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Fully Informed Consent:
Can Public Trust Be Restored and Harms Avoided?

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Fully Informed Consent:
Can Public Trust Be Restored and Harms Avoided?

by

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Currently, research with human subjects is going through a period of tremendous upheavals. In many cases, these upheavals have created a variety of unmet expectations and have given rise to the perception that trust in the research enterprise is eroding. Trust is vital to the responsible conduct of research and, without it, many believe that the entire system of research with humans will inevitably fail. Inherent in the practice of research with humans is a diverse set of physical, social, and psychological risks, the disclosure of which affects a subject's understanding and voluntary agreement to participate. Generally, trust asserts that research personnel can be relied upon to act with integrity, discretion, and competence in their relationships with subjects and the public. Trust in the research process is generated through the subject-investigator relationship and is warranted when role-specific obligations, such as respecting the rights and welfare of participants, are met. Crucial among these obligations is the ethical requirement to respect the autonomy of individual subjects through an ethically competent informed-consent process. Using the Jesse Gelsinger case as an illustration, I will argue that when the doctrine of informed consent is inadequately applied, not only can research volunteers be unjustly harmed, but the foundation of trust is also betrayed.

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INTRODUCTION

Clinical research involving human beings is a moral, scientific, and humanistic endeavor. It is premised on two fundamental commitments: to improve human welfare by advancing scientific knowledge and understanding of disease and illness; and to preserve and protect the dignity and health-related interests of those who participate in it as subjects. Inherent in the practice of research with humans is a diverse set of physical, social, and psychological risks, the disclosure of which affects a subject's understanding and voluntary agreement to participate. In seeking to realize both individual and societal benefits associated with these commitments, researchers and their institutions are obligated to recognize, mitigate, and perhaps prevent a diverse array of potential risks and conflicts. Clearly, whenever societal needs for progress and the rights of individuals and groups come into conflict, the situation becomes ethically problematic, and ethical safeguards are necessary. Whenever the conflicts are not adequately addressed and communicated to those who will be affected by them, the system of trust begins to erode.

Currently, research with human subjects is going through a period of tremendous upheavals. In many cases, these upheavals have created a variety of unmet expectations and have given rise to the perception that trust in the research enterprise is faltering. Trust is vital to the responsible conduct of research and without it many believe that the entire system of research with humans will inevitably fail. Trust in the research process is generated through the subject-investigator relationship and is warranted when role-specific obligations, such as respecting the rights and welfare of subjects, are met. Crucial among these obligations is the ethical requirement to respect the autonomy of individual subjects through an ethically competent informed-consent process. Generally, trust asserts that the organization's culture and its research personnel can be relied upon to act

with integrity, discretion, and competence in their relationships with subjects and the public.

In this thesis, I develop the following claims: By not adhering to the existing standards and norms governing contemporary research practice, investigators and their research teams threaten the ethical integrity of the research enterprise. Further, by deviating from well-established ethical requirements to respect the autonomy and self-determination of research participants, investigators and their research teams are poised to magnify those harms already inherent in the research enterprise. These claims are based upon three assumptions: 1) the investigator and the organization in which the investigator works are two components of a larger integrated system that is entrusted to protect the rights and welfare of those who participate in human subjects research; 2) moral agency resides in the investigator and the investigator's team, who are entrusted with a diverse set of obligations aimed at protecting the safety and well-being of research volunteers, as well as respecting their autonomy and self-determination; 3) the initial point at which trust is established between a research participant and the investigator is the informed-consent process. I will argue that when the doctrine of informed consent is inadequately applied, research subjects can be unjustly harmed, the system fails, and the foundation of trust is betrayed.

In order to develop this argument, I present an analysis of the Jesse Gelsinger case as an illustration of the problems that give rise to breaches of trust. Excerpts from the narrative entitled "Jesse's Intent"[1] published by Jesse's father, Paul Gelsinger, will be used to demonstrate specific instances of violations in the regulations, principles, codes,

[1] "Jesse's Intent" is a brief chronology of Jesse Gelsinger's life growing up with a chronic liver disease called ornithine transcarbamylase (OTC) deficiency syndrome as told by his father, Paul Gelsinger. The story also provides chronologic detail regarding Jesse's participation in and subsequent death from a gene therapy study conducted at University of Pennsylvania in which Jesse was enrolled as a healthy volunteer. The complete story is available at www.circare.org/submit/jintnet.pdf.

and so forth that govern clinical research. This narrative provides the groundwork for my conclusion that adequate moral regard for the rights and well-being of the research subject is not equivalent to mere compliance with rules and regulations. As observed by Kathi Hannas, a Washington, D.C., health and policy consultant:

> In many ways, the case of Jesse Gelsinger highlighted the failures of the more menial and yet subtle aspects of the oversight system. His death most likely resulted not from his underlying medical condition but rather from the experimental intervention combined with a breakdown in the system of protections. These failures are in many ways paradigmatic–lack of accountability, conflicts of interest on the part of the investigators and the research institutions involved, insufficient monitoring once the trial began, questionable scientific review procedures, and inadequate resources for comprehensive and stringent review, monitoring and oversight. These routine but crucial tasks, when conducted comprehensively and in tandem, constitute the daily operationalization of the ethical principles of respect of autonomy, beneficence, and justice. Just believing the principles is not good enough–individuals and institutions must act on them. The Gelsinger case was evidence that that is more easily said than done.[2]

My emphasis on the informed-consent process as a failure of ethical responsibility is not addressed in the quotation by Hannas but, I believe, is an example of a moral failure directly attributable to the erosion of trust. To illustrate, I will present excerpts from "Jesse's Intent." I will focus on the informed-consent process and then link this critical process in human subjects research to Paul Gelsinger's inability to trust the system governing clinical research. I will offer a critique of the conclusions offered by Paul Gelsinger and demonstrate how these might provide a useful mechanism for restoring public trust in research.

[2] Kathi Hannas, "A Systems Approach to Protecting Research Participants: The Institute of Medicine Report on Responsible Research," *Research Practitioner* 3, no. 5 (September–October 2002): 154.

In chapter 1, I will describe the regulatory system's approach as one ingredient for protecting human participants that has developed over the years in response to the atrocities uncovered in research on human beings. In this chapter, I will outline those elements that are integral to a system of trust that values safety and respect for persons above all else in research with human subjects. I will illuminate the interdependencies of the components of a system of trust, and illustrate the potential risks if a breakdown occurs. The informed-consent process, as a critical component, will be introduced.

In chapter 2, I will provide a review of the ethical domain, with special emphasis on informed consent as the second ingredient in the system that serves to protect the rights and welfare of subjects who participate in human subjects research. Included in this review will be the Nuremberg Code of 1947, the Declaration of Helsinki Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (revised 2003), and the Belmont Report. This chapter will include a review of select scholarly publications, such as Henry Beecher's article titled "Ethics and Clinical Research."

In chapter 3, I will substantiate my claim that simply meeting the regulations does not ensure ethical accountability. I will utilize the Food and Drug Administration warning letters, the Office of Human Research Protections findings, and the informed-consent process described by Jesse's dad, Paul Gelsinger, to provide an analysis of the promises and failures of the research protections system, inclusive of the informed-consent process and the doctrine of respect for persons.

In my conclusion, chapter 4, drawing from the information provided in the first three chapters, an analysis of the failures within the regulatory and ethical domains as situated within the context of the Jesse Gelsinger case will be synthesized and thoughts on implementation of a robust system for protecting human subjects will be presented. I

will reaffirm my position that organizations and their investigators who do not embrace the ethical principle of respect for persons defraud the system that has been developed to safeguard those who entrust the research enterprise to protect their rights and welfare when they volunteer to participate as research subjects which results in diminished trust.

CHAPTER 1: History of the Regulatory System for Human Subjects Research

This chapter will provide a selected chronological timeline of the implementation of the regulatory system comprised of laws, policies, and other codified "rules" established in response to specific public concerns about the way research had been conducted in the recent past. The focus of this brief history will be an illustration of the inception of the various regulatory components that, taken together, constitute the current system for protecting human subjects. The significance of this section is to show that regardless of how many components have been added, egregious acts continue to occur, resulting in diminished public trust of the clinical research process. In order to restore this trust, the organization and its investigators must establish a culture that values the safety and welfare of the research subject as the prima facie duty.

The Research Culture

Experiments on human subjects date all the way back to the Hellenistic Greek period (350 B.C.E.), as doctors tried to understand how the human body works. Scholars like Avicenna (980-1037) insisted that "the experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."[3] Experimentation was frequent enough to inspire a discussion of the ethical maxims that should guide would-be investigators. Moses Maimonides (1135–1204), the noted Jewish physician and philosopher, developed a deontological approach to the ethics of human experimentation instructing colleagues always to treat patients as

[3] J. P. Bull, "The Historical Development of Clinical Therapeutic Trials," *Journal of Chronic Diseases* 10, no. 3 (September 1959): 221.

ends in themselves, not as means for learning new truths.[4] Roger Bacon (1214-1294) excused the inconsistencies in therapeutic practices on the following grounds:

> It is exceedingly difficult and dangerous to perform operations on the human body. The operative and practical sciences which do their work on insensate bodies can multiply their experiments till they get rid of the deficiency and errors, but a physician cannot do this because of the nobility of the material in which he works; for that body demands that no error be made in operating upon it, and so experience [the experimental method] is so difficult in medicine.[5]

For most of the nineteenth century, human experimentation throughout Western Europe and the United States was a cottage industry, with individual physicians trying out one or another remedy on neighbors, relatives, or themselves.[6] Claude Bernard (1813–1878) argued in 1865 that "the principle of medical and surgical morality consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others." Bernard did allow exceptions, sanctioning experimentation on dying patients and criminals about to be executed, as "they involve no suffering or harm to the subject of the experiment."[7] Thus, experiments ranged from vivisections of prisoners in the early Greek period to self-inoculations and experiments on the lesser societal classes in the eighteenth

[4] David J. Rothman, "Research, Human: Historical Aspects," in *Encyclopedia of Bioethics*, 2nd ed., ed. Warren T. Reich (New York: Free Press, 1995), 2248.

[5] Bull, "Historical Development," 222.

[6] Rothman, "Research, Human," 2249.

[7] Ibid.

century,[8] and culminated in the numerous controversies over reported abuses of human subjects after 1870 and a host of twentieth-century developments.[9]

In addition to the Federal Food and Drug Act, passed as United States law in 1938, requiring drugs to be shown to be safe before marketing, and leading to the need for human trials,[10] the more significant, transforming event in the conduct of human experimentation in the United States was World War II. During the summer of 1941, President Franklin Roosevelt created the Office of Scientific Research and Development (OSRD) to oversee the work of the two committees in which one–the Committee on Medical Research (CMR)[11]–was to combat the health problems that threatened the combat efficiency of American soldiers. Thus, the occasional and *ad hoc* efforts by individual practitioners had evolved into well-coordinated, extensive, federally funded team ventures. Whereas prior investigations were individually based to help a specific person or community, human experimentation was now designed to utilize one population of individuals for the benefit of others, especially those fighting the war. Likewise, the relationships changed from the investigator having known the research subject to the investigator conducting research on strangers. Research was becoming depersonalized. These developments had important consequences for the ethical justification for how volunteer subjects should be treated.

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[8] Harold Y. Vanderpool, ed., *The Ethics of Research Involving Human Subjects: Facing the 21st Century*, (Frederick, Md.: University Publishing Group, 1996), 5.

[9] Gert H. Brieger, "Human Experimentation: History," in *Encyclopedia of Bioethics*, rev. ed., (New York: Macmillan, 1978), 684-92; David J. Rothman, "Ethics and Human Experimentation. Henry Beecher Revisited." *New England Journal of Medicine* 317, no. 19 (November 5, 1987): 1195-99; Susan E. Lederer, *Subjected to Science: Human Experimentation in America before the Second World War* (Baltimore, MD.: Johns Hopkins University Press, 1995).

[10] Office of NIH History, "Timeline of Laws Related to the Protection of Human Subjects." www.history.nih.gov/01Docs/historical/2020b.htm (accessed June 29, 2007).

[11] The other committee was devoted to weapons research.

Over the course of World War II some six hundred research proposals, many involving human subjects, competed for some twenty-five million dollars in funding that was carried out by investigators from 135 universities, hospitals, research institutes and industrial firms.[12] The general obligation on the part of the researchers, to obtain consent of the participants, was mitigated by the urgency to obtain data.[13] The philosophy of those conducting the research was that volunteering one's body to research was a duty just as much as volunteering to fight the war. Much of the testing was performed on orphans, the mentally ill and prisoners, and was justified as a contribution to the war effort. In effect, the wartime values, in great contrast to the deontological approaches to human experimentation by Maimonides, pushed for a straightforward utilitarian ethic. Its premise, that "the greatest good for the greatest number," became the most compelling justification for sending some men to be killed so that others might live. This same ethic seemed to justify using institutionalized retarded or mentally ill persons in human subject research.[14]

Although there have been numerous questionable acts of experimentation on human subjects, the current system is largely formed on three seminal events: 1) the 1946 Nuremberg Doctors Trial, 2) the 1960s Thalidomide tragedy, and 3) the 1972 Tuskegee Syphilis Study Expose, each of which will be discussed briefly below. These three events are a few of the historical examples that have prompted efforts to build a system which can be entrusted to protect the safety of human subjects.

[12] Rothman, "Research, Human," 2251.

[13] Ibid.

[14] Ibid., 2252.

The Early Years of the System

On August 19, 1947, twenty physicians and three medical administrators were charged with "murders, tortures and other atrocities committed on unwilling victims, resulting in death, disfigurement or disability in the name of medical science" at the Doctors' Trial in Nuremburg, Germany.[15] The standards by which they were judged, although devised during the trial period, were thought to be so fundamental to medicine's moral code that trial leaders agreed the standards should have been known to any civilized person. While the problematic nature of human subjects experimentation had long been recognized, the Nuremberg trial and the Nuremberg Code drew unprecedented attention from the public, from the medical and scientific professions, and from public authorities.[16] The tribunal acknowledged that "certain types of medical experiments … conform to the ethics of the medical profession generally" and went on to delineate ten "basic principles that must be observed in order to satisfy moral, ethical and legal concepts."[17] The Code stated that:

1. Voluntary consent of the human subject is absolutely essential. The Code emphasized consent could be voluntary only if subjects are able to consent, are free from coercion and comprehend the risks and benefits involved.
2. The experiment should be such as to yield fruitful results for the good of society. The experiment can be conducted on humans only if the

[15] Albert R. Jonsen, "Experiments Perilous: The Ethics of Research with Human Subjects," in *The Birth of Bioethics* (New York: Oxford University Press, 1998), 134.

[16] Ibid.

[17] Ibid.

information can not be obtained through other sources and can not be random.[18]

3. The experiment should be designed based on previous animal experimentation and knowledge of the natural history of the disease. The expected results should justify the experiment.
4. The experiment should be conducted so that all unnecessary physical and mental suffering and injury are avoided.
5. No experiment should be conducted where there is *a priori* reason to believe that death or disabling injury will occur.
6. The degree of risk to be taken should never exceed the determined humanitarian importance of the problem.
7. Proper preparations should be made and adequate facilities provided to protect the subject from remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end.
10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, especially if there is reason to believe continuation can result in harm.[19]

The World Medical Association (WMA), founded shortly after World War II, held a general assembly in Rome in 1954. In response to the publicity surrounding the

[18] In other words, the study must be scientifically valid and result in useful information providing knowledge that betters the health of society.

[19] Germany (Territory under allied occupation, 1945-1955: U.S. zone) Military Tribunals, ed., "Permissable Medical Experiments," in *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10: Nuremberg October 1946–April 1949*, vol. 2 (Washington, D.C.: U.S. Government Printing Office, 1949-1953) [hereafter Nuremberg Code]; *The Nuremberg Code* (1949), reprinted in *The Ethics of Research Involving Human Subjects*, ed. Harold Y. Vanderpool, Appendix A, 431-32.

Nazi experiments, the WMA approved "Principles for Those in Research and Experimentation" while at this assembly.[20] An expanded version was approved in June of 1964 at the general assembly in Helsinki, where these principles became known as the Declaration of Helsinki. The statements were introduced as recommendations to serve as a guide to every physician throughout the world conducting research involving human subjects.[21]

In July of 1962, an article broke in the *Washington Post* reporting that a sleeping pill compounded with a new drug call Thalidomide was suspected of causing serious limb deformities in the human fetus.[22] The drug, prescribed widely in Europe, had been taken early in pregnancy as a remedy for morning sickness. Although the drug had been kept out of the American market by Dr. Frances O. Kelsey, despite opposition from the drug's manufacturer and others within the Food and Drug Administration (FDA), she was unable to keep it from being used as an experimental drug under clinical investigation. As an experimental drug, beginning in 1960, Thalidomide had been prescribed to approximately twenty thousand women by twelve hundred well-known and well-respected physicians."[23] During this same time, Senator Estes Kefauver had sponsored Congressional hearings into the practices of the FDA, perceived by some to be aligned with the pharmaceutical industry beginning in 1959. There was concern that physicians and the FDA were more interested in assisting the pharmaceutical industry bringing new drugs to market as opposed to protecting the welfare of patients and research subjects. The investigation resulted in amendments to the Food, Drug and Cosmetic Act in 1962,

[20] Jonsen, "Experiments Perilous," 136.

[21] Vanderpool, *Ethics of Research*, 434.

[22] Jonsen, "Experiments Perilous," 140.

[23] Ibid., 141.

codified as law and promulgated as FDA regulations (21 CFR 130.3) in 1963. These regulations strengthened the government's control over the approval of new drugs, demanding "substantial evidence of efficacy" and requiring for the first time full and free consent of all subjects of drug trials conducted within the United States.[24]

Despite the atrocities uncovered in the Nuremberg trials and the resulting introduction of the Nuremberg Code of 1947, in the early 1960s, only nine of fifty-two American departments of medicine had a formal procedure for approving research involving human subjects and only five more indicated that they favored this approach or planned to institute such procedures.[25] During this time period, the atrocities were associated with Germany, and the attitude of the American public was that the activities were confined to Germany. Atrocities such as those that were uncovered in the Nuremberg trials could not possibly occur on American soil. Therefore formal procedures for approving research with human subjects were not necessary.

In 1964, a statement of ethical principles known as the Declaration of Helsinki[26] was introduced by the World Medical Association to provide guidance to physicians and others engaged in experimentation using human subjects. The Declaration of Helsinki utilized much of the framework laid by the Nuremberg Code, adding that clinical research should be based on animal and laboratory studies; the research should be preceded by a careful assessment of risks and benefits to the patient; participants should be fully informed and must freely consent to the research; results obtained in an unethical manner should not be accepted for publication; responsibility for the human subject rests

[24] Ibid.; Office of NIH History, "Timeline of Laws."

[25] Mark S. Frankel, *The Public Health Service Guidelines Governing Research Involving Human Subjects: An Analysis of the Policy-Making Process* (Washington, D.C.: George Washington University Program of Policy Studies in Science and Technology, 1972).

[26] World Medical Association, Declaration of Helsinki: "Ethical Principles for Medical Research Involving Human Subjects", 5th rev., http://www/wma.net/e/policy/b3.htm (accessed October 29, 2006).

with a medically qualified person–not the subject–and special care is to be taken with the informed consent of minors.[27] The Declaration of Helsinki also provided definitions for *therapeutic* (intent is to find a remedy that affects a disease or illness) and *non-therapeutic* (intent is purely scientific, and the study design is not related to a person's illness–healthy volunteer studies) research, introduced the review of a protocol by a specially appointed committee independent of the investigator and sponsor, and addressed granting of informed consent by a legal guardian. Thus the Declaration of Helsinki introduced surrogate consent into the regulations, enabling the enrollment of mentally and physically incapacitated subjects, as well as minors, provided that a competent adult was willing to provide consent on the subject's behalf. The Declaration also allowed for research of non-therapeutic intent that would not have been permitted under the Nuremberg Code.

In 1966, an article published by Henry Beecher, an anesthesiologist at Harvard Medical School, in the *New England Journal of Medicine* documented twenty-two occurrences of unethical or questionable procedures. Of concern was the recognition that these acts occurred in the most prestigious of institutions–leading medical schools, research institutes, and government entities. Also of concern, was that these unethical or questionable experiments published in leading scientific journals exposed patients to excessive risks, ignored the need for consent, used poor, mentally incapacitated persons, and withheld therapies of known efficacy.[28] In some instances, the scientific validity of the study was called into question, thereby exposing research subjects to unnecessary risks.

[27] Office of NIH History, "Timeline of Laws."

[28] Jonsen, "Experiments Perilous," 144.

As a response to Beecher's article, the U.S. Surgeon General, through the Public Health Service (PHS),[29] issued a policy statement entitled "Clinical Investigations Using Human Subjects" on February 8, 1966.[30] The policy statement required that all recipients of PHS funding institute a review of the proposed research. The review would ensure protection of the rights and welfare of research subjects, discuss the methods of informed consent for their appropriateness and conduct an analysis of the balance between risk and benefit. These independent review boards would later become known as Institutional Review Boards (IRB). Although the PHS philosophically agreed with the importance of the principle of consent, they were not ready to dispel the notion that doctors should protect their patients. Also missing from the policy statement was guidance regarding the interpretation and implementation of the policy. Therefore, each institution receiving PHS funding implemented its own process for review and developed its own standards for determining appropriateness of informed consent methods. The FDA on August 30, 1966, issued a "Statement on Policy Concerning Consent for the Use of Investigational New Drugs on Humans." This statement, subsequently codified as U.S. regulations (21 CFR 130.37, later incorporated in 45 CFR 46), distinguished between therapeutic and non-therapeutic research in alignment with the Declaration of Helsinki and spelled out the meaning of consent. The statement is discussed further in chapter 2.

[29] The PHS is a principal part of the Department of Health and Human Services (DHHS), is considered the major health agency of the federal government, and is comprised of Commissioned Corps officers and Civil Service employees. The history of the PHS can be found at http://www.nlm.nih.gov/exhibition/phs_history/intro.html (accessed July 21, 2007).

[30] Irene Smith-Coleman, "Protection of Human Subjects in Research," Congressional Research Service Report for Congress. http://www.gwu.edu/~nsarchiv/radiation/dir/mstreet/commeet/meet2/brief2/tab_i/br2i1d.txt (accessed July 22, 2007).

The System's Growing Years

On July 26, 1972, the *New York Times* carried a story regarding a study carried out by the United States Public Health Service in which men with syphilis from Tuskegee Alabama were followed in a research study and left untreated for forty years, despite the introduction of penicillin as a treatment.[31] The study was composed of approximately six hundred black men, four hundred of whom were diagnosed with syphilis but never told of the diagnosis, and an additional two hundred of whom served as a control group. The purpose of the study was to understand the natural course of the disease and its manifestations if left untreated. The protocol included performing an autopsy at death. The men were never told they were in a study. Instead they were told that they had "bad blood" and as a result needed to have periodic medical exams, including spinal taps. They were also promised free transportation to and from hospitals, free hot lunches, free medical care and free burial after the autopsy was performed. The subjects were predominantly poor and uneducated. The investigative team placed their quest for science ahead of the welfare of the Tuskegee study subjects. Any respect for the Tuskegee men as autonomous individuals was diminished as a result of the deceit perpetrated by the study team. As a result, the Tuskegee subjects were strictly used as a means for obtaining the investigative team's ends.

Beecher's article, as well as a news article by Jean Heller revealing the Tuskegee experiment in 1972, served as a catalyst for the Food and Drug Administration in 1966 and the National Institutes of Health in 1971 to develop internal policy guidelines. These guidelines were codified as Federal regulations by the U.S. Department of Health, Education, and Welfare on May 30, 1974.[32] The regulations passed in 1974 replaced the

[31] Jonsen, "Experiments Perilous," 146-47.

[32] Smith-Coleman, "Protection of Human Subjects."

policy adopted in 1966 and extended the coverage to all research conducted with DHHS support.[33] Another variation included in the 1974 regulations was the application to all research with human subjects, whereas the 1966 policy applied only to research deemed by the investigator to present risk to the subject. The Regulations serve to protect human subjects by giving detailed attention to organizational and enforcement mechanisms, such as oversight by federal agencies including the Office for Protection from Research Risks (OPRR), rules pertaining to the necessity and structure of IRBs, the documentation of IRB deliberations, and informed consent, record keeping and other IRB procedures.[34]

In July of 1974, Congress passed the National Research Act, establishing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[35] The Commission, composed of eleven members, had as one of its charges to identify the basic ethical principles that should guide the conduct of research with human subjects. Specifically, the Commission was directed to consider: 1) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, 2) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, 3) appropriate guidelines for the selection of human subjects for participation in such research and 4) the nature and

[33] The 1966 policy did not cover research that was conducted internally at DHHS agencies, especially the NIH, known as intramural research.

[34] Harold Y. Vanderpool, "Unfulfilled Promise: How the *Belmont Report* Can Amend the *Code of Federal Regulations Title 45 Part 46–Protection of Human Subjects,"* in *Ethical and Policy Issues in Research Involving Human Participants*, ed. National Bioethics Advisory Commission, sec. O, 1-20 (Bethesda, Md.: NBAC, 2001), 3.

[35] *National Research Act*, Public Law 93-348, codified at *U.S. Code* 42 (July 12, 1974) sec. 2891.202(A)(1)(A), http://history.nih.gov/01docs/historical/documents/PL93-348.pdf (accessed July 22, 2007).

definition of informed consent in various research settings.[36] A prominent social scientist, Bernard Barber, predicted, altogether accurately, that the commission "would transform a fundamental moral problem from a condition of relative professional neglect and occasional journalistic scandal to a condition of continuing public and professional visibility and legitimacy."[37] Outcomes from the commission included an endorsement of the supervisory role of the IRBs; special protections for research on vulnerable subjects such as prisoners, mentally disabled persons and children; establishment of an Ethical Advisory Board within the Department of Health and Human Services to deal with difficult cases and, most notably, the issuance of the Belmont Report.[38] Two prominent texts resulting from the work of the Commission were The Report on Ethical Principles and Guidelines for the Protection of Human Subjects of Research, better known as The Belmont Report,[39] and The Code of Federal Regulations Title 45 Part 46: Protection of Human Subjects.[40] These two documents unified a regulatory and ethical domain aimed at ensuring the public's trust while safeguarding the rights and welfare of those who participate in human subjects research, as set forth in the Nuremberg Code and the Declaration of Helsinki.

The Belmont Report was published in the Federal Register in 1979. The Belmont Report defined three basic principles for evaluating human research and has since served

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[36] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, D.C.: U.S. Government Printing Office, 1979).

[37] Rothman, "Research, Human," 2256.

[38] Ibid.

[39] National Commission, *Belmont Report*.

[40] Protection of Human Subjects, *Code of Federal Regulations*, Title 45, Part 46 (1974), http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm (accessed July 23, 2007).

as the ethical foundation supporting the intent of the federal regulations governing the conduct of human subjects research. These three basic ethical principles are: respect for persons, beneficence, and justice.[41] The Belmont Report, and more specifically the principle of respect for persons, will be discussed in chapter 2.

Based on input from a congressionally convened National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the regulations were modified in 1981 and then accepted by seventeen Federal Agencies to become known as the Common Rule in 1991. The Common Rule established that: 1) clinical research studies must be reviewed and approved by an IRB; 2) all clinical research study participants must provide informed consent; and 3) institutions conducting or sponsoring research on human subjects must provide assurances to the federal government that they will agree to apply the federal regulations, monitor research studies, and to report instances of serious and on-going non-compliance when they occur.

Also of note was the formation of Public Responsibility in Medicine and Research (PRIM&R) in 1974, a professional organization for IRB members and others interested in research ethics. PRIM&R's primary objective was to foster communication and education for IRB offices across the country.

The Institutional Review Board

The IRB is responsible to two different governing entities and therefore has two sets of regulations with which it must comply. The governing entities are the FDA (guidelines set forth in 21 CFR 50, 56) and the DHHS (guidelines set forth in 45 CFR 46). The FDA regulations provide governance for the testing and approval of devices,

[41] National Commission, *Belmont Report.*

diagnostics and therapeutics. The DHHS regulations provide governance for clinical research that is funded by any of the agencies under its umbrella. This leaves any human subject research funded by local institutions, state agencies or other not-for-profits without any IRB-required review and oversight. A representative sample of IRB requirements, as set forth in the regulations, includes:

- Appropriate composition of IRB membership to include a minimum of five members of whom at least one is non-scientific and one is unaffiliated with the institution;
- Operations that are based on written standard operating procedures;
- Authority to approve, require modifications or defer research protocols, regardless of whether the research is ongoing or not yet initiated;
- Authority to provide expedited or an administrative review of protocols;
- Establishment of criteria to be utilized for assessing risk versus benefit, equitable selection, and protection of vulnerable populations, including a look at coercion and sound research design;
- IRB activities, including IRB meetings, are to be documented via minutes of meetings;
- The elements to be addressed in the informed consent document;
- Appropriate documentation of the informed consent process.

The Department of Health and Human Services, through the Office of Human Research Protections (OHRP),[42] provides oversight of IRBs through a federal wide assurance process. This assurance is a written agreement in which the IRB provides

[42] Formerly the Office for Protection from Research Risks–OPRR

documentation, such as IRB membership, policies and procedures, and guarantees that it will comply with all Federal requirements as set forth in 45 CFR 46 Subpart A, B, C and D. The assurance must be renewed every three years. As an example of the two sets of regulations, the FDA does not invoke an assurance process but does require that all IRBs register with its office. Therefore, if an IRB is affiliated with an institution that does not receive any funding from DHHS for the conduct of human subjects research, the IRB is required to be registered with the FDA but does not have to have a federal wide assurance.

In summary, the IRB is charged with protecting the rights and welfare of human subjects participants. As such, the IRB is responsible for reviewing, requiring modifications to, and approving (or disapproving) all research protocols involving the use of human subjects. This entails assessing the risk/benefit ratio, ensuring adequate informed consent, ensuring equitable selection of participants, and reviewing all advertisements to ensure misleading statements are not communicated to the public. The detail of this review process must be documented. Because the protection of human subjects participants is such a broad and general concept, the IRB can undertake other duties that fall outside of their realm of responsibility. These may include: functioning as editor on informed-consent documents or as a medical director for the establishment of policies pertaining to associated medical practice; reviewing medical record or patient confidentiality issues that are part of a quality improvement process and not a research question;[43] and/or overseeing financial conflicts of interest and monitoring activities. Any of these additional tasks can negatively impact the time an IRB has to spend on its primary responsibility.

[43] Robert Amdur, "The Limits of IRB Authority," in *Institutional Review Board Management and Function*, ed. Robert Amdur and Elizabeth Bankert (Boston: Jones and Bartlett Publishers, 2002), 30-32.

Concerns regarding an IRB's ability to fulfill its oversight responsibilities include the lack of a law or national directive defining an IRB or requiring proposed research projects to be reviewed in a uniform manner, regardless of researcher affiliation or funding source.[44] The policies and procedures determining how an individual IRB operates are independently written by an administrative person affiliated with that particular IRB. No guidance is provided as to an *appropriate*[45] size for an IRB, nor is there any stipulation as to the maximum number of protocols that can be fully reviewed by a member of an IRB at each meeting. Additionally, there is not any guidance regarding the frequency of IRB meetings and what is considered ample time for reviewing protocols, consent forms, and other documents associated with IRB submissions. Guidelines for determining potential medical costs associated with the research or for determining the point at which subject remuneration is considered coercive does not exist. Lastly, while the regulations state than an IRB must consist of more than five members with representation from the different disciplines, as well as a non-scientific and a non-institutional affiliated member, there are minimal requirements for which disciplines should be represented. The ability for an IRB to fully comprehend the complex science behind each protocol, and stay abreast of the current practice, without having representation from the protocol-specific discipline represents a significant challenge. To complicate matters, obtaining discipline-specific expertise usually results in a potential conflict of interest situation, because the protocol under review might involve a clinical investigator from the same department or practice as the IRB reviewer.

[44] Ibid., 27-29.

[45] I use the term *appropriate* to represent both a numerical value–i.e., the correct number of members–as well as an appropriate distribution of representative specialists.

The Physician's Perspective

Bioethicist Jonathan Moreno describes the period from 1947 to 1981 as a period of weak protectionism in which physician experimenters were granted enormous discretion.[46] This period saw incredible advances in medicine that were direct results of research, such as Walter Reed's yellow fever studies. Moreno felt that despite Beecher's calling attention to research ethics abuses, Beecher, among others, was not in favor of external review of clinical trials but instead favored reliance primarily on the virtue of the investigator.[47] In his 1959 paper entitled "Experimentation in Man," Beecher argued that the best protection for the human subject would be obtained by ensuring that the investigator possessed *an understanding of the various aspects of the problem* being studied. He was quite critical of the Nuremberg Code's dictum that the subjects themselves should have sufficient knowledge of the experiment before agreeing to participate.[48] This sentiment was echoed by others, including Walsh McDermott, a professor of public health and medicine at Cornell University Medical College. In 1967, McDermott expressed grave doubt that the *irreconcilable conflict* between the *individual good* and the *social good* to be derived from medical research could be resolved, and certainly not by *institutional forms* and *group effort*–apparently references to ethics codes and peer review.[49] In a speech given at the annual meeting of American College of Physicians on "The Changing Mores of Biomedical Research," McDermott stated, "Medicine has given to society the case for its rights in the continuation of clinical

[46] Jonathan D. Moreno, "Goodbye to All That: The End of Moderate Protectionism in Human Subjects Research," *Hastings Center Report* 31, no. 3 (May-June 2001): 10.

[47] Ibid, 13.

[48] Henry K. Beecher, "Experimentation in Man," *Journal of the American Medical Association* 169, no. 5 (January 31, 1959): 461-8.

[49] Moreno, "Goodbye to All That," 13-14.

investigation," and "playing God" is an unavoidable responsibility, presumably one to be shouldered by clinical investigators.[50] In 1971, Louis Lasagna, a physician who practiced clinical pharmacology at Rochester University, wondered "how many of medicine's greatest advances might have been delayed or prevented by the rigid application of some currently proposed principles." Rather, "for the ethical, experienced investigator no laws are needed and for the unscrupulous incompetent no laws will help."[51]

Despite the view of many in medicine, as evidenced by the continued abuses of special populations and other acts of questionable conduct, relying on the virtue of the individual investigator was not enough. The system could only work if the investigator placed respect for persons above the quest for scientific knowledge and career advancement. In addition, the system was, and still is, dependent on the reporting of accurate and timely information. If this does not occur, the system fails and public trust diminishes.

Following the period in which judgments such as treatment versus therapy, assessment of risk, and capacity of the subject to provide consent, labeled by Moreno as the period of weak protectionism, is the period Moreno calls the era of moderate protectionism. The period began in 1981 and lasted twenty years. A catalyst for this move was the media publication of the Tuskegee Syphilis Study scandal. The news regarding this study validated the concerns of Paul Ramsey, a Princeton theologian, who declared in his 1970 work *The Patient as Person*, "No man is good enough to experiment upon

[50] Walsh McDermott, "Opening Comments on the Changing Mores of Biomedical Research," *Annals of Internal Medicine* 67, no. 3, supp. 7 (September 1967): 41-42.

[51] Louis Lasagna, "Some Ethical Problems in Clinical Investigation," in *Human Aspects of Biomedical Innovations*, ed. Everett Mendehlsohn, Judith P. Swazey, and Irene Taviss (Cambridge, Mass.: Harvard University Press, 1971), 105 and 109.

another without his consent."[52] The philosopher Hans Jonas increased the moral burden of the clinical investigator. Jonas stated:

> We can never rest comfortably in the belief that the soil from which our satisfactions spout is not watered with the blood of martyrs. But a troubled conscience compels us, the undeserving beneficiaries, to ask: who is to be martyred? in the service of what cause? and by whose choice?[53]

Jonas' remarks cast a shadow of doubt on the clinical investigator as the sole source for entrusting the well being of the research participant. This attitude was reinforced in a 1977 essay by philosopher Alan Donagan, referring to the Tuskegee experience. Donagan focused on the question of balance between the subjects' interests and those of science and the public. Also questioned was the amount of discretion to be afforded to the lone investigator.[54] The transition from a weak system of protections to a moderate system is largely dependent upon the implementation of the prior review process and is known today as the Institutional Review Board. In this period there was a compromise between physician discretion and modest external oversight:

> … researchers for the most part had the prerogative of identifying potential conflicts of interest themselves, without external review. Researchers' use of human subjects was approved before and after it actually took place, and only very rarely was there third party observation of research activities themselves.[55]

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[52] Paul Ramsey, *The Patient as Person: Explanations in Medical Ethics* (New Haven, Conn.: Yale University Press, 1970), 5-7.

[53] Hans Jonas, "Philosophical Reflections on Experimenting with Human Subjects," *Daedalus* 98, no. 2 (Spring, 1969): 223-24.

[54] Alan Donagan, "Informed Consent in Therapy and Experimentation," *Journal of Medicine and Philosophy* 2, no. 4 (December 1977): 318-29.

[55] Moreno, "*Goodbye to All That,*" 10.

The Current Regulatory System

Today's system of human subjects protections is comprised of oversight and educational organizations, such as the Office for Human Research Protections, Public Responsibility in Medicine and Research, the Office of Inspector General (OIG), the FDA, and consumer groups, among others; sponsors of human subjects research; organizations that conduct research protocols involving human subjects; IRBs; investigators; and the subjects who participate in human research studies. These entities' functions are grounded in laws, codes and acts that have been promulgated during the last half century. Responsibility for the protection of human subjects is dependent on the sponsors of research, the institutions who receive sponsor funding, and the investigators working within the regulatory framework. Once a clinical study has been approved, the investigator assumes the responsibility for protecting the research subjects and establishing a relationship of trust.

The regulatory system alone can not adequately guarantee protections for subjects who participate in research. To properly safeguard the rights and welfare of human subjects, the regulatory system must be augmented with ethics. The ethical domain defines what ought to occur when conducting research on human subjects, thereby moving from a culture that simply meets the letter of the regulations to a culture that embraces the intent behind the regulations. Only by embracing values such as respect for others, beneficence, justice, safety, and integrity will institutions move from a culture of compliance to a culture of conscientious and virtuous practice. Within this reformed culture, institutions and individual researchers have a prima facie duty to respect subjects' rights to freedom and self-determination. The moral center for this obligation is the informed-consent process.

It is this system that engenders or undermines public trust of the research process. As stated by Moreno et al., "… science is a social enterprise. Like all science, biomedical and behavioral research with human subjects can only fulfill its great promise if it is worthy of the wider society's trust."[56] Together, they reflect the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's intent to balance the public's interest in protecting the rights and welfare of research participants, thereby instilling public trust while encouraging the development of knowledge that can benefit individuals, research study populations, and society as a whole. The moral center for this obligation is the informed-consent process.

This ethical domain will be explored in chapter 2. Primary attention will be paid to the principle of respect for persons as it relates to informed consent. It is at this juncture where the potential subject is initiated into the research process and individual trust is established. A synopsis of the values embedded in informed consent will be provided.

[56] Jonathan Moreno, Arthur L. Caplan, and Paul Root Wolpe, "Updating Protections for Human Subjects Involved in Research," *Journal of the American Medical Association* 280, no. 22 (December 9, 1998): 1951.

CHAPTER 2: The Ethical Domain–Values Embedded in Informed Consent

The significance of this section is to show that, despite an increasingly complex array of legal, ethical, regulatory, and professional attempts to inculcate a robust system of protection, institutions must begin to reform their efforts at both the individual and organizational levels and be accountable to the core values and ethical principles that undergird responsible research practice.

The moral center of all clinical research activity, and the most integral component, is the human subject. For without the participation of human subjects, clinical research does not exist. The term *human subjects* is used throughout the federal regulations and international guidelines. The historical justification for referring to the person being studied as the human subject is to distinguish the person being studied from the investigator, to make clear who is the object of the study, and to signal an inherent power asymmetry.[57] Hence, the federal regulations and international guidelines are structured to afford protections to the subjects as a person who is vulnerable to the conflict of the investigator's interest between advancing science and protecting the well-being of the subjects. This becomes especially difficult when the sole purpose of the study is gaining knowledge that is to hopefully benefit future generations, and when the investigator is in the dual role of physician providing medical care and investigator pursuing knowledge. Therefore, within the ethical domain, the intent behind the regulations is to clarify that when conflicts arise, the rights and welfare of the subjects

[57] Hannas, "Systems Approach," 155.

must trump the scientific inquiry of the investigators and the institutions sponsoring the research.[58]

Recently, there is a shift in referring to those who partake in clinical research as *participants* versus *human subjects*. Of concern is that utilization of the new term symbolizes the objects of study as active members engaged in the process, thus mitigating their vulnerability and thereby also reducing the protections afforded to them. As quoted by Hannas, "The term 'subject' highlights the reality of information and power imbalances, whereas the term 'participant' reflects at best a moral aspiration and at worst symbolic political correctness."[59]

An unavoidable facet of research with human subjects is that individuals agree to place themselves at risk in exchange for benefits that will most likely accrue to future patients and not themselves. The moral justification for this dissemination of risks and benefits is dependent on the concept and process of informed consent.[60] As stated by the philosopher T.M. Wilkinson, "The most well-known and best thought-out protection of human subjects participating in research studies is the requirement to obtain informed consent."[61] The term *informed consent* was first introduced in 1957, but serious discussion of the concept did not begin until around 1972.[62] Discussions of the concept of informed consent evolved over a period of time, from the passive activity of disclosing

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[58] Ibid.

[59] Ibid., 156.

[60] Jeffrey P. Kahn and Anna C. Mastroianni, "Moving from Compliance to Conscience: Why We Can and Should Improve on the Ethics of Clinical Research," *Archives of Internal Medicine* 161, no. 7 (April 9, 2001): 926.

[61] Quoted in Thomas May Wilkinson, "Individualism and the Ethics of Research on Humans," *HEC Forum* 16, no. 1 (March 2004): 6.

[62] Tom L. Beauchamp and Ruth Faden, "Informed Consent: History of Informed Consent," in *Encyclopedia of Bioethics*, ed. Warren T. Reich (New York: Free Press 1995), 1232.

information to subjects to an active obligation on the part of the investigator to assess the subjects' understanding of the research protocol in which the patient might participate. In large part, this is due to a resurgence of interest and commitment to fulfilling one of the cardinal principles of the Belmont Report. The principle of "Respect for Persons" obligates the investigator to disclose all information that would enable a reasonable person to make an informed decision and for the investigator to respect that decision of the potential subject as an autonomous individual. As such, the elicitation of informed consent is not just a protection from risk, but instead a protection and promotion of respect for autonomy. It is the means by which a person's right to self-determination and personal dignity is honored. The principle of respect for others includes honoring the needs and dignity of persons incapable of acting autonomously.[63] When the concept of informed consent is not fulfilled, the research subject becomes a mere means to satisfy the ends of the investigator, and respect for persons is not realized.

This chapter will include a synthesis of the values embedded in the doctrine of *informed consent*[64] as it developed and the sentinel documents that gave rise to the ethical requirement. Included will be identification of the elements of informed consent, a discussion of the ethical principles that frame informed consent, and a selected review of the literature depicting the inadequacies of informed consent. I conclude with a discussion of the significance of informed consent for establishing trust.

[63] Ibid., 1236-37.

[64] I will be discussing only informed consent in the research context. The literature used in this chapter is in no way inclusive of all of the literature on this subject.

Definition of Informed Consent

Once a research study has been approved by the IRB, an investigator is authorized to identify potential research subjects and obtain informed consent. Informed consent is a process in which a subject voluntarily confirms his or her willingness as a choice to participate in a research study. Informed consent is both a legal and ethical doctrine. As a legal doctrine, informed consent protects the subjects' right to self-determination. As an ethical doctrine, informed consent promotes respect for persons and entitles the subject to act as an autonomous individual. Therefore, an investigator has both a legal and a moral duty to obtain informed consent.

Informed consent is composed of a document and a process. The content of information provided in the document is set forth in the Code of Federal Regulations and the International Conference on Harmonization (ICH) guidelines. Thus, the consent form is governed under the regulatory domain of human subjects research. The informed-consent process occurs when the investigator, or investigative team member, holds a discussion with the potential subject to discuss the information contained in the informed-consent document and answer questions. There are no rules, laws or policies that govern how the consent process is implemented, aside from regulations pertaining to the signing of the consent document. Therefore, the consent process resides in the ethical domain of human subjects research. The marrying of the consent document with the consent process is critical for executing the doctrine of informed consent.

Ethically valid consent is a process of shared decision making based on mutual respect and participation. It is not the reading of a document by the subject, or the reciting of written passages from the same document by an investigator. Elements of an ethically valid informed consent include: 1) capacity to have a preference and make a decision; 2) disclosure of information by the investigator; 3) comprehension of information and its

consequences; 4) voluntariness to choose without undue coercion; and 5) ability of the subject to accept or refuse participation without fear of retribution.

Informed consent is the exercise of making informed choices and giving permissions to others to act on those choices. It is the outcome of a process in which information is shared between the subject and researcher. The subject is the ultimate decision-maker in accepting or rejecting participation in the proposed study. Kantian ethics espouses the treatment of individuals as an end and not merely as a means to achieving another person's ends. To put a person's health at risk for the sake of advancing science (or one's career) without the person's permission is unethical. The purpose of consent then is to inform the subject, because only subjects who genuinely know the purposes and appreciate the risks of research can assume those risks and adopt those purposes as their own ends.[65] The provision, and signing, of an informed-consent document without dialogue between the investigator and subject for the purpose of clarifying the information provided in the document does not fulfill this obligation. As stated by Levine, "A widespread tendency among researchers to focus on consent forms seems to reflect an assumption that the consent form is an appropriate instrumentality through which they might fulfill their obligation not to treat persons merely as means."[66] Instead, by focusing on the consent form, the investigator is using the form as a legal document through which liability to the institution is mitigated. The trend in recent years of utilizing the consent form as a legal document has resulted in the inclusion of text intended to minimize legal risk to the institution, thereby increasing the length and

[65] Robert J. Levine, "Consent Issues in Human Research," in *Encyclopedia of Bioethics*, ed. Warren T. Reich (New York: Free Press, 1995), 1243.

[66] Ibid.,1248.

complexity of the form itself. As a result, a consent form which is less than ten pages in length is becoming more and more difficult to find.

The entire process of obtaining informed consent involves giving the subject adequate information; providing an adequate opportunity for the subject to consider all options; responding in earnest to the subject's questions; ensuring that the subject is willfully volunteering to participate; and continuing to provide information on an on-going basis, as the subject or situation requires. Additionally, because the informed-consent process plays a critical role in shaping the long-term relationships with the subjects, patient community and general public, it is important that the informed-consent document be established as a reference tool for the subject and from which the investigator points out the critical information during the informed-consent process. When approached in this manner, the informed-consent process becomes a meaningful conversation, and the consent document becomes analogous to an instruction manual to which the subject can refer throughout the life of the study.

Goal of Informed Consent

The goal of the informed consent is to promote the values of autonomy, self-determination, and respect by providing information in a format that is understandable and relevant, enabling the potential subject, as an autonomous individual, to decide if participation is in his or her best interest. The visit in which the informed-consent process occurs is the first opportunity in which the potential subject is provided the details of the research study. While it is called the *informed-consent process*, unfortunately the *process* has, in many cases, become the visit in which the informed-consent document is signed. The document then becomes a source of protecting the institution from liability via the

signing of a lengthy legal document consisting of required verbiage and complex medical and scientific information instead of a source of information for the subject. The *process* is minimized to the provision of time for the potential subject to read the informed-consent document and a brief conversation with the investigator to answer questions. When information is missing, or is not understandable, a person lacks the essential ingredients upon which to base a decision, and consequently the decision is not properly informed. By not adequately informing a subject, not only is the decision uninformed but the subject's right to autonomy is disrespected. If the *process* is implemented as intended, the initial visit becomes an information exchange. The potential subject is informed about the study procedures, the possible risks, alternate options, as well as all other disclosures that are pertinent. The investigator is informed of any concerns or complications that may arise as the subject follows the schedule required for participation. Thus, it is only after the investigator has met both the legal and ethical requirements to disclose, explain and assess the subject's willingness that trust is earned.

The Nuremberg Code

The first document to provide any guidance with regard to obtaining informed consent of human subjects was the Nuremberg Code of 1947. Although the Nuremberg Code laid the foundation for the duty of obtaining informed consent, the quality of the informed-consent process rested on the virtue of the investigator. In the words of the first article of the Nuremberg Code, "The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity."[67] Additionally, because the Code did not lay out any type of

[67] Nuremberg Code.

review board, the determination of risk versus benefits, importance to society and study design were assessed the investigator conducting the experiment. As history has shown, reliance on the virtue of an investigator does not adequately protect human subjects. Lastly, based on the Code, only experiments of therapeutic benefit to the subject would be permissible to conduct as human experiments in adult populations.

The Declaration of Helsinki

As stated in chapter 1, the Declaration of Helsinki utilized the framework established by the Nuremburg Code, granting discretion to the physician investigator. Whereas the Code strongly established the requirement for voluntary and uncoerced consent as the first principle, the Declaration of Helsinki introduced the need for voluntary consent as the 9th principle in section 1, adding the necessity of "… obtaining freely-given informed consent … preferably in writing."[68] Further weakening the Code's requirement of consent was the provision provided in the Declaration that would allow an investigator also serving as physician to waive the consent requirement if application of the experiment was deemed to be the best course of action in the physician's medical judgment. Additionally, the Nuremberg Code provided no opportunities for obtaining surrogate consent, while the Declaration permitted surrogate consent for subjects who are mentally or physically incapacitated or minors. Whereas the Nuremburg Code left minimal room for discretion subject to the virtues of the investigator, the Declaration of Helsinki placed all responsibility on the virtues of the investigator, "It is the mission of

[68] Vanderpool, *Ethics of Research*, 435.

the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission."[69]

United States Federal Regulations

The Food, Drug and Cosmetic Act in 1962 codified as law and promulgated as FDA regulations (21 CFR 130.3) in 1963 required for the first time full and free consent of all subjects of drug trials conducted within the United States.[70] While it was an ethical victory in theory, in practice, this provision for informed consent only required the physician to "obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interest of such human beings" and to inform the subject that the new drug is "being used for investigational purposes."[71] This language provided a loophole in the regulations, leaving the judgment of 'best interest for the patient' to the physician's discretion. Thus, the safety and welfare of the subject was not established as a regulatory or ethical priority.

In June 1966, Henry Beecher's article "Ethics and Clinical Research," published in the *New England Journal of Medicine,* provided specific examples in which he highlighted the disregard for informed consent and abuse of vulnerable populations. Beecher's concern for the informed-consent process was made evident as noted by his statement:

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[69] Ibid., 433.

[70] Jonsen, "Experiments Perilous," 141; Office of NIH History, "Timeline of Laws."

[71] *Federal Food, Drug, and Cosmetic Act of 1962, U.S. Code* 21 (1962), sec. 505(i).

> ... it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them. Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment…[72]

Of concern to Beecher was the erosion of trust in the physician-patient relationship. Beecher felt that patients often will submit to requests by their physicians and subject themselves to minor inconveniences, but not agree to jeopardize their health. By not obtaining informed consent, the investigator was exploiting his or her role as an entrusted physician to further a science agenda. Beecher cited this as an unethical practice. Investigators who have existing physician-patient relationships have an additional obligation to ensure the subjects understand they are being asked to participate in a research project and that the decision to participate rests solely with the subject. As mentioned by Beecher, to take advantage of the existing physician-patient relationship, and not respect the subject's right to self-determination, is unethical.

Following Beecher's article, in July of 1966, the National Institutes of Health, through its parent, the Public Health Service (PHS), decentralized and moved "responsibility to the institution receiving the grant for obtaining and keeping documentary evidence of informed patient consent." It then mandated "review of the judgment of the investigator by a committee of institutional associates not directly associated with the project." Additionally, the guidelines defined the standards in which the committee was to operate. This committee would become known as the Institutional Review Board and would have as one of its responsibilities a review and approval of the informed consent document. The PHS set forth that "the review must address itself to the

[72] Henry K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274, no. 24 (June 16, 1966): 1354.

rights and welfare of the individual, the methods used to obtain informed consent, and the risk and potential benefits of the investigation."[73]

While the PHS guidelines focused more on assessing potential harm to patients, the FDA on August 30, 1966, issued a "Statement on Policy Concerning Consent for the Use of Investigational New Drugs on Humans." This statement, subsequently codified as U.S. regulations (21 CFR 130.37, later incorporated in 45 CFR 46), distinguished between therapeutic and non-therapeutic research in alignment with the Declaration of Helsinki and spelled out the meaning of consent. Non-therapeutic research was not allowed without obtaining subject consent. For research of therapeutic potential, offered to patients already under treatment, consent was to be obtained except in those instances where consent was not feasible or in the patient's best interest. To give consent, the subject had to have the ability for self-determination and to have a "fair explanation" of the procedure, including an understanding of the experiment's purpose and duration, "all inconveniences and hazards reasonably to be expected," what a controlled trial was (and the possibility of the use of placebos), and any existing alternative forms of therapy available.[74] Although the FDA regulations pertaining to consent were more substantive than the PHS guidance, the regulations were vague with regard to the difference between research and treatment.

[73] Rothman, "Research, Human," 2254.

[74] William J. Curran, "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," *Daedalus* 98 no. 2 (Spring 1969): 558-69.

The Belmont Report

The Belmont Report served to promulgate the ethics of research through general principles 1) that reflect basic, readily understood, and commonly shared moral values found in and advanced by philosophical ethics, law, and religious traditions, and 2) that are strengthened and expanded by the ethical requirements and guidelines specified in its applications.[75] Three basic principles were defined for evaluating human subjects research: respect for persons; beneficence; and justice.[76] These three principles provide the ethical framework for discussions pertaining to research studies and often serve as the criteria used by IRBs in their review of research protocols.

Application of the principles requires that there be a balance among the three. For instance, the principle of beneficence can not be applied in a manner such that respect for persons is reduced. Conversely, respect for persons cannot be implemented across all populations. Vulnerable populations, such as the mentally challenged, require that extra attention be given to the principle of beneficence since autonomy in this population is diminished.

The Belmont Report further clarifies the principle of respect for persons through incorporation of additional ethical convictions, codes, and rules such as autonomy and protections for those who are do not have the capacity to act as autonomous individuals. In the discussion regarding respect for persons, the Belmont Report states, "In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily *and with adequate information*."[77] Since autonomy is expressed within a cultural context and can be weaker or constrained in some individuals,

[75] Vanderpool, "Unfulfilled Promise," 8.

[76] National Commission, *Belmont Report.*

[77] Ibid. (emphasis added).

contextualizing informed consent in a manner that promotes respect and protection ultimately serves to promote respect for persons in the global sense.

By 1970, the ethical requirement for informed consent was well established throughout the research enterprise, although it was poorly implemented in practice. While there is much debate regarding the ability to provide truly informed consent as stated by Beecher, "... it remains a goal toward which one must strive for sociologic, ethical and clear-cut legal reasons. There is no choice in the matter."[78]

Regulatory Elements of Informed Consent

The Department of Health and Human Services and FDA regulations governing human subjects research and the International Conference on Harmonisation (ICH) contain sections that address informed consent. Within these sections are defined the elements that are to be included in the informed-consent document. These elements are defined in DHHS 45 CFR § 46.116,[79] FDA 21 CFR § 50,[80] and ICH E6 § 4.8.10.[81] The subject's written agreement to participate in research study is based on:

- Full disclosure by the investigator about the research study;
- Potential risks and benefits;
- Other treatment options, if any;

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[78] Beecher, "Ethics and Clinical Research," 1355.

[79] Protection of Human Subjects, *Code of Federal Regulations*, Title 45, Part 46, rev. November 13, 2001, http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm (accessed July 24, 2007).

[80] Protection of Human Subjects, *Code of Federal Regulations*, Title 21, Part 50, rev. April 1, 2002, http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html (accessed July 24, 2007).

[81] Food and Drug Administration, International Conference on Harmonisation, *Good Clinical Practice*, *Federal Register* 62, no. 90 (May 9, 1997): 25,691-709.

- Duration, possible inconveniences;
- Invitation to participate in research voluntarily;
- Purpose of the study;
- Differentiation of experimental procedures vs. standard practice;
- Experimental procedures: description, risks, costs and benefits;
- Alternatives to research participation;
- Agreement to participate in research–must be voluntary and can be withdrawn;
- Subject's rights to confidentiality, comprehension, and when applicable, compensation.

Of concern is the tendency on the part of researchers to concentrate on fulfilling the regulatory requirements of informed consent, resulting in a tendency to focus on following the rules which obscures the ethical intent that led to the promulgation of the regulations. This approach can obfuscate researchers' understanding of the purpose of research protections, the rights and welfare of the subjects themselves; and the safeguarding of the subjects can get lost in the completion of paperwork necessary to satisfy the letter, not the spirit, of the regulations.[82] Those who are interested in making operational the requirement for consent have a tendency to focus nearly all of their attention on the consent form.[83] In doing such, the investigator marginalizes the concept behind the regulation. Furthermore, reliance on the document for the exchange of information leaves the interpretation of terms such as *reasonable*, *minimal risk*, and

[82] Kahn and Mastroianni, "Moving from Compliance to Conscience," 925.

[83] Quoted in Levine, "Consent Issues in Human Research," 1243.

benefit to the subject's interpretation and could mislead them into underestimating the potential risk and/or overestimating the anticipated benefit. Lastly, it is argued that the general public's comprehension level is lower than their reading level.[84] Thus, adherence to the reading level requirement in the regulations does not guarantee an understanding of the information on the part of the subjects. As will be discussed further below, reliance on the document without the incorporation of a dialogue between the investigator and subject undermines respect for autonomy.

Ethical Elements of Informed Consent

Direct application of the doctrine of respect for persons provides that all prospective subjects: 1) must be granted "the opportunity to choose what shall or shall not happen to them;" 2) must be given all the information (much of it detailed in the report) that "reasonable volunteer[s]" would need to know to decide "whether they wish to participate;" 3) must comprehend this information (which involves the way the information is organized, the time needed to understand and ask questions, and communication suited to subjects' language and levels of intelligence, maturity, rationality); and 4) must be situated in "conditions free of coercion, undue influence (due to excessive or improper rewards, overtures, or inducements), and "unjustifiable pressures" from "persons in positions of authority or commanding influence" over either the prospective subject or "through the controlling influence of a close relative."[85] Application of the doctrine ensures that the subject's right to self-determination has been recognized and the ability to act as an autonomous individual has been honored. The key

[84] Mark Hochhauser, "Informed Consent: Reading and Understanding Are Not the Same," *Applied Clinical Trials* 13, no. 4 (April 2004): 42-48.

[85] Vanderpool, "Unfulfilled Promise," 7.

element to fulfilling this obligation is open and honest communication. The communication must be bi-directional in the form of a dialogue, so that the subject is engaged in the process and understands his or her role in choosing a course of action.

In the research milieu, the principle of respect for persons obligates the investigator or research team member to fully disclose all aspects of the study in a manner that assures comprehension on the part of the subject. Included is the avoidance of any possible deception, thereby treating the subject as an autonomous individual whose right to self-determination is not obstructed. Stated in another way, according to Belmont, the principle of respect for persons "requires" that persons "should be treated as autonomous agents, which involves giving 'weight' to the opinions and choices of individuals who are capable of deliberating about and acting in accord with their *personal goals*.[86] The investigator has additional ethical responsibilities when the subject, either through immaturity or reduced mental competence, displays impaired decision-making capacity.

In order to achieve the concept of informed consent, and not simply go through the motions of protecting the institution from liability through the signing of the consent form as a legal document, the informed consent must be approached as a communication process tailored to the individual subject. To be respectful, the dialogue has to be sensitive to the subject's culture, race, educational level, and values. The information must be presented in a format that facilitates a thorough comprehension of the procedures, the possible risks, burdens or harms, any potential benefits to the subjects or society, as well as an explanation of the alternatives. It is through this exchange that an appropriate investigator-subject relationship is established and trust is built.

[86] Ibid.

Studies on Informed Consent

As an example of the issues that can occur when the document is the source for obtaining informed consent, in a 2005 Harris Survey only 61 percent of clinical trial subjects strongly agreed with the statement that their informed-consent form was easy to read and understand.[87] Also revealed in the same survey:

- Only 83 percent strongly agreed with the statement that their participation was voluntary.
- Only 65 percent strongly agreed with the statement that they were made aware of the risks.
- Only 63 percent strongly agreed with the statement that they could choose other treatment options, including no treatment at all.
- 48 percent agreed or strongly agreed with the statement that they participated to get the best possible treatment.

In a CenterWatch study, "2007 National Survey of Study Volunteer Experiences,"[88] of 620 study volunteers across the United States, it was determined that 86 percent said they understood the consent form "very well," 13 percent understood it "somewhat well," and 1 percent reported "not understanding the form at all." In trials involving a placebo, 19 percent of volunteers reported that they did not understand they might receive a placebo, and another 6 percent were not sure whether they understood they might only be taking a sugar pill during the trial. Similarly, nearly one-quarter of the patients surveyed did not understand or were unsure about whether their doctor would know which medication they would be receiving; 21 percent did not understand or were

[87] "Participation in Clinical Trials Lower in Europe and India than in the United States," *Harris Interactive,* June 27, 2005, http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=942 (accessed July 2, 2007).

[88] Susanna Space, "2007 National Survey of Study Volunteer Experiences," *CenterWatch,* July 2007, 13-14.

unsure about whether their study would carry additional risks and discomforts; and 18 percent of patients said they were not aware or were unsure of whether they could contact someone other than the investigator if they had questions about their rights as a trial subject.

A study by Williams, Burman, et al. reviewed and evaluated consent forms from two studies of the Centers for Disease Control and Prevention funded Tuberculosis Trials Consortium.[89] Twenty-five sites and subsites were included in the evaluation. Of the twenty-five sites and subsites, fourteen used one local IRB, eight used two IRBs, and three sites used three local IRBs. The additional IRBs were due to the incorporation of health departments and Veteran's Administration hospitals. While the subject of this paper is not an analysis of the IRB review process, the findings are worthy of discussion, as they pertain to the information provided, or in some instances not provided, in the informed-consent document. The findings from the Tuberculosis Trials Consortium consent review were as follows:

1. Of the fifty (41 percent) locally approved consent forms, twenty-one had an inappropriately high reading grade level.
2. Of the changes requested as a result of IRB review 117 changes were due to errors in protocol presentation or required parts of the consent form.
3. Of the fifty consent forms, forty had a least one error with thirty-three having an error of protocol presentation or a required consent-form element.

[89] Williams Burman et al., "The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium," *Controlled Clinical Trials* 24, no. 3 (June 2003): 247-52.

4. Thirty-two out of the 117 errors were substantive: deletions of significant side effects, major errors in the description of study procedures (e.g., incorrect information on study duration), or the complete removal of a required section of the consent form (e.g., the right to withdraw from the study).

Additionally, in a randomized trial comparing different strategies for mechanical ventilation, a review of the consent forms showed that only three of sixteen forms contained all the elements required by federal regulations.[90]

The studies above reflect deficiencies in the informed-consent document. Historically, the regulations have placed much of the attention on the informed-consent document instead of concentrating on the informed-consent process. According to Kahn and Mastroianni, if significant shortcomings in informed-consent documents are still being found, even after so much focus has been placed on them, of greater concern is the quality of the informed-consent process. The findings argue for greater attention to the professional-patient interaction in the process of informed consent in research, as part of research oversight, and far less reliance on the signed consent form as evidence of adequate informed consent.[91]

Although there is a plethora of literature discussing and emphasizing the duty to obtain informed consent from a research subject, observers such as Katz claim that many patients asked to serve as subjects insufficiently appreciate the notion that research is

[90] Henry Silverman, Sara C. Hull, and Jeremy Sugarman, "Variability among Institutional Review Boards' Decisions within the Context of a Multicenter Trial," *Critical Care Medicine* 29, no. 2 (February, 2001): 235-41.

[91] Kahn and Mastroianni, "Moving from Compliance to Conscience," 926.

fundamentally designed to provide answers that are intended to benefit others. Furthering the issue is the concern that physician investigators are not attentive to this lack of understanding.[92] Katz also suggests in his book titled "The Silent World of Doctor and Patient" that a subject's right of self-determination can be left unfulfilled even when presented with carefully written information, due to a lack of understanding the general principle that the purpose of research is to gather knowledge that will benefit future members of society and might impose unforeseen risk to the subject.[93]

Within the context of clinical research, outside of the healthy volunteers, the potential subjects must not only have some comprehension of their disease, its course, and its impact on their quality of life, they must also learn the dynamics of research and how this intersects or diverges from their current course of treatment. In this situation, decisions can be made on incomplete information, coupled with personally biased information regarding the subject's disease, as well as their current and prospective experiences with regard to the disease. The communication between the investigator and subject is further hampered by the amount and complexity of information, the uncertainty inherent in the decision, the time added to the typical encounter, and the unfamiliarity of most potential subjects with the specifics of medical research.[94] If the investigator is serving as both physician and investigator, the research subject becomes confused as to which role the physician/investigator is assuming. Furthermore, it becomes more complicated deciphering whether the consent and protocol is representative of standard of care or research.

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[92] Laura A. Siminoff, Marie Caputo, and Christopher Burant, "The Promise of Empirical Research in the Study of Informed Consent Theory and Practice," *HEC Forum*,16, no. 1 (March 2004): 54.

[93] Jay Katz. *The Silent World of Doctor and Patient* (New York: Free Press, 1984).

[94] Siminoff, Caputo, and Burant, "Promise of Empirical Research," 56.

A survey of 1,900 subjects at sixteen U.S. research institutions revealed that 53 percent were not even aware they were part of a clinical study.[95] The Advisory Committee on Human Radiation Experiments reviewed research projects funded by federal agencies from 1990 to 1991, including the review of initial and revised consent forms from 125 studies. Their findings were that 1) forms that had IRB approval were difficult to read, uninformative, and at times misleading; 2) consent forms for subjects with limited life expectancies exaggerated potential benefits while omitting potential burdens; 3) some proposals involving children failed to include forms obtaining the child's assent; and 4) four studies involving adults with questionable decision-making capacity omitted information on potential burdens and failed to address the reduced decision-making capacity through utilization of a surrogate decision-maker.[96] In other studies, including a follow-up survey of those who participated in research, it was determined that while the subjects acknowledged that they understood research is conducted to advance knowledge for the treatment of future patients, they were confident that physicians and hospitals would not enroll them into research studies that would potentially cause harm or not be of benefit. Additional studies researched by Siminoff, Caputo, and Burant discovered that:

> in a 1984 study almost 25 percent of patients who participated in trials could not recall the nature of the research or were unaware that they were receiving treatment associated with a research protocol; in a 1994 study of patients participating in a Phase I oncology trial, it was determined that 67 percent were unable to state the purpose of the trial, and only 33 percent knew the trial was

[95] Jeremy Sugarman, Nancy E. Kass, Steven N. Goodman, Patricia Parentesis, Praveeh Fernandez, and Ruth R. Faden, "What Patients Say about Medical Research," *IRB: A Review of Human Subject Research* 20, no. 4 (July-August 1998): 1-7.

[96] Advisory Committee on Human Radiation Experiments, Final Report (Washington, D.C.: U.S. Government Printing Office, 1995).

> looking at dosage and safety – most were motivated to participate by hope for therapeutic benefit.[97]

These studies emphasize the need for improvements in the informed-consent process. In order to respect the potential subject as an autonomous individual, it is imperative that the investigator understand the subject's motivations for participating in research studies. Additionally, the investigator must take full responsibility for assuring that the subject understands the concept of clinical research and the specifics of the particular study for which the subject is being recruited.

In the next chapter an illustration of a case in which the process of informed consent deviated from established regulatory and ethical norms resulting in a breech of trust will be presented.

[97] Siminoff, Caputo, and Burant, "Promise of Empirical Research," 58.

CHAPTER 3: An Illustration of System Failures and Erosion of Trust

On September 13, 1999, eighteen-year-old Jesse Gelsinger enrolled in a research study, funded by the National Institutes of Health (NIH), exploring an experimental application of gene therapy to correct a lethal disease. Four days later, after receiving an injection of an adenovirus vector, the previously healthy,[98] normal volunteer died. Although inspections by the FDA and OHRP uncovered multiple findings of inappropriate implementation of the study protocol, the focus of this chapter is an analysis of the components of the informed consent requirements applicable to his participation.[99] The analysis will be conducted through a review of the FDA warning letters, OHRP investigation letter and excerpts from "Jesse's Intent" to substantiate that: complying with regulations does not ensure ethical standards are upheld; instilling ethical standards does not equate to maintaining compliance; and finally that, while achieving compliance does constitute following the rules, and is a necessary ingredient for the system of public trust, it is not sufficient. Rather, trust in the research process requires an attitude that respects the autonomy and values the rights of research subjects above the quest for scientific knowledge.

[98] Although it could be argued that Jesse Gelsinger was not a healthy subject, for the purpose of participating in this study, he was defined as a healthy volunteer because he was able to manage his illness through a strict regimen of diet and medication.

[99] It is important to establish my goals in this chapter at the beginning because the intent of this particular chapter is not to cast judgment on the University of Pennsylvania, Dr. Steve Raper, Dr. James Wilson, Dr. Mark Batshaw, Paul Gelsinger, Jesse Gelsinger, or anyone else involved with this study. Instead, my intent is to use the Jesse Gelsinger story as a rich case model in which the regulatory system described in chapter 1 and the ethical domain, specifically informed consent presented in chapter 2, can be analyzed to depict what can occur when the intent of the regulations is not met or when there is a breach in the human subjects protection system.

The Disease and the Gene Therapy Study: An Overview

Jesse Gelsinger was an eighteen-year-old who lived with his father and step mother in Tuscon, Arizona, and suffered a mild form of a rare genetic disease called ornithine transcarbamylase deficiency (OTC). OTC affects the body's ability to get rid of ammonia. Half of the children with OTC die in their first month of life, and half die before their fifth birthday.[100] Jesse was considered a relatively healthy, or at least a medically stable, individual. A special diet and the thirty-two pills he took daily maintained his health.

The gene therapy study was funded by the NIH and was subject to review and approval by the Recombinant DNA Advisory Committee (RAC). Because the product under test was hopefully going to result in a future therapeutic, the gene therapy study was also overseen by the FDA. Therefore this protocol underwent two separate reviews by independent organizations and governing bodies. In 1995, the OTC protocol was submitted to the NIH's RAC and the FDA for review and approval. The protocol called for the enrollment of eighteen adults in a dose-escalating study. The adult participants would receive an infusion of the OTC gene, encapsulated in an adenovirus vector, through the hepatic artery. The purpose of the Phase I study was to determine the maximum tolerable dose with minimum side effects with the intent of using this gene transfer product in the future as a treatment for babies born with the most crippling form of the disease. The study had been substantiated through multiple animal models: twenty mouse experiments for efficacy, and mice, rhesus monkeys and baboons for safety. These results, including the deaths of three monkeys at a higher dose than intended for human experimentation, accompanied the protocol for the RAC and FDA review.

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[100] Sophia M. Kolehmainen, "The Dangerous Promise of Gene Therapy," abridged article from *GeneWatch*, February 2000, www.actionbioscience.org/biotech/kolehmainen.html (accessed November 23, 2002).

The RAC was troubled by previous animal data in which three monkeys died. There were not any existing data regarding the injection of an adenovirus vector directly into the blood or liver of human subjects, therefore the scientists conceded it would be difficult to predict how humans would respond. Despite misgivings, the RAC approved the protocol and the corresponding informed-consent document that had been submitted, with the restriction that the vector would be injected only into the blood. The restriction of injecting the vector directly into the blood was lifted by the FDA during its independent review of the protocol. The RAC was never informed of this change.

Specific to the conduct of the protocol, previous participants from this study had experienced serious side effects which should have been reported as adverse events to the FDA but were not.[101] Additionally, the informed-consent document that had been approved for use by the RAC contained language regarding the outcome of the rhesus monkey studies. The informed-consent document provided to Jesse Gelsinger was not the document that had been approved by the RAC and did not contain this information.[102]

Issues Affecting the System

After Jesse's death, there were news reports that other patients had died during the course of gene therapy experiments, reportedly from their diseases, as opposed to the experimental gene therapy, and that the scientists involved did not report those deaths to

[101] An *adverse event* (AE) is defined as any side effect experienced by the research subject and must be reported to both the sponsor (the person or entity that owns the Investigational New Drug (IND) application who, in this particular instance, was Dr. James Wilson) and the IRB. If an adverse event is classified as a *serious adverse event* (SAE) in which the side effect is considered life threatening and results in hospitalization, disability or even death it must be reported to both the sponsor and IRB in a twenty-four hour period. In both instances, the sponsor is responsible for reporting adverse and serious adverse events to the FDA and RAC (if the study is funded by any DHHS entities). Reports of adverse and serious adverse events are known collectively as *safety reports*.

[102] Kolehmainen, *"Dangerous Promise."*

the RAC, as was required.[103] Also released was news regarding the delinquent reporting of safety reports to the NIH, specifically, 691 serious adverse events had occurred, of which 652 were not reported timely as per the regulations.[104] In a system of human protections, the system can only work if proper communication occurs and everyone fulfills the obligations entrusted to them. If appropriate information is not conveyed, the information can not be reviewed and proper actions don't occur. In this instance, it was impossible for the RAC to provide oversight for gene therapy research when the clinical investigators did not report the required safety information within the time period set forth in the regulations. Lapses in activities such as safety reporting impair the system's ability to safeguard the rights and welfare of the subjects. When the system is impaired, individual and public trust begins to erode.

Dr. James Wilson, head of the Institute for Human Gene Therapy (IHGT) at the University of Pennsylvania, was also the founder of Genovo, Inc. Genovo secured the rights to any discoveries made by Wilson in his University of Pennsylvania laboratory. Genovo also had a financial stake in the adenovirus variation Wilson developed and used in the research on Jesse. Also of concern, another biotech company, BIOGEN, had paid Genovo thirty-seven million dollars beginning in 1995 for the rights to market any liver and lung related therapies developed by Genovo. Funding from BIOGEN accounted for 20 percent of the Institute's budget.[105]

It would be difficult to surmise how the financial ties Dr. Wilson had with Genovo and BIOGEN influenced the implementation of the study. The perception is that Dr. Wilson had a major conflict of interest because of the potential for personal and

[103] Ibid.

[104] Ibid.

[105] Ibid.

professional gain that would be forthcoming if the study had favorable outcomes. This conflict should have been recognized and an objective third party, such as a Contract Research Organization, should have been brought in to manage the study. The conflict of interest represents both a system failure, because the conflict was not identified and therefore was not managed, as well as an ethical failure because the conflict was not disclosed at any point during the design and implementation of the study. The loss of public trust that results when financial conflicts of interest, whether real or perceived, are uncovered is tremendous.

Results of the FDA Inspections

On March 3, 2000, the FDA issued a Warning Letter to Wilson, as the sponsor of the investigational drug and owner of the Investigational New Drug (IND) application.[106] The Warning Letter was a result of an inspection conducted from November 30, 1999, through January 19, 2000. Observations were then submitted to Wilson on Form FDA 483–List of Inspectional Observations–and a written response from Wilson was requested. The Warning Letter uncovered deficiencies in the major categories of IND maintenance, fulfillment of sponsor responsibilities, monitoring, and review of ongoing investigations. More specifically, the infractions included the lack of submission of protocol amendments, including changes to the inclusion and exclusion criteria (each significant amendment to a protocol should result in an amendment to the consent form), lack of inclusion of FDA recommended protocol changes, lack of incorporation of exclusion criteria that were identified as risk factors available in a medical history (this

[106] Food and Drug Administration, Warning Letter issued to James M. Wilson, March 3, 2000, http://www.accessdata.fda.gov/scripts/wlcfm/resultswl_archive.cfm (accessed June 25, 2007).

was identified after an enrolled subject developed a Grade III toxicity),[107] lack of timely reporting of adverse events, lack of FDA recommended information in the informed consent document, lack of appropriate and required study documentation, deviations from the agreed upon protocol, as well as other infractions. In other words, there was a serious lack of oversight by Wilson in his role as the sponsor of the study, the study's principal investigator and the owner of the investigational therapeutic.

Wilson was issued a separate letter, entitled "Notice of Initiation of Disqualification Proceeding and Opportunity to Explain," on November 30, 2000.[108] The FDA asserted that Wilson did not fulfill his duty as the principal clinical investigator of protecting the safety and welfare of the subjects because of the following: lack of adherence to safety provisions outlined in the protocol; enrolling subjects who did not meet eligibility criteria; and not obtaining proper IRB approvals. The IRB did not receive notification of changes to the inclusion/exclusion criteria, adverse event reports and, upon continuing review, were provided misleading and inaccurate information.

On November 30, 2000, the FDA also issued a Warning Letter to Mark L. Batshaw, M.D., for his role as sub-investigator in the OTC study. Batshaw was cited for failure to provide accurate and timely notification to the IRB of adverse events and protocol amendments; enrollment of subjects who did not meet the inclusion/exclusion criteria; and failure to provide proper informed consent (details of which are discussed below).[109]

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[107] A grade III toxicity is a severe form of toxicity with persistent fever between 103-105°F, extreme fatigue, and lethargy, http://www.kendallasmith.com/follow/Essay_IL2_Toxicity_12_24_00.pdf (accessed July 22, 2007).

[108] Food and Drug Administration, Notice of Initiation of Disqualification Proceeding and Opportunity to Explain, November 30, 2000, http://www.fda.gov/foi/nidpoe/n12l.pdf (accessed June 25, 2007).

[109] Food and Drug Administration, Warning Letter issued to Mark L. Batshaw, November 30, 2000, http://www.accessdata.fda.gov/scripts/wlcfm/resultswl_archive.cfm (accessed June 25, 2007).

Also on November 30, 2000, the FDA issued a Warning Letter to Steven E. Raper, M.D., an additional sub-investigator in the OTC study. Raper's violations included failure to implement the study as per the protocol; enrollment of subjects who did not meet the inclusion/exclusion criteria; failure to report safety problems to the IRB; failure to submit protocol changes to the IRB and receive approval prior to implementation of the changes; failure to provide proper informed consent; and improper study documentation.[110]

All of the FDA-issued letters were based on a review of the documentation, thereby judging adherence to the regulations. The investigative team initiated the study within the regulatory system. Their protocol was judged to be scientifically valid through the NIH peer review system, resulting in an award of NIH funding. The RAC and the FDA approved the study, although the two agencies independently approved a protocol with slight variations. The local IRB also approved the study and the informed-consent document. Within the regulatory domain, at least at the onset of the study, the investigative team was compliant. Although not specifically addressed in the letters issued by the FDA, it is evident that the ethical domain was ignored. The safety of the subjects who participated in this study was less of a priority than obtaining scientific data related to the adenovirus vector. The quest for knowledge resulted in a lapse of judgment on the part of the investigative team; and therefore, the correlation between the actions of the investigators and the effect on the study subjects was not thought through. In fairness to the principle investigator and investigative team, functioning in the role of Investigator and Sponsor assumes that the investigator is able to navigate the complex system of regulations required by both the NIH and the FDA. The amount of paperwork and study

[110] Food and Drug Administration, Warning Letter issued to Steven E. Raper, November 30, 2000, http://www.accessdata.fda.gov/scripts/wlcfm/resultswl_archive.cfm (accessed June 25, 2007).

documentation can be overwhelming. It is conceivable, but not justifiable, to see how an investigator gets caught up in the paperwork and loses sight of the ethical requirements needed to protect human subjects.

The Informed Consent of Jesse Gelsinger

In the early stages of developing this study, once it was determined that the experimental therapy was ready for testing in humans, the study team encountered an ethical dilemma: who should be their test subjects? After consulting with the university's bioethicist, they decided that it would be difficult for the mothers of newborns dying of the OTC deficiency to give uncoerced informed consent, so the advice was to test on stable adults, such as female carriers or male adults who had partial enzyme deficiencies and were controlling their disease through diet and medication.[111] "Jesse's Intent" tells the story of a child who, upon entering his early teenage years, resisted taking medications. By the age of sixteen, Jesse was up to nearly fifty pills a day to control the OTC. Having acquired a part-time job and an off-road motorcycle, Jesse was having difficulty maintaining the medication regime and adhering to the strict diet. This lifestyle culminated in Jesse's spending a week in a hospital, with a couple of those days spent in a coma as a result of the high ammonia levels in his blood. Jesse was placed on a new medication to control the increased ammonia levels, at the cost of three thousand three hundred dollars for a one-month supply. As Jesse was finishing his senior year of high school, his father initiated a discussion that it would be important for Jesse to have a job that provided insurance coverage. So when the possibility of the gene therapy experiment was presented to Jesse in April 1999, by his doctor in Arizona, Jesse, Paul, and his local

[111] Sheryl Gay Stolberg, "The Biotech Death of Jesse Gelsinger," *The New York Times, Sunday Magazine,* November 28, 1999, 137.

physician shared some hope that Jesse could gain some benefit by participating as a normal volunteer.

By late May, arrangements had been made for Jesse to meet with the doctors conducting the gene therapy experiment in Philadelphia on June 22nd. During a forty-five-minute informed-consent conversation, the doctor described the technique that would be used should Jesse qualify and consent to the gene therapy experiment. Recounted by Paul:

> … Jesse would be sedated and two catheters would be placed into his liver; one in the hepatic artery at the inlet to the liver to inject the viral vector and another to monitor the blood exiting the liver to assure that the vector was all being absorbed by the liver. He explained the dangers associated with this and that Jesse would need to remain immobile for about eight hours after the infusion to minimize the risk of a clot breaking free from the infusion site. The doctor also explained that Jesse would get flu-like symptoms for a few days. He briefly explained that there was a remote possibility of contracting hepatitis. When I questioned him on this, he explained that hepatitis was just an inflammation of the liver and that the liver was a remarkable organ, the only organ in the body with the ability to regenerate itself. In reading the consent form, I noticed the possibility of a liver transplant being required if the hepatitis progressed. The hepatitis seemed such a rare possibility and the need for transplant even more remote that no more alarms went off in my head. The doctor proceeded to the next phase and what appeared the most dangerous aspect of the testing. A needle biopsy was to be performed of Jesse's liver one week after the infusion. Numbers explaining the risks of uncontrolled side effects were included. There was a one in ten thousand chance that Jesse could die of the biopsy! I said to Jesse that he needed to read and understand what he was getting into, that this was serious stuff. The risks seemed very remote but also very real. Still one in ten thousand weren't bad odds in my mind. There would be no benefit to Jesse, the doctor explained. Even if the genes worked the effect would be transient because the body's immune system would attack and kill the virus over a four to six week period.
>
> Four weeks later, back in Tucson, we received a letter addressed to Mr. Paul Gelsinger and Jesse. It was from another of the principal investigators of the clinical trial, a world renowned OTC expert, confirming Jesse's 6 percent liver efficiency due to the OTC and stating that they would like to have Jesse in their study… This same doctor called about a week later to follow-up on his letter and spoke to Jesse briefly. Jesse told him that he would need to call back and talk to

> me and explain everything. Jesse was deferring to me to understand this and the doctor was well aware of that… Since they had forgotten to include the graph showing Jesse's N15 results he faxed it to us. I asked if Jesse was the least efficient patient in the study. The doctor explained that he was and steered the conversation to the results they had experienced to date. He explained that they had shown that the treatment had worked temporarily in mice, even preventing death in mice exposed to a lethal injection of ammonia. He then explained that the most recent patient has shown a 50 percent increase in her ability to excrete ammonia following gene therapy. My reaction was to say, "Wow! This really works. So, with Jesse at 6 percent efficiency you may be able to show exactly how well this works." His response was that that was their hope and that it would be for these kids. Those kids were newborn babies with the worst form of Jesse's disorder, having no OTC efficiency, and with little chance of survival. He explained that there were another twenty-five liver disorders that could be treated with the same technique and that overall these disorders affected about one in every five hundred people…. This doctor and I never discussed the dangerous side of this work.[112]

The consent process, as related by Paul, complied with the regulations of informed consent in that Jesse did choose to participate as indicated by Jesse's signing of the consent form, but violated Jesse's ability to make a determination as an autonomous individual and right to self-determination because he was not fully informed. As noted in the FDA warning letters, all of the pertinent safety data was not presented to Jesse. Additionally, the benefits were overstated. Although Jesse was the individual providing consent, the follow-up conversations were not with him. Even though Jesse created the dilemma of relying on someone else (his father) to obtain and understand the study information, extra time should have been taken to get Jesse more involved with the decision-making process. Lastly, it is surmised in the story that both Paul and Jesse were confusing the dual roles of the clinician investigators. Although the clinicians were functioning strictly in the role of investigator for this study, Paul and Jesse were basing their trust on the investigators as if they were in a physician-patient relationship. One in

[112] Paul Gelsinger, "Jesse's Intent," www.circare.org/submit/jintnet.pdf, 2002 (accessed October 5, 2005).

which the clinician looks out for the best interest of the patient. Therefore, their individual trust was misplaced, and the comprehension of what it means to participate in human subject research may not have been fully explored.

Review by OHRP and FDA of Informed Consent

During a review by the OHRP, it was noted that the informed-consent document provided to Jesse and approved by the University of Pennsylvania IRB did not adequately address the required elements as set forth in DHHS regulations (45 CFR 46.116(a)(1). Missing was a complete description of the procedures that Jesse would undergo and identification of the procedures that were considered research. The informed-consent document stated that "[t]he gene therapy process involves the following steps … (3) the virus carries the OTC gene into your liver cells. (4) In your liver cells, the OTC gene produces the OTC enzyme that is missing in OTC deficiency." [113] The implication is that the steps mentioned in the informed-consent document do not emphasize the experimental nature of the course of action. Instead the term *therapy* is used, implying that the process of the gene therapy is proven, when in fact the intent of the protocol was to prove that the steps above would occur.

Other informed-consent issues identified during the OHRP review included the discrepancy between procedures identified in the protocol but not listed in the consent form (ECG, additional blood draw). The use of angiography for the delivery of the gene therapy and the radiation exposure from the angiography were not adequately described. There was an inconsistency between the study consent form and the liver biopsy consent form representing the risk of serious complications: 1 in 10,000 to 1 in 5,000

[113] Office of Human Research Protections, U.S. Department of Health and Human Services, Letter to Neal Nathanson, May 7, 2001, http://www.hhs.gov/ohrp/detrm_letrs/may01a.pdf (accessed June 25, 2007), 3.

respectively. The informed-consent document as noted in the OHRP report stated "by giving the virus directly into the right side of the liver, we hope to obtain the maximal effect of the gene in the liver and to keep to a minimum any exposure of left-sided liver cells and non-liver cells to the virus."[114] There was no evidence from the animal studies to substantiate this statement. Furthermore, a revision of the grant application submitted to the FDA in early 1998 stated that the baboon biopsies transduced with the second generation vector administered via the hepatic artery displayed liver toxicity in the both the targeted and nontargeted lobes of the liver.[115]

Additional findings by OHRP included the discovery that a packet of information was distributed to prospective subjects and their families which had not been reviewed and approved by the IRB.[116] Finally, an article published in the *Philadelphia Inquirer* spoke of Drs. Wilson and Batshaw's attendance at a national meeting of the National Urea Cycle Foundation in which the study was discussed, subjects were solicited, and screening blood draws were taken. An IRB-approved consent form did not exist at the time providing approval for the screening procedure, nor had this recruitment mechanism been reviewed and approved by the IRB.

During the FDA inspection, it was noted that, although the FDA had recommended via a letter, dated June 13, 1996, that language be added to the informed-consent document advising potential subjects that they would have to refrain from donating blood or gametes, the language was never incorporated.[117] The informed-consent document was not amended again to advise new subjects about the possible risks

[114] Ibid., 4.

[115] Ibid.

[116] Ibid., 3.

[117] Food and Drug Administration, Warning Letter to Wilson, 9.

of participating after all of the subjects receiving the lower dose of the investigation vector experienced significant adverse events.[118] The informed consent process–i.e., the describing of the study to prospective subjects–was not well documented. In a review of the signed consent forms, the FDA inspectors noticed that the signature date of the subject was different from that of the witness and/or clinical investigator, leading one to question whether the clinical investigator was present during the informed-consent discussion.[119]

As mentioned earlier, although it is apparent the legal/regulatory aspects of informed consent were not followed, the information above does not correlate to the conduct of an ethically competent informed-consent process. Without actually recording the informed-consent process, there is no evidence as to what information was provided to the subject, who provided the information, or the subject's ability to comprehend the information provided.

The FDA Warning Letter issued to Mark Batshaw also included a list of violations in the informed-consent process as set forth in 21 CFR Part 50. Specific allegations included: 1) not amending the informed-consent document following the elevated liver enzymes experienced by previously enrolled subjects; 2) failure to amend the informed-consent document and properly inform the next dose cohort of the elevated liver enzymes experienced by each of the four subjects in the fourth dose cohort, which was deemed to be a serious adverse event; 3) failure to amend the informed-consent document to inform potential subjects that (a) higher doses of vector were associated with disseminated intravascular coagulation (DIC) in animals, and (b) that the infusion of the vector could result in DIC for the human subjects; 4) failure to amend the informed-

[118] Ibid., 11.

[119] Ibid., 17.

consent document to include that discomforts (significant periods of chills, nausea and vomiting) experienced by previous subjects were likely to occur.[120]

The FDA Warning Letter issued to Steve Raper contained the identical informed-consent issues filed with Batshaw, with the addition of Raper's having provided informed consent to a patient utilizing a consent form that had not been approved by the IRB. The subject in question was infused on June 6, 1998, and had signed a consent form that was not the IRB-approved consent form on November 11, 1999.[121]

An example of the FDA's concern for the welfare of the patients was documented in the Initiation of Disqualification Notice provided to Wilson on November 30, in which the FDA asserts:

> The consent form section titled, "We are doing a number of things to reduce these risks" states, "We also will *discuss* (emphasis added by FDA) the results of testing of each group of patients within a single dose level with the Food and Drug Administration before proceeding to the next dosage group." Although the Institute for Human Gene Therapy submitted a report about the Grade III adverse events that occurred for each of the four subjects in dose cohort four, IHGT representatives did not have a conversation with FDA or obtain verbal permission to proceed to the next dose level, as had occurred for each previous dose escalation. Therefore, the prospective patients for dose cohort five were misled as to FDA's active involvement in the decision to proceed to these dose levels.[122]

A general concern noted by OHRP and the FDA was the referral to the protocol as *gene therapy*. As Ruth Macklin, a bioethicist and member of the Recombinant DNA Advisory Committee (RAC), stated bluntly, "Gene therapy is not yet therapy."[123] The misuse of the term *therapy*, the lack of inclusion of potential side effects, and the lack of

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[120] Food and Drug Administration, Warning Letter to Batshaw, 7.

[121] Food and Drug Administration, Warning Letter to Raper, 8-9.

[122] Food and Drug Administration, Notice of Initiation Letter, 2.

[123] Quoted in Stolberg, "The Biotech Death of Jesse Gelsinger," 137.

inclusion of the animal data all ignore the requirement to fully disclose all aspects of the study and thereby diminish the subject's capacity to function as a competent, autonomous individual. The respect for the person is obliterated by the scientist's quest for knowledge. In addition, breeches by the investigator, whether intentional or unintentional, cause the system to fail. IRBs, committees such as the RAC, and other oversight functions established to protect human subjects can not react to information not provided to them. When the ethical requirement of informed consent is not upheld, trust is diminished between the investigator and subject. When the system fails, public trust erodes. In the words of Paul Gelsinger:

> Our current system of research protection did not protect my son. Unexpected SAEs went unreported, and because nobody detected this, they were not disclosed in the consent form. As a result, my son did not give legally effective voluntary informed consent, yet the "system" obligates both the investigator and the IRB to ensure that he did so. The institution and investigators were subjected to the severest penalties the system can muster, yet this is inadequate because the investigators will conduct research on humans again, and will do so within a system that lacks the capacity for pro-active oversight or the will and the means to enforce compliance. I now question the integrity of the entire system, and I distrust it.[124]

The system inclusive of both the regulatory and ethical domain did fail the Gelsingers. Although Jesse voluntarily agreed to participate in the gene therapy study, he did so without having all of the information and disclosures necessary to invoke his right of self-determination. The non-compliance with the regulatory system that resulted in an undue burden of risk being placed on the research subjects was unconscionable. The investigative team's modus operandi resulting from Jesse's death was a scientific quest for knowledge that would provide clinical answers to what occurred. In none of the

[124] Paul Gelsinger, CIRCARE Presentation given to Secretary's Advisory Committee on Human Research Protections, August 2, 2005, www.circare.org/informTOC.htm (accessed October 29, 2006).

literature was there a concern for an ethical inquiry to determine actions that ought to have occurred. The FDA and OHRP reviews concentrated on documents that were not completed or filed appropriately. As a result, Paul's distrust of the individual investigators is genuine and understandable. When trust is lost at the individual level between investigator and subject, and the investigator is a critical component of the larger system, the diminishing of public trust becomes apparent.

In the concluding chapter, an analysis of the failures within the regulatory and ethical domains as situated within the context of the Jesse Gelsinger case will be synthesized and thoughts on implementation of a robust system for protecting human subjects will be presented.

CHAPTER 4: An Analysis of the Failures in the System and Recommendations

Clinical research is a social good and a public trust. Clinical trials are essential for the evaluation of diagnostics and therapeutics, resulting in the advancement of knowledge in medicine. Clinical trials can be pursued successfully only if society believes in their usefulness and safety. This, in turn, can occur only if those in charge of the clinical trials ensure that, on the one hand, the study is important scientifically with potential for significant benefit and that, on the other hand, the subjects' welfare is given the highest priority.[125] As such, those who are engaged in the medical research enterprise have a moral obligation to safeguard the rights and welfare of subjects who volunteer as social servants by becoming research subjects. The human subjects' protection system is just that: a system of interdependent components grounded in regulations, codes of ethics, and the virtues of human beings. In order to provide oversight, the regulatory agencies, such as the FDA, OHRP, and so forth, rely on the sponsors and investigators of the research to be truthful in their disclosures of information. Likewise, IRBs rely on the timely receipt of information that portrays exactly what will and what has occurred to fulfill their duty of protecting those who participate in human subjects research.

The codes of ethics–*Belmont* and the *Declaration of Helsinki*–are grounded in the assumption that the person or institution is committed to the virtues of honesty and truth-telling. The principle of beneficence can not be attained if all of the safety data and procedures are not enlisted or are misrepresented. During the consent process, if the

[125] Quoted in Report of Independent Panel Reviewing the University of Pennsylvania's Institute for Human Gene Therapy, April 27, 2000, http://web.archive.org/web/20010728225238/www.upenn.edu/almanac/v46/n34/IHGT-review.html (accessed May 18, 2006).

investigator does not fully disclose all the existing data (regardless of whether the results thus far are positive, negative, thought to be related or unrelated), then the subject is no longer in the position of an autonomous agent with decision-making capacity, and respect for the person has been violated.

The subjects who participate in clinical research generally place an extraordinary degree of trust in investigators, the institutions in which research is conducted, and the research enterprise as a whole that their best interests will be served in the context of research.[126] D. E. Cooper defines three dimensions of trust that are applicable to the research milieu: trust in the context of fiduciary relationship between a patient or research subject and her or his physician or research physician; trust in the context of perceived competence of the institution and physician; and trust in the context of the perception of trustworthiness.[127] LaVera M. Crawley elaborates: "The role of communication in developing and maintaining trust is vital to all three categories, but is particularly salient in influencing the perception of researcher trustworthiness."[128] This trustworthiness of the researcher, from the subject's perspective, is established at the time of informed consent. If individual trust between the investigator and subject, as happened in the Jesse Gelsinger case, is betrayed at the time of informed consent, trust in the system erodes.

[126] Nancy E. Kass, Jeremy Sugarman, Ruth Faden, and M. Schoch-Spana, "Trust: The Fragile Foundation of Contemporary Biomedical Research," *Hastings Center Report* 26, no. 5 (September-October 1996), 25-29.

[127] D. E. Cooper, "Trust," *Journal of Medical Ethics* 11, no. 2 (June 1985): 92-93.

[128] Lavera M. Crawley, "African American Participation in Clinical Trials: Situating Trust and Trustworthiness," in *For the Health of the Public: Ensuring the Future of Clinical Research*, vol. 2, ed. Roger E. Meyer, (Washington, D.C.: Association of American Medical Colleges, 2000), 19.

The Regulatory System under Review

In chapter 1, a brief history was provided of the system that has developed over the years, unfortunately, usually as a result of harms placed on individuals, to protect human subjects who participate in research studies. This system of human subjects protections relies heavily upon two processes to ensure that research participants are adequately protected: approval and oversight by an ethics review board, most commonly known as an IRB, and informed consent."[129] Based on the growing concern that the system is fragmented, the perception that the IRBs are not fulfilling their obligation, and evidence that public trust is diminishing, the Department of Health and Human Services' Office of Inspector General (OIG) conducted an investigation of the IRB process and issued a report distributed in 1998 concluding that "the effectiveness of the IRBs is in jeopardy."[130] During the course of the investigation, it was recognized that IRBs are overworked and under-resourced, resulting in less than desirable reviews of proposed research studies and adverse events. Beginning in 1999, based on site reviews of IRBs, the Office of Human Research Protections (OHRP) began restricting and, in some cases, suspending institutional assurances and the individual protocols associated with those assurances. Corrective actions and instances of re-review of protocols were required prior to allowing the research to restart. During this same period, the FDA was conducting protocol reviews at sites. As a result of their reviews, studies were placed on hold or suspended until deficiencies could be adequately addressed.

The Federal government did not escape scrutiny either. In 2001, the National Bioethics Advisory Commission (NBAC) issued a comprehensive report on ethical and

[129] Greg Koski, "Resolving Beecher's Paradox: Getting beyond IRB Reform," *Accountability in Research* 7, no. 2-4 (December 1999): 213.

[130] Office of Inspector General (OIG), U.S. Department of Health and Human Services, *Institutional Review Boards: A Time for Reform,* Report No. OE1-01-97-00193 (Washington, D.C.: Government Printing Office, 1998).

policy issues in human subjects research, recommending that federal oversight be centralized and that various components of the federal oversight system be revised to clarify regulatory responsibilities and to provide more guidance to assist institutions in formulating and implementing policies.[131]

By late 2000, the Institute of Medicine (IOM) was also brought into the picture. The IOM was charged with conducting a full assessment of the federal system for human subjects protections. It was to recommend any changes needed to the structure and function of current protection activities, as well as to discuss a method for continual review. The IOM separated the task into two phases. Phase I focused on an accreditation process and resulted in the report *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs.*[132] During Phase II, the committee was charged with the following tasks:

- Review the ethical foundations for protecting human participants in research.
- Assess and describe the current system protecting human participants and make recommendations for potential enhancements and improvements to:
    i. ensure informed consent
    ii. monitor ongoing research,
    iii. accommodate private IRBs, multicenter research, and nonmedical research,
    iv. ensure continuous improvement in the system, and

[131] National Bioethics Advisory Committee (NBAC). *Ethical and Policy Issues in Research Involving Human Subject Participants,* vol. 1 (Bethesda, Md.: NBAC, 2001).

[132] Institute of Medicine, *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs,* (Washington, D.C.: National Academy Press, 2001).

v. educate researchers, participants, and others involved in research with human participants

- Assess the potential impact of recommended changes on resource needs and how to address them.
- Consider the effects of accreditation on improving human participant protection activities.
- Determine the need and develop potential mechanisms for ongoing independent review of the national system.[133]

Failures in the Regulatory System

The regulatory system is in a state of flux. The system is complex and places a tremendous administrative burden on those who sponsor and carry out research with human subjects. By itself, the focus of the regulatory system on administrative paperwork places a naïve responsibility on the regulations to protect human subjects and removes responsibility from the investigator. The regulations governing IRBs concentrate on the development of standard operating procedures, IRB membership and documentation of IRB meetings. None of these directly relate to the protection of human subjects. Additionally, many of the mishaps in human subject research occur once a protocol has been reviewed and approved by the IRB. This was true in Jesse's case.

Specific to the Jesse Gelsinger case, a safety review of the gene-therapy protocol was conducted by two federal agencies, the FDA and the RAC, with different instructions regarding the site in which the adenovirus vector was to be injected. In addition, the RAC had misgivings about the safety of the study but allowed it to proceed anyway. Therefore,

[133] Hannas, "Systems Approach," 155.

if the initial review of the protocol is isolated, regulatory requirements were met, but the fulfillment of ethical requirements is questionable.

Serious adverse events, including deaths, from this and other gene transfer experiments were not reported to the RAC in a timely manner, thereby minimizing the RAC's ability to monitor the safety of the study and react as warranted. During implementation of the protocol, safety procedures were not adhered to, ineligible subjects were enrolled, data collection was mismanaged, proper IRB approvals were not obtained, and proper informed consent was not provided. Therefore, once the study was approved by the RAC, during the implementation of the study, regulations were not followed, ethical obligations were not met and research subjects were placed at risk. The regulatory system did not work.

Informed Consent and the Establishment of Trust

Chapter 2 offered a review of the ethical domain with a specific focus on informed consent, reviewing both the document and the process. While certain aspects of informed consent are governed within the regulatory domain, the concept behind the regulations is grounded in the ethical domain. Ethically valid informed consent establishes a foundation from which trust is built.

Trust is established between two persons, or among a group of people, when basic expectations about values such as honesty, respect, and truth-telling are upheld. Within the research environment, trust is built when the investigator honors the intent of the informed-consent regulations and enters into a dialogue with the potential subject regarding the research protocol. This dialogue presents an opportunity for the investigator to show that he values and respects the rights of the subject with whom he is engaged in a conversation. The discourse also presents the subject with the opportunity to evaluate the

investigator for his professionalism, interest in the subject as an autonomous person and his compassion. It is the investigator's duty to ensure that the subject knows 1) that she is being enlisted to participate in research and that the purpose of the study is to gain knowledge to benefit future patients; 2) that there could be unforeseen risks that are not yet known (any currently known risks must be disclosed, regardless of how insignificant they might seem); 3) that the investigator is being funded by a third party to conduct the study; and 4) what to expect as far as the number of study visits, the procedures conducted at each, and any other activities the subject will have to engage in to be compliant. In addition, if the investigator or any other study team member has any potential for financial gain from any aspect of the study, it must be disclosed. The information must be relayed in a format that enables full comprehension by the subject. Trust resides in the confident belief that the investigator will be truthful, respectful, and honor the potential subject's right to self-determination and autonomy. As summarized by Kahn and Mastroianni:

> The success of clinical research relies on the element of trust–trust in researchers, trust in hospitals, and trust in the research process itself. Patients who are potential research subjects rely on physicians to provide medical care that is in their best interest, and trust that when research participation is offered or suggested, it is not motivated by self-serving interests. Similarly, patients and research subjects trust that the health care institutions in which they receive their care or entrust their health and safety in research will not take advantage of them. Finally, subjects and potential subjects expect that there is a system of research protections in place that will safeguard their rights and interests in ways they can trust.[134]

[134] Kahn and Mastroianni, "Moving from Compliance to Conscience," 927.

Failures in the Ethical Domain and Informed Consent

Failures in informed consent are most often associated with the content of the informed-consent document and the signing of the form. Without the taping of the informed-consent process or the inclusion of a research subject advocate, there is little data regarding the effectiveness and validity of the informed-consent process. Based on the studies presented in chapter 2, there is evidence that proper informed consent is still a challenge that must be addressed.

Specific violations in the Jesse Gelsinger case included that, prior to receipt of IRB approval, subject recruitment began. The informed-consent document provided to the subjects was not the informed-consent document approved by the RAC. Information specific to the results of animal studies and adverse events was omitted from the document. Also missing from the informed-consent document were the description of the procedures and identification of those procedures considered research–required elements as per the regulations. The existence of the informed-consent document would satisfy compliance with the minimum requirements of informed consent as per the regulations. That being said, errors in the documents described above don't conform to the full requirements of the informed-consent document. In both instances, the ethical duty of informed consent is absent.

A forty-five-minute discussion of a gene therapy experiment to someone who has never participated in a research study is completely inadequate. In both the informed-consent discussion and follow-up phone call, potential risks were understated and potential benefits were exaggerated. While not a requirement, during the course of obtaining consent to participate in this study, conversations were held with three different physicians. Nowhere can it be discerned that the roles of the various physicians were

explained. Again, here is an instance in which there was compliance with the regulations, although loosely, but the ethical obligation was neglected.

Although much work still is to be done, and many more studies are needed to determine how much information is too much, there is quite a bit of attention being paid to the doctrine of informed consent and appropriate methods for implementing the concept behind the regulation. In *Rethinking Informed Consent in Bioethics,* Neil C. Manson and Onora O'Neill introduce a transactional model for informed consent in which the focus is not only on what is being stated but how the information is relayed both by those who request consent, *and* by those who respond by giving or refusing their consent.[135] In the transactional model, commitments are established–a commitment on the part of the investigator and of the research subjects. From this transactional conversation trust can be established through reliance on *what others say,* on *what they undertake to do,* on the truth of their claims, and the reliability of their commitments.[136]

It is widely discussed throughout the research and medical communities that to maintain trust, the informed-consent process must not be static or end with the signing of the consent form. An open and respectful conversation at the onset combined with on-going dialogue throughout the course of the study must occur. By continuing this dialogue, the participant is no longer a means to the investigators' ends, but instead is an active partner in the project and the larger research process. After all, in the end, "the statement that consent has been obtained has little meaning unless the subject or his

[135] Neil C. Manson and Onora O'Neill, "How to Rethink Informed Consent and Some Conclusions and Proposals," in *Rethinking Informed Consent*, (Cambridge, U.K.: Cambridge University Press, 2007), 69.

[136] Ibid., 160.

guardian is capable of understanding what is to be undertaken and unless all hazards are made clear."[137]

Paul Gelsinger Presents to the SACHRP (August 2, 2005)

On August 2, 2005, Paul Gelsinger, on behalf of Citizens for Responsible Care and Research (CIRCARE), a not-for profit organization composed of citizen advocates interested in effective protection of human subjects, was granted an opportunity to present their views on the adequacy of the current system to protect the rights and welfare of human subjects under OHRP to the Secretary's Advisory Committee on Human Research Protections. In the presentation, Paul presented CIRCARE's opinion that the current system under OHRP does not work. He described how compliance activities are *post hoc:* issues are uncovered–after they have occurred–through random audits, for-cause audits, or reported allegations. Paul also expressed concern about the reliance on the good will of the institutions and investigators who carry out the research. He felt it was not just that penalties for breech of regulations fall to the institution, not the investigator. He also discussed the failure of investigators to report serious adverse events and the impact this non-reporting has on study monitoring and informed consent. As a legacy to Jesse, CIRCARE proposed the adoption of five core principles and national reform to increase the legal and ethical safeguards for all human subjects that participate in experimental research studies.

Speaking for CIRCARE, Mr. Gelsinger stated:

> In order to restore trust, we believe that it is critical to respect the dignity of a person as a human being and to preserve her autonomy. Practices which constrain autonomy and cause human subjects to become merely the means to

[137] Beecher, "Ethics and Clinical Research," 1360.

> investigators' ends are reprehensible and unacceptable, and the burden imposed on individuals outstrips the benefit of research to society.[138]

The system and the informed-consent process betrayed Jesse. Many factors can be pinpointed as a cause for this failure: conflict of interest; pressures of conducting leading-edge science; bureaucratic processes that resulted in lots of paperwork and had minimal impact on subject safety; poor communication; and lack of training on research ethics to name a few. The end result is that any one of these can impact the public's ability to engender trust.

Necessary Reforms to the System

The system for protecting human subjects must establish regulations and ethics as equal partners. Without the indoctrination of ethics, the system will continue to rely on compliance with regulations, and investigators will continue to focus on the paperwork to be completed, losing sight of the protection of the human subject as the *prima facie* duty. A necessary step in reforming the system is implementation of a Human Research Participant Protection Program (HRPPP) as recommended by the IOM and also endorsed by CIRCARE as reparation for Jesse. The HRPPP is an all-encompassing system of protections combining regulations and ethics that is intended to extend the scope of the current regulations and protection systems. Currently, the HRPPP is voluntary and is achieved through an IRB accreditation process. The accreditation process evaluates not only IRB processes, but also the institutional support for an HRPPP and contractual elements that facilitate involvement of the sponsors to the program. It places accountability and responsibility on the investigators conducting the research, the institutions employing the investigators, the organizations sponsoring the research, those

[138] Gelsinger, CIRCARE Presentation, 8.

responsible for monitoring the research and the participant. The functions that define the program include a comprehensive review of protocols (added to the existing review of science and ethics is a review for conflict of interest); interactions between participant and investigator that are based on mutual respect and ethics versus authority; monitoring that is customized to the degree of risk assessed to the study; and activities that continuously review processes to ensure compliance and safety. Underlying the implementation of a HRPPP is the establishment of a shared vision, or culture, within the institution or organization that values and places in the highest regard, the protection of those who volunteer to participate in research studies.

Four specific conditions that lay the foundation for the establishment of this culture include:

1. accountability–to assure the quality and performance of the protection program,
2. adequate resources–to assure that sufficiently robust protection activities are in place,
3. ethics education programs–to provide research personnel and oversight committees with the knowledge necessary to carry out their obligation to conduct or oversee ethically sound research, and
4. transparency–to ensure open communication and interaction with the local community, research participants, investigators, and other stakeholders in the research enterprise.[139]

The HRPPP provides additional focus on a more robust ethics education program for everyone involved in clinical research: IRB members, investigators and other study

[139] Hannas, "Systems Approach," 157.

team members, designers of study protocols, and so forth. The educational program moves from a brief history of the regulations to thought provoking analysis of ethical quandaries. The anticipated result would be a conscientious change from simply following the regulations to understanding and implementing the intent behind them. In this system, while the virtue of the investigator is still an integral component, the welfare of the participant is not solely dependent on the investigator. As stated by Greg Koski prior to his becoming the first director of the Office for Human Research Protections,

> In truth, investigators are much better positioned during the course of their studies to protect the interests of individual research subjects than are the IRBs. Paradoxically, the person most likely to do something to harm a subject, the investigator, is also the person most capable of preventing such harm. And so, as Beecher … concluded many years ago, the only true protection afforded research subjects comes from a well-trained, well-meaning investigator.[140]

Additionally, implementation of a HRPPP provides an avenue to elevate the role of society from a conduit for carrying out human subjects research to an active partner in the research process. It emphasizes society's acceptance that the benefits derived from biomedical research are worthy of pursuit as long as individuals are not harmed or subjected to unacceptable risk, and that all research on human beings must conform to certain ethical guidelines.[141]

Additional Possible Remedies

Listed below are possible remedies, in addition to the establishment of an HRPPP, to prevent future betrayals and restore public trust.

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[140] Koski, "Resolving Beecher's Paradox," 221.

[141] Ibid.

1. Deploy public education regarding the generalities of human subjects research. The content of this education should include an overview of clinical research, a description of the human subjects' protection system, including the informed-consent process, their rights as research subjects and suggested questions to ask. By doing so, the public will be better prepared to invoke their right of self-determination.
2. Establish the protection of research subjects as an organizational priority. Implementation of robust research ethics programs would be one component of setting the priority. Institutions that educate future physicians and other health-care providers should incorporate research ethics into the medical curriculum.
3. Subjects entering studies considered high risk (e.g., gene transfer/gene therapy studies) or studies with no therapeutic benefit (Phase I studies, physiology studies, and others) should have the informed consent provided by the principal investigator. The investigators should be trained in the conduct of transactional conversations to ensure both parties are engaged in the conversation and obtaining the requisite information so that commitments can be established.
4. The process for reporting adverse events, especially serious adverse events, needs to be overhauled. A central, national database should be used so that, if desired, potential research subjects, among others, can query the database to review existing events that have been previously reported from the local as well as other sites. This database would also provide a mechanism to assist IRBs with the review of adverse events and consent forms, enabling them to get a full picture of the issues that may influence the safety of the subjects.

In summary, while there exists much debate about the current regulatory environment and its ability to keep pace with the rapidly changing research paradigm, the regulations establish the framework, but the first line of protection afforded to a research subject is that of a well-trained, well-intentioned, conscientious investigator working in an organization that embraces the ethical obligation for protecting human subjects. To restore the public's trust, the investigator, as part of a larger organization within a system, will have to embrace the ethics of human subjects' protections as an *a priori* duty in conducting research on human subjects.

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Vita

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