morally permissible to sacrifice the well-being of some individuals without their consent in order to extend our knowledge of disease. Yet, this suggestion seems ethically unacceptable. Although the goal seems worthy, the means used to achieve that goal are morally flawed. The Tuskegee study highlights two issues concerning human subjects research: first, the ethical importance of informed consent and, second, the ethical duty of scientific professionals to ensure that human subjects are treated with respect.

Scientific professionals possess specialized expertise and skill in their discipline. The public turns to professionals, such as physicians, to benefit from their knowledge. Proper exercise of their expertise and skill requires discretionary judgment in the

<sup>3</sup> Jones, James. 1981. Bad Blood: The Tuskegee Syphilis Experiment. The Free Press, New York, NY, p. 179.

assessment of situations and responses to the problems posed by those situations. As a result, it has been suggested that a social contract exists between professionals and society: society agrees to give professionals independence in decision-making in return for an agreement by professionals that they will use their special expertise to benefit society.<sup>4</sup> The obligation to benefit society takes two forms, an obligation to expand a discipline's knowledge and an obligation to apply that knowledge to solve pressing human problems. Thus, professional scientists, as a group, have two commitments, a research commitment and a therapeutic commitment.<sup>5</sup>

In therapy, the knowledge of a discipline is used as a tool to benefit an individual client or patient. Therapies are treatments that have been demonstrated to be efficacious and many of their risks are known. Practitioners have two ethical duties to patients, a duty to benefit them and a duty to respect patients' moral rights, including informed consent. As opposed to therapy, research is designed to increase the systematic knowledge within a discipline in order to benefit science and society rather than an individual. The risks involved in scientific investigation may be unknown. The protocol to which subjects must adhere may not benefit them. The aim of research is not therapy, but knowledge. However, in research involving human subjects, ethical considerations require us to balance the value of the knowledge to be gained with the value of treating subjects with respect and concern for their well-being. As in therapy, one element of respectful treatment is informed consent.

Although scientific professionals have expertise in their discipline, they typically have little training in ethics. Their scientific education has prepared them to determine fruitful research aims and to design experiments which will meet those aims. However, they are less prepared to assess the ethical merits and effects

of research design on human subjects. As a result, scientific researchers have begun to collaborate with ethicists who may assist them in evaluating the ethical strengths and weaknesses of research design. The purpose of this article is to offer three general guidelines for balancing research objectives with ethical concerns for human subjects. The focus is informed consent by competent subjects. My discussion is limited to competent subjects, because gaining informed consent from them raises a number of ethical concerns. This article presents arguments for two conclusions. First, fully informed voluntary consent provides the best safeguard to ensure that subjects are treated with respect and dignity. Second, researchers, as professionals, have a moral duty to exercise due care to ensure that informed consent is afforded subjects.

Cost/benefit analysis embodies its own unique "problems of measurement."<sup>6</sup> It requires that we assess each feasible option that might be used to achieve a given consequence. Hypothetically, this is accomplished by asking each individual in society to quantify the level of benefits and costs associated with each option under consideration. Once all individuals have provided estimates of the benefits and costs they personally expect of each option, these are summed, providing the total costs and benefits to society for each option. One is then in a position to assess which option offers the greatest benefit with the least cost. Three problems may be encountered in performing cost/benefit analyses. First, Bentham's classical cost/benefit analysis requires us to consider future as well as current costs and benefits. Second, some things, such as life and health, are difficult to quantify, thus are difficult to incorporate into cost/benefit calculations. Finally, cost/benefit analysis does not permit proper weighting of risks or burdens when these are born by only a few of society's members. Let's briefly examine each problem.

First, cost/benefit calculations require us to consider future as well as current costs and benefits. However, experience has shown that

<sup>4</sup> Firmage, D.A. 1991. The Definition of a Profession. pp. 63-66. In D. Johnson (Ed.) *Ethics Issues in Engineering*. Prentice Hall, Upper Saddle River, NJ.

<sup>5</sup> Marquis, Don. 1989. An Ethical Problem Concerning Recent Therapeutic Research on Breast Cancer. *Hypatia*, 4:2: 140-155.

<sup>6</sup> The following discussion is taken from Velasquez, Manuel. 1998. *Business Ethics*. Prentice Hall, Upper Saddle River, NJ, pp. 76-82.

it is difficult, if not impossible, to foresee all the risks and benefits of an experimental treatment. An example was the use of diethylstilbestrol (DES) to aid women in carrying their pregnancies to term. It was later found to result in abnormally high rates of cancer of the reproductive organs among their children.<sup>7</sup> Examples such as this indicate the difficulty of adequately assessing the costs of research.

A second problem of measurement is the fact that quantification of costs and benefits are required. Some things, such as life, health, and self-esteem, however, are difficult to quantify; thus, they may be difficult to assess in a cost/benefit calculation. The design of the Tuskegee study failed to rank the intrinsic value of life and health over the instrumental valuable of expansion of knowledge, and it continued to do so even after that knowledge became less useful as a tool to benefit society due to the development of antibiotics.

Another scheme for rank ordering goods depends on the distinction between needs and wants. A failure to meet individuals' needs for food, clothing, shelter, education, and health results in harm. Hence, needs are requirements, which must be met if harm is to be avoided. By contrast, wants are desires that may remain unfulfilled without harm to an individual. Because deprivation of needs causes harm while deprivation of wants does not, needs take precedence over wants. Rank ordering of needs and wants suggests that it is unethical for research protocols involving patient/subjects to include control groups receiving no therapy if some approved therapy is available. To do so is a failure to meet subjects' needs, resulting in unnecessary harm. The design of the Tuskegee study failed to meet this criterion when it sacrificed individual needs to the desire of society for increased knowledge of syphilis.

A third problem of measurement is that, in assigning equal weight to individuals' assessments of costs and benefits, cost/benefit analysis makes it possible to sacrifice the well-being of some individuals in order to benefit the majority. That is, what may be viewed as a

benefit by one person may be viewed as a cost by another person. This is a problem principal investigators (PIs) may face when soliciting patients for clinical trials of a new drug. A patient's primary concern is cure or relief of symptoms while a PI's primary concern is completion of an experimental design which will effectively prove or disprove a hypothesis, in this case, the efficacy of a drug. During phase II and III clinical trials, some subjects will be placed in a group receiving the experimental drug while others will be placed in a group receiving standard therapy or no therapy if none is available. From the subjects' point of view, consenting to research that may not benefit them appears to carry a large cost accompanied by little or no benefit. For society and the PI, however, the subjects' participation affords a large benefit if it enables a hypothesis to be properly tested. The problem with impartially weighting an option's cost to individuals can be seen in the effects of the Tuskegee study.

Because cost/benefit calculations give equal weight to individual assessments, then aggregate those assessments, it is possible for the health or well-being of some individuals to be easily outweighed by the desire of many members of society for additional benefits. This may permit a small number of societal members to be sacrificed in order to benefit the remaining majority. In the Tuskegee study, it is clear that the perspectives of society and PIs prevailed over those of individual subjects, permitting the majority to override the right to life and health of the few.

In moral deliberation, the theories and principles described are applied to the facts of a given situation to reach a moral judgment regarding proper ethical conduct. In many cases, more than one ethical theory may be applicable. Often, as the Tuskegee study illustrates, ethical theories and moral principles agree in their judgment of conduct.

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<sup>7</sup> Mike, Valerie and Alfred N. Krauss, Gail S. Ross. 1998. Responsibility for Clinical Innovation. *Evaluation & the Health Professions*. 21: 3-26.

## Ethical Evaluation of the Tuskegee Study

Although the aim of the Tuskegee study may appear to be supported by utilitarian calculations, it is doubtful that the study's aim was achieved or, if it was achieved, that other experimental designs might not have provided comparable benefits with fewer costs. The costs to individuals and society were unnecessary loss of life and health as well as taxpayers' \$10 million payment to survivors in 1974. The benefits were few, especially after the introduction of antibiotics. So, a cost/benefit analysis suggests that the research was unethical by utilitarian standards.

The design of the study also demonstrated blatant disregard for professionals' moral duty to avoid harm and to exercise due care. The Tuskegee subjects were vulnerable for a number of reasons, some of them having to do with the design of the study. They were vulnerable due to the need created by their illness; they were vulnerable because relevant information regarding their condition and options for care were withheld; they were vulnerable because they were not afforded the opportunity for informed consent. The decision of the PHS to actively impede treatment of the subjects violated the Harm Principle while its failure to use its expertise to protect the subjects from harm violated the Principle of Due Care. Although research cannot be expected to aim at beneficence, ethically it must prevent avoidable harm to subjects. We feel moral outrage because the Tuskegee study consistently failed to meet the requirements of ethical theory and moral principle. As a result, the study sacrificed individual needs to the desire of society for increased knowledge of syphilis.

There are, however, two important inferences to be drawn from an ethical analysis of the Tuskegee study. First, the unethical procedures employed, in all likelihood, would not have been used if subjects had been offered the opportunity to provide fully informed voluntary consent. Thus, informed consent provides a major safeguard to protect subjects from unethical conduct. Second, in cases in which fully informed voluntary consent is limited by either the withholding of information or need, subjects are treated with less than full

respect for their moral personhood. Such breaches of ethics and professional conduct are justified only when greater knowledge is required to preserve society in the face of pressing need. They are not justified when the aim of research is to enhance societal well-being.<sup>8</sup>

## Informed Consent

Informed consent, as a condition for participation in research, is founded in Kantian theory: we have a duty to respect others' right to autonomous self-determination. The exercise of autonomy, including informed consent, requires a genuine choice of options, full information relevant to those choices, and an absence of coercion, duress, or need which might limit the voluntary choice of an option. These three conditions are interactive. Deception, practiced by either lying about the truth or withholding information, limits full knowledge on which to base a decision. Deception may also be used to manipulate or limit the options subjects believe to be available or acceptable, hence may serve as a form of coercion, limiting voluntary choice. In some cases, deception and coercion may undermine autonomy completely. Need, on the other hand, is a form of duress in which autonomy is not completely lost, however, individuals' choices may be limited to those which will fulfill their needs. Need has special relevance to subjects who are also patients. Typically, patient/subjects desire beneficent care, therefore minimizing the coercive force of need poses a challenge in obtaining informed consent.

The nine basic elements of informed consent are:<sup>9</sup>

1. A description of the study and its purpose, provided in language that is appropriate and understandable by the proposed subjects.
2. A statement of what is required of the subject, including a description of the

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<sup>8</sup> Jonas 1992.

<sup>9</sup> Adapted from Penslar, Robin Levin (Ed.). 1995. Research Ethics: Cases and Materials, Indiana University Press, Bloomington, IN, pp. 134-135.

experimental procedures, specific procedures the subject may be asked to follow, and the duration of participation.

3. Disclosure of foreseeable risks and discomforts of the experimental procedure as well as disclosure of medically acceptable alternatives to experimental procedures, if any, which might be advantageous to the subject.
4. Notice of whether the data will be collected anonymously or the extent to which confidentiality is assured.
5. A statement that the subject's participation in the research study is voluntary, and the subject has the right to withdraw from the study at any time without penalty and without loss of benefits to which the subject is otherwise entitled.
6. An explanation of whom to contact if the subject has questions or concerns regarding the study, the procedures to be followed, or the subject's rights in the event of a research-related injury.
7. A statement of the compensation, if any, available if an injury is incurred during the study.
8. A statement of the risks and benefits of the study for the subject and for society.
9. A description of fees or other compensation to be made to subjects, specifying the amount of compensation and how it will be prorated should the subject withdraw from the study prior to its completion.<sup>10</sup>

The elements of informed consent may be conveyed to subjects verbally or in writing or both. In anonymous studies involving minimal risk, verbal informed consent may be appropriate. At a minimum, elements 1, 2, 4, 5,

and 8 should be disclosed to a subject verbally. In studies involving more than minimal risk, all elements of informed consent should be explained to subjects verbally and in writing. The National Institutes of Health defines only two levels of experimental risk, 'minimal risk' and 'at risk.' 'Minimal risk' is defined as a study in which "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."<sup>11</sup> 'At risk' studies are those involving greater than minimal risk.

It has been suggested that informed consent be best thought of as a process rather than a document. A document is but one portion of the process. Debate exists between those who emphasize full disclosure of as many risks as possible, and opponents who fear that long informed consents, necessitated by full disclosure, may actually be less informative and more intimidating to subjects, hence, discourage participation. The goal of the informed consent process, opponents advocate, is to gain subject understanding, not to convert a subject into an expert.<sup>12</sup> In either case, the purpose of fully informed voluntary consent is to permit subjects to confirm that, in their own minds, the research and their participation in it is worthwhile. A process, rather than a document alone, ensures that subjects have access to those who can answer their questions, not only prior to consent, but during the course of the study. In longitudinal studies (or those in which risk is little known) the rapport established during the informed consent process provides a forum for PIs to: determine the suitability of proposed subjects for participation in the study; to ease subjects' doubts; to ensure that untoward reactions are reported on a timely basis; and, to maintain an open discussion which may decrease the number of subjects who leave a study prior to its completion.

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<sup>10</sup> According to Stein, most states have informed consent policies, therefore, informed consent must meet both Federal and State laws. Stein, Mary. 1992. Workshop on Problems and Issues Associated with Catastrophic Disease Research. Presented at the NIH/FDA National IRB Workshop, Philadelphia, PA.

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<sup>11</sup> Code of Federal Regulations, Title 45, section 46.102 (I).

<sup>12</sup> Kehoe, Douglas. April 1992. Workshop on the Role of the Investigator. Presented at the NIH/FDA National IRB Workshop, Philadelphia, PA.

There are a number of barriers to informed consent by competent subjects, which may create ethical problems. Seven are briefly described. The imbalance of power between a PI/practitioner (PIP) and patient/subject, conflict of interest and the practice of deception raise the most serious ethical questions.

**Illness.** Even competent adults may find cognitive functioning and decision-making impaired by their disease state. The fact that one does not feel well, or that one may fear for one's future, may serve as a barrier to understanding one's disease state as well as the risks and benefits of therapies known to be effective. The additional burden of being asked to understand treatments whose benefits and risks are uncertain may appear daunting. The dual role of a PIP poses an additional barrier to understanding. It may mistakenly lead a patient to assume that the professional's primary motive in soliciting the patient's participation in research is one of beneficence, to improve the patient's well-being, although this is not necessarily the case. Because illness creates need and vulnerability, PIPs must exercise due care to ensure that subjects are protected from unnecessary harm.

**Risk.** Experiences, such as that with DES, highlight the difficulty of affording subjects adequate information regarding the risks posed by participation in research. In addition, it has been argued that double blind studies involve special problems for subjects' evaluation of risk because neither the PI nor subject knows whether a subject will receive an experimental treatment, a standard therapy, or no therapy if none is available. In response, it may be countered that it is important to distinguish between risk of assignment to an experimental treatment and risk posed by treatments themselves. The first risk cannot be eliminated, however, explanations of the known or suspected risks of experimental treatments are required by the principle of due care.

**Payment.** Payments to subjects are controversial. Although some subjects welcome payment for the inconvenience they experience, others may interpret payment, especially large payments, as an inducement or bribe. From

their perspective, payment is offered only if the research is risky, hence, the size of the payment is proportional to the size of the risk. In such cases, offers of payment may be interpreted as an attempt by the PI to unduly influence the voluntariness of consent. From the PI's perspective, large payments may impede unbiased data collection. Subjects may be reluctant to report side effects if this may mean that they will be terminated from a study, thus receiving only partial payment.

**Institutional Embeddedness.** Subjects are 'institutionally embedded' when research takes place within an institutional setting which governs the benefits or burdens available to the subjects. Prisoners, those residing in institutions, employees, and students are examples of institutionally embedded subjects when research takes place within their institutional setting. Due to the potentially coercive nature of institutions, PIs must exercise due care to ensure that those in institutional power do not offer or withhold benefits in order to influence subject participation, research responses, or voluntary withdrawal from research. However, the extent of the manipulation by those in power may be difficult for PIs to assess. Because adverse consequences may result if subjects' responses become known by those in power, PIs have a duty to maintain confidentiality if it has been promised to subjects.

**Power Imbalances.** PIs, as experts in their field, are acknowledged authorities in society. This represents a form of power, which may serve as a barrier both to subjects' understanding and to the voluntariness of consent. Patient/subjects may confuse a PIP's research role with the practitioner role. Although both roles aim at compassionate and respectful treatment of the patient/subject, a PI is concerned with testing a hypothesis using a properly designed and executed research protocol, while a practitioner is concerned with beneficent care of the patient. Failure to recognize this distinction may lead patient/subjects to minimize the risks associated with participation in research.

On the other side of the coin, PIPs may not be as objective about their research as one might expect. In their role as practitioner, they may be overly optimistic about the advantages of an experimental treatment, hence, unintentionally present biased estimates of subjects' benefit. In their role as PI, they may be less than candid in their discussion of anticipated risks in order not to discourage participation. Unintentional bias may be conveyed through subtle nuances of language and demeanor which are not overtly recognized by either the PIP or the subject. Although undetected, these biases may influence a patient/subject's decision to consent, hence present a barrier to informed and voluntary decision-making.<sup>13</sup>

**Conflict of Interest.** A conflict of interest arises when a person is subject to competing interests. Because a professional is expected to exercise discretionary judgment, it is possible for discretion to be used to further the interests of the decision-maker at the expense of other parties. Apparent conflict of interest is a euphemism for a conflict of interest situation in which the potential for conflict of interest exists. Some have argued that a conflict of interest exists when PIPs solicit their own patients for research which, in turn, stands to benefit the PI financially or in terms of status or reputation. The problem with conflict of interest is that it serves to undermine trust, both on the part of subjects, who cannot be sure that they are not used as mere means, and on the part of those sponsoring the research, who cannot be sure that all subjects are appropriate for the study.

Three possible solutions to conflict of interest are, first, changing the conditions of the situation to eliminate the conflict; second, withdrawing the decision-maker from the situation; or finally, disclosing conflict of interest to participating parties.<sup>14</sup> Because a conflict of interest situation provides the opportunity to

treat others as means to one's own ends, it has been suggested that PIPs in apparent conflict of interest situations disclose the situation to subjects in the informed consent. Of course, PIs often stand to gain some value from research, such as grant money or professional recognition. Thus, those who suggest disclosure, limit this suggestion to cases in which professionals stand to gain personal financial benefit from the research. Others advocate that PIPs withdraw as decision-maker when double blind studies involve their own patients. In their dual role of PI and practitioner, professionals' primary ethical duty is beneficent treatment of the patient, however, this is not possible when the treatment to be provided is unknown.<sup>15</sup>

**Deception.** Deception may take two forms, either the intentional withholding of information or deception of subjects about the truth. Some PIs intentionally practice various forms of deception, which may hinder informed consent.<sup>16</sup> Some intentionally limit information in order to manipulate subjects' decision to participate. This treats subjects as means only, therefore is ethically unacceptable.

Others may intentionally limit information because they believe that subjects are incapable of understanding the purpose of the research. However, the purpose of even complex or highly technical research may be summarized in terms which competent individuals are capable of understanding.<sup>17</sup> Certainly, this will be required if the treatment or test proves efficacious and practitioners must describe it as a requirement of the Patient Self-Determination Act. If persons have a moral right to autonomy, then PIs have an ethical duty to disclose information precisely because they have the knowledge and expertise to do so.

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<sup>13</sup> For a discussion of the nuances of language and demeanor which may subtly bias a patient/subject's decision to consent, see Fisher, Sue. 1988. In the Patient's Best Interest. Rutgers University Press, New Brunswick, NJ.

<sup>14</sup> Davis, Michael. 1994. Conflict of Interest. Presented at a Training Session in Ethics Education for Federal Government Agencies, Indiana University, Bloomington, IN.

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<sup>15</sup> Marquis, 1989.

<sup>16</sup> Much of the following discussion is adapted from the American Psychological Association. 1982. Ethical Principles in the Conduct of Research with Human Participants. American Psychological Association, Washington, D.C.

<sup>17</sup> See Bok, Sissela. 1992. Lies to the Sick and Dying. In R. Munson (Ed.) Intervention and Reflection: Basic Issues in Medical Ethics. Wadsworth Publishing Company, Belmont, CA, pp. 289-297, for an excellent discussion of disclosure.

Still other PIs fail to describe research procedures because they claim that the “degree of potential discomfort, harm or embarrassment”<sup>18</sup> cannot be ascertained prior to participation. In our culture, psychological harm is typically assigned lesser importance than physical harm. However, there are good philosophical and empirical reasons to reject the dichotomy between mind and body which underlies this view; the placebo effect is an example. Thus, risk of psychological harm, such as embarrassment or loss of self-esteem ought to be considered as serious as risk of harm in physiological experiments. Qualified research professionals ought to be capable of informed judgments regarding the discomfort and embarrassment subjects may experience. Thus, the principle of due care requires that every effort be made to inform subjects in advance of the experiences to which they will be subjected so that they may decide for themselves whether experimental conditions are acceptable.

In addition to withholding information, PIs may intentionally deceive subjects regarding a study’s purpose or procedures if they believe that valid data cannot be obtained otherwise. Deception may be permissible if risk to the subject is minimal. However, full and immediate debriefing concerning the purpose and procedures of the research is required. In addition, subjects must be offered the opportunity for informed consent regarding the use of their data. If informed consent for use of data is withheld by a subject, the data must be withdrawn from the study. To fail to afford informed consent, through debriefing and the subjects’ ability to withdraw data, is to treat subjects as a means only. In addition, due care requires PIs to recognize that, in some cases, debriefing may not be sufficient to eliminate beliefs which undermine self-esteem or subjects’ assessment of their own competence. This is true especially when these beliefs have been instilled and supported by the authority of a professional as part of a deceptive research procedure. In such cases, the subject has been harmed by the research. This violates PIs’ moral and professional responsibility to avoid harm to

subjects, and compensatory justice requires that the harm be remedied.

Limitations on full disclosure and voluntary decision-making are ethically questionable because they render healthy subjects vulnerable to manipulation and increase the vulnerability of needy subjects. The degree of possible manipulation is typically proportional to the degree of deception exercised. In other words, increasing levels of deception render subjects increasingly vulnerable to being treated as means rather than as ends-in-themselves. No matter how small, deception sacrifices one person’s interests and well-being to benefit another’s. The goal of the informed consent process is to ensure that subjects believe, in their own minds, that participation in research is worthwhile without manipulation of those beliefs. Therefore, PIs have an ethical and professional duty to ensure that barriers to informed consent are minimized or eliminated.



We continue to invite contributions, comments, suggestions, letters and articles for future editions from faculty, graduate students and administrators. Please contact the editor, Julie Reyes at: reyesjul@msu.edu



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**INSTITUTIONAL LAPSES:**

<sup>18</sup> American Psychological Association. 1982. p. 34.

## **WHAT HAPPENED AND WHY?**

Contributed by

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During 1999, five highly-regarded institutions (Duke University in North Carolina; Rush-Presbyterian-St. Luke's Medical Center in Illinois; West Los Angeles Veterans Hospital; University of Illinois-Chicago ; and the University of Colorado Health Sciences Center) have had their Federal approvals to review and approve research on human subjects either suspended by the National Institute of Health, the Office for the Protection from Research Risks (OPRR) or severely restricted by other federal actions. In some cases, on-going research was terminated; however, on-going treatments and therapies were continued for patients where stoppages would have placed them at risk.

The effect of these actions is wide-reaching, not only to the institutions involved, but also to institutions of higher education and health sciences centers generally which are awakening to the realization that there are consequences for less than strict compliance and that the costs are great. Therefore, it is worthwhile to consider the reported factors leading to these actions and the lessons to be learned.

**Duke University** - OPRR suspended approval for four days in May 1999 for failure to correct 20 ethics and safety violations that remained from a mid-December 1998 review. OPRR found that Duke's sole IRB provided only perfunctory oversight of many of the 2,000 studies that were underway.<sup>19</sup>

**Rush-Presbyterian-St. Luke's Medical Center** - The OPRR received multiple complaints alleging that the institution "used ineligible patients,

pushed others to participate, or failed to obtain adequate consent."<sup>20</sup>

**University of Colorado Health Sciences Center** - The Chronicle of Higher reported the suspension of the Center's research involving human subjects by the Food and Drug Administration (FDA) for "not properly maintaining documents" about human subjects research.<sup>21</sup> The university halted all clinical research, a decision that went beyond the mandates of the FDA order in response to a follow-up letter from OPRR requesting, but not requiring that action. The FDA had audited the institution's procedures in 1997 and issued a warning about deficiencies that had not been corrected by April 1999. Included among these deficiencies was the fact that the IRB had not properly operated a computerized record-keeping system to document periodic reviews and re-evaluations of on-going studies.

**University of Illinois-Chicago (UIC)** - Science Magazine reported that problems at the institution began about two years ago when it was discovered that a study involving brain scans performed on subjects who were going through an induced episode of dissociative disorder had never been submitted to the IRB.<sup>22</sup> The Institution established a task force to determine how to prevent this from occurring in the future. Despite efforts to comply with Federal requirements, there was "continuing friction between the IRB and its support staff, and university officials anxious to keep the stream of grants coming in." The UIC's research program was undergoing a rapid growth with funding from DHHS doubling to its current annual level of \$80 million in just 4 years. The Chronicle of Higher Education reported that OPRR cited 28 violations of federal guidelines, the most serious of which

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<sup>19</sup> Walker Campbell, P. Government Restores Duke U.'s Right to Conduct Research on Humans. The Chronicle of Higher Education, May 28, 1999, pg. A30.

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<sup>20</sup> Foubister, V. More Centers Cited for Ethics Lapses in Research. American Medical News. November 1, 1999.

<sup>21</sup> Brainard, J. Facing FDA Order, U. of Colorado Health Sciences Center Suspends Clinical Research. The Chronicle of Higher Education - Today's News. September 27, 1999.

<sup>22</sup> Holden, C. University of Illinois: Chancellor Quits after Research Shutdown. Science Magazine, September 24, 1999; pg. 2047.

included failure to review some proposed research projects.<sup>23</sup>

#### **West Los Angeles Veterans Hospital –**

The Chronicle of Higher Education reported that OPRR began an investigation in 1993 and reprimanded the hospital for its “inadequate informed consent procedures.”<sup>24</sup> Five letters detailing the shortcomings were issued prior to the facility being placed on probation in 1995. The Department of Veteran’s Affairs subsequently (1997) observed “deficiencies” in the hospital’s management of research programs which led to termination of the hospital’s contract to conduct research paid by the Department of Health and Human Services (DHHS).

Gary B. Ellis, Director of OPRR summarized the current process for “Protecting the Rights and Welfare of Human Research Subjects” as “a succession, or chain, of judgments made by people in the context of federal regulations.”<sup>25</sup> He added: “One size doesn’t fit all. This is custom work.” This chain begins with the most critical link between the research volunteer and the research investigator. This is where the process begins to communicate the facts and risks of the research, in order to enable the volunteer to make an informed decision of whether or not to consent to participate. Federal regulations specify eight required elements (along with six optional elements) that must be conveyed to prospective subjects. The nature and details of the research, including the process of obtaining informed consent must be reviewed and approved by an Institutional Review Board (IRB) which is the keystone of our current system. IRB review is prospective and must be continued throughout the course of the study. Further separated from

the research, but equally important in the chain is the institutional official responsible for the research review process at the institution, the scientific review body at the sponsoring agency, and the program or administrative staff at the sponsoring agency. Oversight for the entire chain is provided by the OPRR and, when investigational drugs, devices, or biologics are involved, the FDA. Additional independent reviews might even include a Data and Safety Monitoring Board (DSMB) to oversee and evaluate a large research investigation.

Ellis concludes his summary by stressing that, “In the final analysis, research investigators, research institutions, and federal regulators are stewards of a trust agreement with the people who are research subjects. For research subjects who are safeguarded by the federal regulations, we have a system in place that (1) minimizes the potential for harm, (2) enables and protects individual, autonomous choice, and (3) promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow citizens who make a remarkable contribution to the common good by participating in research studies. We owe them our best effort.”

Our “best effort” requires collective dedication, care, cooperation, and good judgment by many. The proper choice of action may not always be clear, may be costly and/or time consuming, and is too easily ignored in the face of competing interests. Geoffrey Grant, Odell Guyton, and Robert Forrester have collaborated to outline the compelling reasons for “Creating Effective Research Compliance Programs in Academic Institutions.”<sup>26</sup> Such programs should be established and maintained with care, “because the culture in academic institutions, specifically in academic medical centers, has several characteristics (e.g., undefined roles and responsibilities, decentralized administration, possible conflict-of-interest situations) that can create compliance risks.” The lapses cited as

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<sup>23</sup> Brainard, J. Watchdog Agency Halts 1,000 Human-Research Projects at U. Illinois at Chicago. The Chronicle of Higher Education - Today’s News, August 31, 1999.

<sup>24</sup> Walker Campbell, P. Government Punishes Hospital Tied to UCLA. The Chronicle of Higher Education, April 2, 1999, pg. A42.

<sup>25</sup> Ellis, G.B. Protecting the Rights and Welfare of Human Research Subjects. Academic Medicine, Vol 74 No. 9, September 1999, p. 1008-1009.

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<sup>26</sup> Grant, G.G., O. Guyton, and R. Forrester. Creating Effective Research Compliance Programs in Academic Institutions. Academic Medicine, Vol 74, No. 9, September 1999, pg. 951-971.

causing suspensions of research at academic medical centers by NIH includes:

1. unacceptable conflicts of interest - IRB members must not review projects in which they have a potential interest;
2. lack of attention to details for regular, continuing reviews of on-going research;
3. failure to provide full consideration for studies involving children;
4. reduced standards for obtaining patient consent;
5. incomplete information concerning risks provided to mentally ill patients; IRBs did not record certain findings required for waiving requirements of consent or in considering research on vulnerable populations;
6. incomplete and unclear records of IRB deliberations/reasons for specific decisions;
7. failure to include an interested member of the community in all board meetings;
8. failure to establish clear criteria for determination of exempt research;
9. inadequate procedures for investigating issues of noncompliance; and
10. failure to implement administrative best practices for insuring the integrity of the informed consent process.

The situations highlighted here are clear examples of the consequences for failure to attend to legal and ethical requirements for reviewing, conducting, and monitoring human subjects research in a timely manner. Such failure resulted from cumulative lapses by investigators and their institutions in not maintaining comprehensive and cohesive systems for protecting human research subjects. Individual lapses might be explained away as an error or lack of understanding. However, when taken as a whole they were viewed as violating the promises made to the Federal government to be responsible in conducting such research.

These situations do not simply happen by chance; they result from a combination of bad judgment, bad choices, and erosion of high standards of conduct. A limited few can make bad judgments and bad choices anywhere. In contrast, erosion of high standards of conduct requires the passive acceptance by many. We cannot always prevent others from violating accepted standards, but we can contribute to the

maintenance of high standards through education, action, and example. That is why it is so important for each of us (students, faculty, IRB members, and administrators) to commit to the principle of responsible conduct and accept individual responsibility for making sure it happens not only for ourselves but also for our colleagues, academic disciplines, communities, institutions, and professions.



## **GOVERNMENT RESTORES DUKE UNIVERSITY'S RIGHT TO CONDUCT RESEARCH ON HUMANS**

Contributed by

Paulette Walker Campbell

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***The Chronicle of Higher Education***

(May 28) Washington D.C.<sup>27</sup>

A federal agency on Friday reinstated Duke University Medical Center's license to conduct government-sponsored research involving humans. The action came four days after the agency, the federal Office for Protection from Research Risks, surprised top university administrators across the country by suspending much of the scientific work done at the respected clinical-research institution.

The research-protection office imposed the punishment after concluding that Duke officials had not acted quickly enough to correct more than 20 deficiencies in the institution's system for protecting people enrolled as subjects in clinical studies there. (See a story from *The Chronicle*, May 13.) Most of the problems cited had to do with the operation of the center's institutional review board, or I.R.B. -- a panel of doctors, scientists, and members of the public that is responsible for screening all research proposals involving human beings.

Officials from the medical center met with federal regulators Thursday to present

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their plan for correcting the problems. The research-protection office said in a letter Friday that it “has determined that D.U.M.C. has developed the satisfactory plans that were required.”

The medical center's plans include:

- Requiring members of its I.R.B. to undergo training, by May 25, in the ethics of human research and the regulation of human subjects.
- Excluding individuals from the medical center's Office of Grants and Contracts from serving as voting members on the I.R.B.
- Providing adequate justification for approving experiments involving children.
- The medical center will also establish a second I.R.B. by May 26. The existing 25-member review board assesses about 70 research proposals each month and is responsible for monitoring the more than 2,000 clinical trials typically underway at any one time at the medical center. The research-protection office had said that the deficiencies in the medical center's I.R.B. “were indicative of an I.R.B. overburdened by a large volume of research.”

Duke's reprieve came with several strings attached. For instance, all of the research projects approved during three meetings at which there was not a quorum will remain suspended until they have been reviewed again. And the medical center must submit, until further notice, quarterly progress reports to the research-protection office documenting its efforts to improve the management of its I.R.B.

Ralph Snyderman, the dean of Duke's School of Medicine and the chancellor for health affairs at the medical center, said he was “pleased, as I know our faculty and members of our research community will be, that we can ensure all participants in D.U.M.C.'s research projects that their health and safety continues to be our highest priority.”

He added: “We are grateful to O.P.R.R. officials for their assistance in helping us work through the necessary steps that have enabled us to resume the important work being done by our faculty and our I.R.B.”



## **UNIVERSITY COMMITTEE ON RESEARCH INVOLVING HUMAN SUBJECTS (UCRIHS): WHAT IT IS, WHO NEEDS IT, AND WHERE TO GET IT**

Contributed by

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So, you've passed your comprehensive exams, defended your proposal, and are ready to swing into action with your dissertation or thesis. Congratulations! Did your committee tell you where to obtain approval for the use of human subjects or materials for your research? How do you know if your study falls under the rubric of “research involving human subjects”? How do you go about obtaining approval for your project? This article will explain the kinds of research that UCRIHS reviews, how approval impacts graduate students, and how you can apply for UCRIHS approval of your project.

It is important to note that the Graduate School **will not accept** a thesis or dissertation without UCRIHS approval if it involves human subjects. Please see the Academic Policies and General Information handbook, page 62, for further information. Check with your department secretary for a copy of this handbook. It is also available in the Office of the Registrar and on the web at : <http://www.msu.edu/unit/ucandc/>

### • **What is UCRIHS?**

UCRIHS stands for the University Committee on Research Involving Human Subjects. It is an “Institutional Review Board” (IRB), and is charged with ensuring the rights and protection of all human subjects of research conducted at MSU. Federal and university regulations require that **all** research projects involving human subjects and materials of human origin be reviewed and approved by an IRB before initiation. Other articles in this issue describe the origin and history of IRBs in the United States.

- **Why is UCRIHS Approval Important?**

Under federal and university regulations, all investigators (faculty and graduate students) who will conduct research that involves human subjects or materials of human origin must submit an application to UCRIHS. Approval of the research protocol must be in place BEFORE the investigator begins data collection.

These regulations are of specific concern to graduate students because "research" includes the preparation of Master's Theses and Doctoral Dissertations. By regulation, UCRIHS may not approve data gathered without its prior review and approval of the project. Only in exceptional circumstances will the Graduate School accept a thesis or dissertation containing data from human subjects that does not have UCRIHS approval. Therefore, if you do not receive UCRIHS approval for your project prior to beginning data collection, and keep your approval current during the entire time that you collect data, your project may not receive approval by the Graduate School.

- **What Constitutes Research Involving Human Subjects?**

Examples of research involving human subjects that you may be familiar with include:

- Interviews, telephone or mail surveys
- Behavioral or educational testing
- Observation of individual or group behavior
- Collection of blood (or other biologic) samples, and
- Clinical studies of drugs and medical devices

So, your survey of consumer satisfaction, observation of teachers in their classrooms, or study of the blood chemistry of elite athletes would all apply. There are other types of projects, however, that you may not have considered as "human subjects research, but are considered so by federal regulations. These include:

- Research involving observation of public behavior
- Study of existing data, documents, archives, or databases in these areas

- Study of existing pathologic samples or diagnostic specimens
- Research involving collection of data through non-invasive procedures (weighing, sensing procedures, moderate exercise) or collection of biologic samples through non-invasive procedures (such as hair and nail samples, saliva, or sweat)
- Research involving materials that have been collected, or will be collected solely for non-research purposes

Therefore, your research in a private collection of family photographs or with historical documents not available to the public is research involving human subjects. Likewise, your secondary analysis of the data collected by your advisor for another project would apply, as would your use of human genetic tissue that your lab purchased for other projects. The point is that there are many kinds of research outside of medical trials that fall under the review of UCRIHS. If you have a question about whether your project would be considered research involving human subjects, please ask your advisor, or call the UCRIHS office at 355-2180.

- **Nuts and Bolts**

There are three possible occasions prior to and during collection of your data in which you will need to involve UCRIHS. These are initial approval of your protocol, renewal of your approval, and revisions to your project.

### 1. Initial Approval

Application materials are available on the UCRIHS website at [www.msu.edu/user/ucrihs](http://www.msu.edu/user/ucrihs). You should apply for UCRIHS approval for your project *AT LEAST* one month prior to the time you plan to begin data collection. Review generally takes 15 working days, but you'll want to leave room for any comments or questions by reviewers, since you cannot collect data before you receive approval.

If you are a graduate student, your advisor serves as the "Responsible

Investigator” on the UCRIHS application for your thesis or dissertation. Therefore, you will need to work with him or her to complete the application, and UCRIHS must have his or her signature prior to reviewing the application.

Along with your application, you will need to submit any survey or testing instruments, interview questions, intervention scripts, brochures or recruiting materials, and consent forms that will be used with your study. Review of your protocol cannot proceed without these materials!

## **2. Renewal of Approval**

Approval is only effective for up to one calendar year (occasionally for shorter periods, if the research is considered of risk to subjects and UCRIHS believes it necessary to monitor the project more closely). Therefore, if your data collection or contact with subjects extends beyond one year, you will need to *RENEW* your approval. If you let your approval lapse while you are collecting data, you may not use the data collected during that time.

## **3. Revision of Your Project**

If you change your subject recruiting strategy, your survey instrument, your interview questions, your consent form language, or any other part of your project in a way that affects your participants, you'll need to submit that revision to UCRIHS and receive approval prior to implementing the change.

Instructions for each of these actions is on the UCRIHS website, or you can stop by the UCRIHS office at 246 Administration Building and consult with staff about your project.

### **• Informed Consent - The Cornerstone of Protecting Human Subjects**

One of the most important elements of an application for UCRIHS approval is the provision by the investigators for the informed consent of research subjects. While informed consent is usually written, occasionally it may be obtained verbally in situations in which written consent is deemed culturally disrespectful or inappropriate. Verbal informed

consent may also be useful in research involving informal data collection methods (i.e., student research in courses). In all cases -- for written or verbal consent -- the IRB must review in advance the language that will be used in the informed consent process.

Due to the diverse nature of research involving human subjects it is nearly impossible to provide a "template" for informed consent. There are, however, specific recommendations regarding the types of information that should be offered to participants, and the type of language that should be used in informed consent documents.

### **Informed Consent is a Process, Not Just a Form**

Information must be presented to enable persons to decide voluntarily whether or not to participate as a research subject. It is a fundamental mechanism to ensure respect for persons who may be willing to offer their bodies and experiences to assist investigators in research without promise of benefit. The procedures used in obtaining informed consent should be designed to educate the subjects in terms that they can understand. Therefore, informed consent language and its documentation must be written in "lay language" (i.e. understandable to the people being asked to participate). Think of the document primarily as a **teaching tool, not as a legal instrument.**

Simple declarative sentences are most appropriate for explaining the study's purpose, duration, experimental procedures, alternative treatments (if applicable), risks, and benefits.

Use of the first person (e.g., "I understand that...") or statements starting with "You understand that" are **not recommended** because they could be interpreted as suggestive and can constitute coercive influence over a subject. The only "I" statement necessary is one above the signature line declaring that participants understand the procedures and voluntarily participate. Use of scientific jargon and legalese is not appropriate.

- **Basic Elements of Informed Consent**

Federal Policy 46.116 requires that the following information must be provided to each subject:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. Statements concerning confidentiality should include language equivalent to the following: "Your privacy will be protected to the maximum extent allowable by law." Since there are situations in which a researcher may be compelled to break the confidentiality of subjects (e.g. in response to a subpoena), absolute guarantees are not possible.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject. IN ADDITION, the form should contain contact information for the IRB separate from the Principle Investigator for

participants with questions about their role as a subject of research. Please include David Wright as that contact:

David E. Wright, Ph.D.

Chair, University Committee on Research Involving Human Subjects  
(517) 355-2180

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of any benefits to which the subject is otherwise entitled.

You can obtain more information about necessary elements of informed consent at the NIH website:

<http://www.nih.gov/grants/oprr/humansubjects/guidance/ictips.htm>



**THE "COMMUNITY MEMBER"**  
**DISCUSSES UCRIHS AND HUMAN**  
**SUBJECT RESEARCH**

Contributed by

The Reverend **David Dressel**

**M.Div, Th.M., M.A.**

Pastor, Martin Luther Chapel

**East Lansing, Michigan**

Community Member, UCRIHS

Federal regulations promulgated by the Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA) require that any research institution such as Michigan State University include at least one independent, non-university-affiliated individual as a member of an approved Institutional Research Board (IRB). At Michigan State University, among the other members representing the various departments, colleges, and facets of the university, the University Committee on Research Involving Human Subjects (UCRIHS)

has one community member who serves as a full working/voting member of the board.

The basic premise of this requirement is to ensure that the fundamental principles of the Board are carried out. This individual, who is not subject to university control, is supposed to reflect the moral/ethical climate of the community and represent the individuals who are subjects of research.

The mandate of UCRIHS is to ensure:

- that the rights of the subjects are protected;
- that the risks do not exceed the benefits;
- that subjects understand the research and their role in it; and
- that subjects have the voluntary right to participate, not to participate, or to withdraw at any time without penalty.

I have found that the members of the MSU University Committee on Research Involving Human Subjects have consistently been committed to the principles of protecting the rights of subjects. At the same time, they have worked to find the most effective ways for a researcher to conduct productive research and contribute to the general knowledge pool.

The role of the community member becomes particularly critical if at any point the basic functioning of UCRIHS is threatened. While researchers and administrators are committed to protecting the rights of subjects, they also face strong competing pressures, e.g. advancing the research agenda of the university with its associated grant or contract income, or advancing the career of the researcher. While researchers and contractors can often speak forcefully to those in power, and possibly even to their colleagues on the IRB, potential subjects usually cannot participate in that dialogue, and as a result, may be vulnerable. This may mean that subtle and even unintended pressure is exerted on the IRB to value the interests of the institution and researcher above those of the subjects. Since the community member is not subject to university pressure or sanctions, he/she should be able to ensure that no inappropriate pressure can be applied from a researcher or administrator or member(s) of the

committee that might cause the rights of the subjects to be abrogated.

The very presence of a community member is a consistent reminder to the whole committee that what they do is done on behalf of all society. The UCRIHS exists not only to protect those individuals of high economic, academic, or social standing, but also especially to protect the rights of the more vulnerable members of society who may be subjects of research and need special consideration, advocacy, or protection.

Risks to subjects involve not only medically identifiable risks, but also social and psychological risks, which vary dramatically depending upon the social or cultural context and situation of the subjects. What may appear as a non-risk situation for one subject may in fact be a serious threat to another. A community member may be particularly helpful in identifying these risks, while also helping the researcher do effective research and, above all, protect the subjects.

There are two issues that I see as being particularly significant in this regard. The first is recruitment and involvement of subjects without coercion, manipulation, or a paternalistic attitude, which implies the researcher or another entity, knows what is best for the subject. This means that the subject or subject guardian/advocate must be free to choose whether or not to be and stay involved.

The second issue, closely linked to the first, is that the subject him/herself (or guardian/advocate), is the only one who can determine whether participation in the research is appropriate. The shorthand for this is commonly called "Informed Consent." It is inadequate, however, simply to have subjects sign a "Consent Form", unless, in doing so, the subjects are empowered with sufficient understanding of the research. This means an understanding of the potential risks as well as the potential benefits for their particular situation, so that they have ability to decide whether or not they should participate.

In my service on UCRIHS, I have grown in my respect for researchers, their desire to expand knowledge in their fields, as well as their care and appreciation for those individuals who consent to participate as

subjects. I celebrate the fact that the researcher who conducts research upon subjects and does not seek their greater good is the rare exception. While UCRIHS exists to protect all subjects, it is for the protection of subjects of those researchers, in particular, that the Institutional Review Board exists.



### **A NOTE OF THANKS**

A special thanks goes to **The Graduate School** for providing the necessary funds and staff to distribute *Research Integrity* to all graduate students and faculty at Michigan State

University. We wish to acknowledge this contribution with thanks and appreciation as **The Graduate School** continues its dedication to research ethics and integrity.



### **INTERNET ACCESS**

***Research Integrity* can be accessed through the World Wide Web on the Graduate School**

**Home Page at:**

<http://www.msu.edu/user/gradschl/integrity.htm>

### **USEFUL RESOURCES FOR RESEARCH ETHICS INVOLVING HUMAN SUBJECTS**

**MSU's Center for Biomedical Research**

<http://www.msu.edu/~biomed/rcr>

**The Belmont Report**

<http://grants.nih.gov/grants/oprr/humansubjects/guidance/belmont.htm>

**Veterans Administration Research and Development**

<http://www.va.gov/resdev/fr/preventrisk.htm>

**Office of Research Integrity**

<http://ori.dhhs.gov/>

**National Science Foundation**

<http://www.nsf.gov>

**Nuremberg Code**

[http://www.ushmm.org/research/doctors/Nuremberg\\_Code.htm](http://www.ushmm.org/research/doctors/Nuremberg_Code.htm)

**Department of Energy**

<http://www.er.doe.gov/production/ober/humsubj/hsindex.html>

**World Health Organization**

<http://www.who.int/dsa/cat98/ethics8.htm>

**National Institutes of Health**

<http://www.nih.gov>

**National Bioethics Advisory Commission**

[http://bioethics.gov/cgi-bin/bioeth\\_counter.pl](http://bioethics.gov/cgi-bin/bioeth_counter.pl)

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