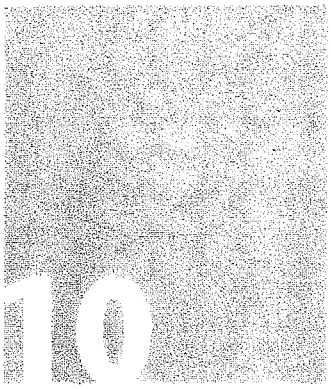

Robert Steinbrook

The Gelsinger Case

Background

The death of Jesse Gelsinger in September 1999 is one of the defining cases in the recent history of research with humans. Gelsinger, 18, died during a gene transfer experiment at the University of Pennsylvania School of Medicine.[1] His death—the first directly attributed to gene transfer—raised profound questions about the protection of patients in this high-profile research field, as well as in other clinical studies. It also raised questions about adherence to research protocols, the reporting of adverse events, informed consent, and financial conflicts of interest. It shook the confidence of the public and the federal government in the competence and ethics of clinical researchers and the institutions where they work, and led to efforts to improve the protection of research participants.

Although the terms gene transfer and gene therapy are often used interchangeably, gene transfer is more precise. Gene transfer refers to the transfer to a person of recombinant DNA, or the transfer of DNA or RNA derived from recombinant DNA. The aim is to modify or manipulate the expression of a gene in the body or to change the biological properties of cells. Although the promise of gene transfer is great, progress has been slow. A 1995 review of the investment in the field by the National Institutes of Health (NIH) advocated caution: "Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and inadequate understanding of the biological interaction of these vectors with the host."[2]

As of February 2000, several months after Gelsinger's death, more than 4,000 patients had participated in gene transfer studies. Of the 372 clinical trials that were registered with the NIH, 89% were Phase I studies of safety and toxicity.[3] For many years, the public and scientists have been concerned about the potential environmental and infectious disease risks of recombinant DNA technology. This is one reason that the federal government has treated gene transfer studies differently from other clinical research. Extensive data about all trials registered with the NIH are publicly available—far more than for most other studies. Investigators who are funded by the NIH or who conduct their work at institutions that receive NIH support for any type of recombinant DNA research must comply with specific NIH guidelines. In addition to this, a Recombinant DNA Advisory Committee (RAC) was established within the NIH in 1974. The RAC is a public forum for discussion of novel and substantial issues related to gene transfer trials, including the review of specific protocols. Although the guidelines and the specific duties of the RAC have changed over time, it has a critical role in the oversight of this research.[4] The Food and Drug Administration (FDA) also regulates clinical gene transfer trials.

Gene Transfer for Ornithine Transcarbamylase Deficiency

Ornithine transcarbamylase (OTC) deficiency is a recessive X-linked autosomal genetic defect that interferes with the metabolism of ammonia by the liver. Although the mutations that lead to this enzyme deficiency are rare—affecting 1 in 40,000 to 1 in 80,000 people—they are the most common of the inborn errors of urea synthesis. Correction of this single gene enzyme deficiency

has been viewed as a model for gene transfer directed at the liver.[5] The reason is that restoration of the enzyme activity should treat the disorder, as has been demonstrated by treatment with liver transplantation.[6] Gene transfer for OTC deficiency has been studied in the sparse fur mouse, which is deficient in the enzyme. Studies in this animal model suggest that the gene defect can be corrected.[1]

People with OTC deficiency can develop profound hyperammonemia. Excessive levels of ammonium ion in the brain can lead to life-threatening encephalopathy, coma, and brain damage. Complete deficiency usually leads to death during infancy. Without a liver transplant, only about half of those born with OTC deficiency will survive to age 5, and many survivors have profound mental impairment. For people with partial enzyme deficiency, a low protein diet supplemented with oral medications (sodium benzoate and sodium phenylacetate/sodium phenylbutyrate) can be used to minimize the risk of complications or death. Such treatment eliminates excess urea and precursors of ammonia. However, adherence to diet and medical therapy is difficult, and only partially effective.

Background to the Research Study at the University of Pennsylvania

A chronology of events leading up to and following Gelsinger's death is shown in Table 10.1. In 1993, James M. Wilson was recruited to the University of Pennsylvania from the University of Michigan. At the time of Gelsinger's death, Wilson was widely considered to be one of the leading gene transfer researchers in the world. He was director of the Institute for Human Gene Therapy and professor and chair of the Department of Molecular and Cellular Engineering in the university's School of Medicine. In 1992, while working in Michigan, Wilson was a founder of Genovo, Inc., which had the rights to market his discoveries related to gene transfer. Wilson held patents related to the use of vectors derived from the adenovirus for gene transfer.

There were many financial links between Genovo, whose principal offices were in a Philadelphia suburb, Wilson, the Institute for Human Gene Therapy, and the University of Pennsylvania. By 1999, Genovo provided more than $4 million a year to the institute, a substantial portion of its budget. Wilson and his immediate family had a 30% nonvoting equity stake in Genovo, and the University of Pennsylvania had a 3.2% equity stake.[7] Other shareholders included past and present employees of the university and the institute. In the late 1990s, Penn was aggressively seeking to profit from the discoveries of its professors. The *Philadelphia Inquirer* quoted the managing director of Penn's Center for Technology Transfer: "For years, Penn wasn't even in the game. Now we're in the game and we're looking for some home runs"[8] (see Chapters 68–71).

In December 1994, Penn's Center for Technology Transfer had officially requested that the Conflict of Interest Standing Committee at the University of Pennsylvania Medical Center review Wilson's involvement with Genovo. The committee had the authority to review the case and to make recommendations for managing potential conflicts of interest. The committee considered the case of great importance and conducted a detailed review. For example, according to the minutes of the committee's February 6, 1995, meeting, many comments and questions were considered. Members were concerned that Wilson's multiple roles would "conflict" with his responsibilities at Penn and "create conflicts" for the medical school in allocating resources or implementing ethical and academic policies. According to the minutes, "Since Dr. Wilson's research efforts will be directed towards the solution of a problem in which he has a financial interest in the outcome, how can Dr. Wilson assure the University that he will not be conflicted when making decisions that could have an impact on either Genovo, Biogen [another biotechnology company that had invested in Genovo], or the further development of his intellectual property?" Another question appeared in the draft version of the minutes, but not in the final version: "How can Dr. Wilson and the University avoid liability for damages if a patient died from any products produced or studied at the University?"

The Conflict of Interest Standing Committee recognized the potential conflicts of interest involving Wilson's commitments to Genovo and to the University of Pennsylvania. It also recognized that his research program could lead to important medical advances that might benefit the public. In 1995, it did not seek to end his financial arrangements with the company. Instead, it recommended actions to manage the conflicts by reducing his managerial and scientific control. These included making Wilson's stock nonvoting and prohibiting him from being a member of the company's scientific advisory board.

The Research Study

Between 1997 and 1999, Gelsinger and 17 other subjects participated in the clinical protocol, "Recombinant Adenovirus Gene Transfer in Adults With Partial Ornithine Transcarbamylase Deficiency."[5,9] Wilson was a coinvestigator and the sponsor of the research. His main collaborators were Steven E. Raper, a surgeon at the University of Pennsylvania, who was the principal investigator, and Mark L. Batshaw of the Children's National Medical Center in Washington, D.C., who was the coprincipal investigator. Batshaw had pioneered the drug and diet treatment that was widely used for OTC deficiency. On June 21, 1997, Wilson signed FDA form 1572, in which he agreed to conduct the study in accordance with the investigational plan and applicable federal regulations.

The adenovirus-derived vector contained a functional OTC gene. The vector was rendered incapable of replicating by the deletion of two adenoviral genes; it was designed to be safer than earlier versions of the vector. The purpose of the research was "to establish a safe dose of recombinant adenovirus to serve as a treatment for adults with partial OTC [deficiency]."[5] Like most gene transfer studies at the time, the trial was a Phase I safety study of escalating doses of the vector, not a study of the effectiveness of the treatment. Thus, subjects were not expected to benefit directly from their participation. The protocol was reviewed and approved by many oversight bodies, including the RAC, the FDA, and human subjects review boards at the University of Pennsylvania Medical Center and the Children's Hospital of Philadelphia. The NIH and Genovo, the company that Wilson had helped to found and in which he held equity, were the major funders of the research and of Wilson's laboratory.

The protocol called for groups of three or four participants to be assigned to one of six dosing regimens; each group received a progressively higher dose of the vector, with adjustment for their body weight. The genetically altered adenovirus was administered

Table 10.1
Timeline of Events Leading Up To and Following the Death of Jesse Gelsinger

Date	*Event*
1992	While at the University of Michigan, James M. Wilson is a founder of Genovo, Inc., a company involved in gene transfer research and development. The company has rights to market Wilson's discoveries related to gene transfer.
1993	Wilson is recruited to the University of Pennsylvania to be the director of the Institute for Human Gene Therapy.
1995	The Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health approves a clinical protocol from the Institute for Human Gene Therapy, "Recombinant Adenovirus Gene Transfer in Adults With Partial Ornithine Transcarbamylase [OTC] Deficiency." The principal investigator is Steven E. Raper, also of the University of Pennsylvania. The coprincipal investigator is Mark L. Batshaw of the Children's National Medical Center in Washington, D.C. Wilson is a coinvestigator.
1997	Enrollment of patients in the gene transfer protocol begins. The informed consent document includes a one-sentence statement about the financial interest of the University of Pennsylvania, Wilson, and Genovo, Inc., in "a successful outcome of the research involved in this study."
1998	Jesse Gelsinger, an 18-year-old man with partial OTC deficiency and a resident of Tucson, Ariz., learns about the Penn study from his physician.
June 1999	Gelsinger and his father go to the Institute for Human Gene Therapy. Blood tests to determine his eligibility for the gene transfer trial are performed.
Sept. 9, 1999	Gelsinger returns to Philadelphia to begin the trial.
Sept. 13, 1999	Gelsinger receives an infusion of 3.8×10^{13} particles of the adenoviral vector through a femoral catheter into the right hepatic artery. He is the 18th, and last, subject in the study.
Sept. 17, 1999	Gelsinger dies. After his death, the study is halted.
Sept. 29, 1999	*The Washington Post* reports on Gelsinger's death. Serious problems with the conduct of the OTC deficiency trial and the financial relationships between Wilson, Penn, and Genovo subsequently become widely known.
Dec. 1999	The RAC considers Gelsinger's death at a public meeting.
Jan. 2000	After conducting multiple inspections at Penn, the FDA closes down all clinical trials at the Institute for Human Gene Therapy.
Apr. 2000	An independent, external panel appointed by the president of the University of Pennsylvania reports on the Institute for Human Gene Therapy.
May 2000	The University of Pennsylvania announces that the Institute for Human Gene Therapy will stop conducting clinical studies and sponsoring clinical trials.
Aug. 2000	Targeted Genetics Corp. of Seattle agrees to acquire Genovo, Inc. Wilson receives stock valued at about $13.5 million and the University of Pennsylvania stock valued at about $1.4 million.
Sept. 2000	Gelsinger's family files a civil lawsuit against Wilson, other researchers, and the University of Pennsylvania.
Nov. 2000	The lawsuit is settled out of court; details are not disclosed.
Nov. 2000	The FDA, citing six violations of federal regulations, begins proceedings to disqualify Wilson from performing clinical research with investigational drugs.
Sept. 2001	The Office for Human Research Protections, in the Department of Health and Human Services, accepts Penn's corrective actions with regard to the OTC deficiency protocol and the University's system for protecting human subjects.
Feb. 2002	The FDA concludes that Wilson's explanations "fail to adequately address the violations."
Apr. 2002	Wilson announces that he will step down as director of the Institute for Human Gene Therapy.
Summer 2002	The Institute for Human Gene Therapy closes.
Apr. 2003	The University of Pennsylvania revises its conflict of interest policies for faculty participating in clinical trials.
Oct. 2003	A report on Gelsinger's death, "Fatal Systemic Inflammatory Response Syndrome in a Ornithine Transcarbamylase Deficient Patient Following Adenoviral Gene Transfer," is published in the medical literature.[1]
Feb. 2005	Resolving investigations by the Office of Criminal Investigations at the FDA and the Office of Inspector General of the Department of Health and Human Services, the Department of Justice reaches civil settlements with the University of Pennsylvania, the Children's National Medical Center, Wilson, Raper, and Batshaw.

as a single two-hour infusion of one ounce of fluid through a femoral catheter into the right hepatic artery. Participants were not compensated.

The informed consent document cited three major risks:

1. The possibility that the adenovirus would inflame the liver. "It is even possible that this inflammation could lead to liver toxicity or failure and be life-threatening," the consent document stated.
2. The possibility that the adenovirus would provoke an immune response that would damage the liver.
3. The possibility that receiving the vector would prevent the research participants from receiving it as part of a therapy in the future. If used again, the vector would likely trigger an immune response and the body would eliminate it.

The consent document also stated that if a subject developed liver failure, "a liver transplant could be required." Participants were to

undergo a liver biopsy; the document stated that this procedure was associated with a "very small risk (1 in 10,000) of serious unpredicted complications which can include death."[10]

A particularly controversial aspect of the study was the decision to enroll adults with mild disease, rather than children with severe disease. The investigators had initially planned to use dying newborn infants as subjects but changed their minds.[11] According to the informed consent document, "Because this is a study of safety and long-term metabolic improvement is not expected, we felt it most appropriate to study adults (ages 18–65) who have a mild deficiency of OTC rather than children."[10]

One reason for the switch was that adults without mental impairment were better able to provide informed consent than the parents of children with terminal illness. Another was that it would be difficult to recognize adverse or life-threatening events in children who were already dying from their disease. Arthur L. Caplan, a leading bioethicist, a professor of bioethics at Penn, and a member of Wilson's department, advocated this approach.[11] Wilson has stated that the decision to use adults "was based on the collective input and recommendations from the University of Pennsylvania's own bioethicists, as well as from families of diseased children and other metabolic disease experts not associated with the study."[12] In some ways, the choice between enrolling adults with mild disease or children with severe disease represented a no-win situation for the investigators. Although this was a Phase I safety study, terminally ill newborns potentially had the most to gain.[13] Both positions can be justified, and both can be criticized.

The enrollment of subjects with only mild disease was criticized before and after Gelsinger's death. The RAC (which at the time had to approve gene transfer studies) had approved the protocol in December 1995.[14] The approval, by a vote of 12 to 1, with 4 abstentions, followed a lengthy discussion during which some members questioned the safety and wisdom of the proposed experiment. One concern was the enrollment of patients with mild disease. Another was the infusion of large quantities of the vector directly into the blood supply of the liver. For example, one reviewer of the protocol said that it would "be more acceptable if the vector can be repeatedly delivered by the less invasive intravenous route" and if the treatment was "given to affected children with life threatening OTC deficiency."[14] At the time, the researchers agreed to infuse the vector into the bloodstream, not directly into the liver. This decision was subsequently reversed, as the FDA requested when it approved the protocol in 1997. The rationale was that because the vector would travel through the circulation to the liver anyway, it was safer to put it directly where it was needed with the hope that it would not travel elsewhere. The RAC was not informed of this change.[15]

The informed consent document also included a one-sentence statement about the financial interests of the sponsors: "Please be aware that the University of Pennsylvania, Dr. James M. Wilson (the Director of the Institute for Human Gene Therapy), and Genovo, Inc. (a gene therapy company in which Dr. Wilson holds an interest), have a financial interest in a successful outcome from the research involved in this study."[10] Such a statement was highly unusual at the time. The form did not specify what the financial interests were, or their potential magnitude. According to the University, Wilson had no role in recruiting patients, obtaining informed consent, or treating patients, including Gelsinger. Wilson, however, was a coinvestigator. As the director of the Institute for Human Gene Therapy, he was the sponsor of the study. It was his gene transfer research that made the trial possible. Wilson was extensively involved in activities such as the preclinical animal work, the development of the gene transfer vector and its mode of delivery, the design of the trial, protocol modifications, laboratory work during the trial, and the analysis of the results.

Jesse Gelsinger

Jesse Gelsinger was diagnosed with partial OTC deficiency when he was a young child. He was subsequently found to have a unique mutation. Some of his cells had a defective OTC gene with a large deletion, whereas others had a normal gene—a condition known as mosaicism.[16] Despite diet and drug therapy, he developed serious hyperammonemia many times, including an episode of hyperammonemic coma in December 1998 that required treatment with mechanical ventilation. He recovered from this episode without apparent adverse effects. In 1999, his disease was considered generally controlled.

Gelsinger lived in Tucson, Arizona. He was the 18th subject in the study and, at age 18, the youngest person enrolled. He had learned about the trial in 1998 from his physician. His father said after his death that he "was doing this for other people."[17] Jesse Gelsinger set aside his personal life to participate, and took an unpaid leave from his job.[18] According to his father, "One night he even said, 'The worst that could happen is that I could die and maybe help doctors figure out a way to save sick babies.' I've never been more proud of my son than the moment he decided to do this experiment."[17]

The doses of the vector in the study ranged from 2×10^9 to 6×10^{11} particles/kg of body weight. (The second-highest dose was 2×10^{11} particles/kg.) On September 13, 1999, Gelsinger became the second subject to receive the highest dose of 6×10^{11} particles/kg; his total dose, based on his weight, was 3.8×10^{13} particles. In the other study participants, including the first to receive the highest dose, the adverse effects were transient muscle aches and fevers and laboratory abnormalities such as thrombocytopenia, anemia, hypophosphatemia, and elevated levels of the liver enzymes known as transaminases. The adverse events in other study participants, however, were not life threatening.

About 18 hours following infusion of the adenovirus vector, Gelsinger developed altered mental status and jaundice—neither of which had been seen in the first 17 study participants. He subsequently developed the systemic inflammatory response syndrome, disseminated intravascular coagulation and multiple organ system failure, and the acute respiratory distress syndrome.[1] Gelsinger died on September 17, 1999, 98 hours following gene transfer.

An autopsy and subsequent studies indicated that his death was caused by a fulminant immune reaction (with high serum levels of the cytokines interleukin-6 and interleukin-10) to the adenoviral vector.[1] Substantial amounts of the vector were found not only in his liver (as expected) but also in his spleen, lymph nodes, and bone marrow. According to an NIH report on adenoviral safety and toxicity that was prompted by Gelsinger's death, "The data suggested that the high dose of Ad [adenoviral] vector, delivered by infusion directly to the liver, quickly saturated available receptors . . . within that organ and then spilled into the circulatory and other organ systems including the bone marrow, thus inducing the systemic immune response."[19] The report added, "Although the Ad vector used in the OTC trial was incapable of replicating, the capsid

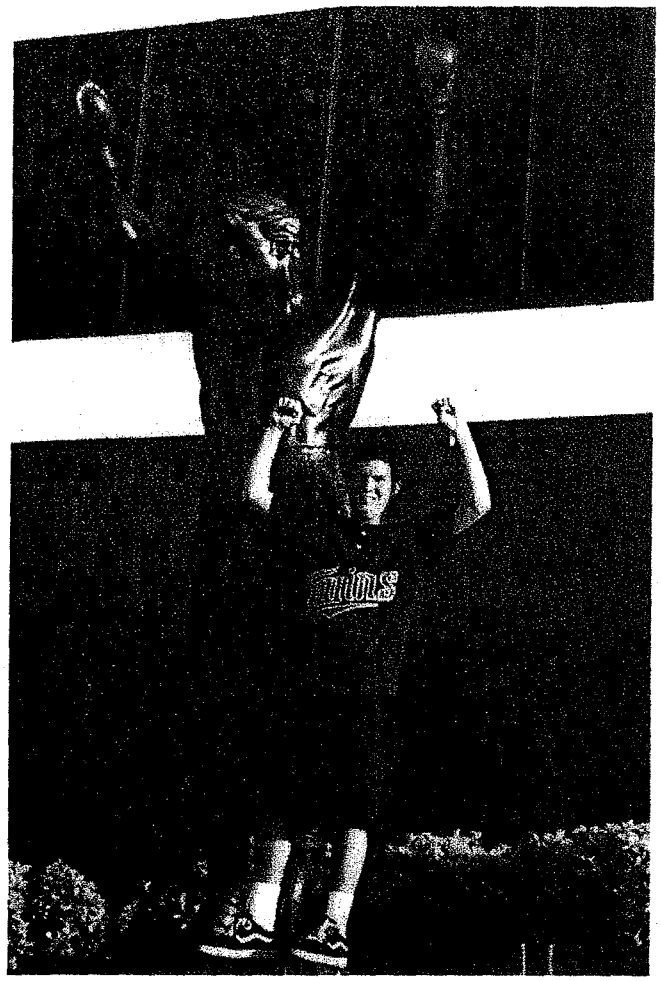

Figure 10.1. Jesse Gelsinger, June 22, 1999. "Having just been screened for participation in the Ornithine Transcarbamylase Deficiency clinical trial, Jesse Gelsinger was ready, just like Rocky Balboa was ready for battle, to help advance treatments for his disease," says Jesse's father, Paul Gelsinger. "Jesse had no real idea of the concealed dangers involved in what he was about to do, nor of the ethical awareness his death would bring." Source: Mickie Gelsinger and Paul Gelsinger. Reproduced with permission.

proteins encoating the vector [the shell of the vector] likely contributed to the participant's immune response."

In October 2003, the research team published a report on "the unexpected and tragic consequences of Jesse Gelsinger's participation in this trial."[1] They concluded that his death pointed to "the limitations of animal studies in predicting human responses, the steep toxicity curve for replication defective adenovirus vectors, substantial subject-to-subject variation in host responses to systemically administered vectors, and the need for further study of the immune response to these vectors."[1]

Subsequent Developments at Penn

After Gelsinger's death, the study was halted. Although a Tucson newspaper had reported on his death a few days earlier, the events were not widely known until an article appeared in the *Washington Post* on September 29, 1999.[20,21] The FDA, the NIH, and the Office for Protection from Research Risks at NIH began intensive reviews of the protocol and other gene transfer research.

Serious deficiencies in the conduct of the study soon became widely known.[22] One was that Gelsinger should not have been allowed into the study, because his liver was not functioning at the minimal level required for inclusion on the day he received the infusion. Another was that the researchers failed to immediately notify the FDA when earlier participants had "Grade III" liver toxicity. Their liver enzyme abnormalities were sufficiently severe that the study should have been put on hold, as the research protocol required. Still another was that the FDA was not promptly informed about the results of tests in laboratory animals that suggested a significant risk of the adenoviral vector for human subjects. When given higher doses of the vector (1×10^{13} particles/kg), rhesus monkeys developed disseminated intravascular coagulation and liver failure; some died. However, at the dose administered to Gelsinger (6×10^{11} particles/kg), which was about 15-fold less, only minor toxicities to the liver were observed in the monkeys. Yet another deficiency was that the researchers had changed the protocol multiple times without notifying the FDA, and failed to make changes they had agreed to make. These included tightening the exclusion criteria in a way that would have made more potential subjects ineligible, because they were at risk for liver toxicity on the basis of their medical histories. Other questions had to do with Wilson's and Penn's financial interest in the study's success, deficiencies in the informed consent process, including downplaying the risks by failing to give potential participants all the relevant safety information, such as the monkey deaths and the serious side effects in other subjects, failure to follow the protocol, failure to maintain complete and accurate records, and the adequacy of the review of the trial by Penn's institutional review board (IRB).[22–29]

In January 2000, after conducting multiple inspections at Penn, the FDA issued a "list of inspectional observations" and closed down all clinical trials at the Institute for Human Gene Therapy.[25] Neither the FDA nor the Office for Protection from Research Risks sought to halt all clinical research at Penn.

Although acknowledging mistakes and extending its sympathy to the Gelsinger family, the research team vigorously defended its work, and Penn defended its researchers.[30] According to Wilson, "the alleged lure of potential financial gain played no role in any clinical decisions."[12] Penn's position has been that "as deeply regrettable as Gelsinger's death was, it was simply not foreseeable based on informed medical judgment and the best scientific information available at the time," according to a written statement in October 2003 by Rebecca Harmon, the chief public affairs officer for the University's School of Medicine.

After Gelsinger's death, Penn initially sought to reopen its gene transfer program. Soon, however, it changed its mind. In early 2000, Judith Rodin, then the president of the university, appointed an independent, external panel to evaluate the issues. William H. Danforth, former chancellor of Washington University in St. Louis, chaired the panel. In April 2000, the panel recommended that the university do a better job of evaluating and monitoring clinical trials and ensuring that informed consent is properly obtained.[31] The panel also recommended that Penn review its policies on conflict of interest, especially with regard to clinical trials. For clinical trials, the panel found that

> [E]quity positions by an investigator and/or the University may be ill advised, even if, in reality, there is no practical effect whatsoever. Given that the overriding responsibility of the University and its investigators is to the welfare of patients, the avoidance of conflict of interest that even remotely might detract from putting the needs of patients first becomes paramount. In that regard, investments in new therapies differ from those in other ventures, such as computer technology, which involve no responsibility for patient care.

The panel also questioned whether it made sense "to have an entire Institute devoted to gene therapy."

Rodin also requested a second report, an internal review by Penn faculty of all aspects of research involving human subjects at the university. In an interim report, also in April 2000, the internal Committee on Research Using Humans recommended that Rodin carry out a comprehensive review of the university's IRB system, and develop formal monitoring mechanisms for clinical trials as well as "standard operating procedures" that apply to human subjects research.[32] At the time, Penn had more than 3,900 ongoing research protocols involving humans, of which more than 750 involved the use of investigational drugs. The committee also recommended that the IRB "act expeditiously to require that principal investigators and coinvestigators disclose on the forms requesting IRB approval any proprietary interest in the product or procedure under investigation, including potential future compensation both for themselves and their immediate family. The IRB should then determine on a case-by-case basis whether disclosures in the patient consent document or other protections are required."[32] The committee never issued a final report, as the university quickly implemented changes.

In May 2000, the University of Pennsylvania announced that the Institute for Human Gene Therapy would stop conducting clinical studies and sponsoring clinical trials. Instead, it would conduct animal experiments and preclinical research. The university also announced other changes, including reforms in its IRB system, educational programs for researchers, and a more comprehensive infrastructure to protect research subjects.[33] According to a university publication, the work of the internal review committee and other efforts by faculty and administrators "have generated unprecedented change in Penn's research infrastructure and culture."[34]

In August 2000, Targeted Genetics Corp. of Seattle agreed to acquire Genovo, the company that Wilson had helped to found.[35] The acquisition enriched Wilson and the University of Pennsylvania. Under the agreement, Wilson was to receive Targeted Genetics stock that was then valued at about $13.5 million. The University of Pennsylvania was to receive stock valued at about $1.4 million.[7] Although the actual amount of money that Wilson and the university received is not known, it may have been considerably less, because the value of the stock plummeted.

In September 2001, the Office for Human Research Protections of the Department of Health and Human Services (DHHS), which had replaced the Office for Protection from Research Risks at the NIH, accepted Penn's corrective actions with regard to the OTC deficiency protocol and the University's system for protecting research participants.[36] In April 2002, Wilson announced that he would step down as director of the Institute for Human Gene Therapy. He continued as chairman and professor of the Molecular and Cellular Engineering Department. The institute closed in the summer of 2002.

The University of Pennsylvania also revised its conflict of interest policies. In April 2003, a policy on "financial disclosure and presumptively prohibited conflicts for faculty participating in clinical trials" became effective.[37] An earlier version had been used as an interim policy. The policy prohibited clinical investigators from maintaining certain "significant financial interests" such as service on the board of directors or as an officer of a company or entity that sponsors a clinical trial, significant equity interest in the sponsor, or ownership of a proprietary interest in the tested product. The policy defined "significant equity interest" as

> [A]ny ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $10,000 (or exceeds 5% ownership) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study. Interest in any publicly traded mutual fund is excluded.

Like policies at many academic medical centers, Penn's policy allowed for exceptions on a case-by-case basis when there are "compelling circumstances." The policy defined "compelling circumstances" as "facts that convince the [Conflict of Interest Standing Committee] that an investigator should be permitted to participate in a specific trial in spite of a Significant Financial Interest." Relevant information "includes the nature of the research; the magnitude of the financial interest; the extent to which the financial interest could be influenced by the research; the degree of risk to human subjects; and whether the interest is amenable to management."[37]

The Response of Gelsinger's Family

Following his son's death, Paul Gelsinger became an outspoken advocate of improved protection for research participants. In the first months after the death, he continued to support his son's doctors—"believing that their intent was nearly as pure as Jesse's"—even as the news media exposed the flaws in their work.[18] However, while attending the discussion of his son's death at a RAC meeting in December 1999, he became convinced that he and his son had not been given all the relevant information. He changed his mind. "It wasn't until that three-day meeting that I discovered that there was never any efficacy in humans," he later wrote. "I believed this was working based on my conversations with Mark Batshaw and that is why I defended Penn for so long." At a meeting with FDA and NIH officials and the Penn doctors during the RAC meeting, "after touching on many issues I let them know that I had not to this point even spoken to a lawyer, but would be in the near future. Too many mistakes had been made and unfortunately, because of our litigious society, it was the only way to correct these problems."[18] In September 2000, Gelsinger's family filed a civil lawsuit against the lead researchers, the University of Pennsylvania, and others.[38] In November 2000, the suit was settled out of court; details have not been disclosed.[39,40]

The Response of the Federal Government

At the time of Gelsinger's death, adenoviral vectors were used in one quarter of the 372 gene transfer trials that were registered with the NIH. After reviewing safety and toxicity data from these trials, the RAC recommended that human gene transfer research with adenoviral vectors continue, but with greater caution.[19] The committee also recommended a centralized data base for collecting and organizing safety and toxicity data on gene transfer vectors, greater standardization of the experimental data collected during trials, improved informed consent documents, and more extensive monitoring of research participants.

Prompt and complete reporting of serious adverse events was a particular concern. After Gelsinger died, the NIH and the FDA both reminded researchers of their obligations to report adverse events in gene transfer trials. The NIH soon received nearly 700 such reports, including reports of deaths that occurred before Gelsinger's.[41] For example, the NIH learned that a gene transfer trial at another academic medical center had been suspended in June 1999 after three of the first six participants died and a seventh became seriously ill. The study participants were terminally ill cancer patients. The NIH also had not been promptly notified of two deaths at a third institution during trials involving genes for a vascular endothelial growth factor aimed at growing new blood vessels in patients with coronary or peripheral artery disease. In 2000, the FDA halted the experiments.[42] The FDA and the NIH subsequently tightened the monitoring procedures for gene transfer trials, increased federal oversight and public access to information about the trials, increased inspections of gene transfer clinical investigators, and improved the reporting of serious adverse events. In March 2004, the agencies launched the Genetic Modification Clinical Research Information System, known as GeMCRIS. This Web-accessible database on human gene transfer (http://www.gemcris.od.nih.gov) provides information about clinical gene transfer trials. It also allows investigators and sponsors to report adverse events using a secure electronic interface, thus improving and centralizing reporting procedures.

In March and July 2000, the FDA sent warning letters to Wilson, outlining what the agency viewed as widespread deficiencies in the conduct of the research.[26,27] In November 2000, the FDA sent warning letters to Batsaw[43] and Raper[44] and began proceedings to disqualify Wilson from performing clinical research with investigational drugs.[28] It is unusual for the FDA to seek such a disqualification. In a 15-page letter, the FDA detailed the evidence that Wilson had "repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs."[28] It cited six violations: failure to fulfill the general responsibilities of investigators; failure to ensure that an investigation was conducted according to the investigational plan; failure to submit accurate reports about the safety of the study to the University of Pennsylvania IRB; failure to accurately and completely identify changes in the research for review and evaluation by the review board; failure to properly obtain informed consent; and failure to maintain accurate case histories of the research subjects. Wilson contested many of the allegations.

In February 2002, the FDA concluded that Wilson's written explanations failed "to adequately address the violations."[45] The agency told Wilson that, although he was assisted by "several subinvestigators," as "the clinical investigator you were responsible for all aspects of the study." It added, "While you assert that you delegated many aspects of the subject recruitment and subject management to others, you were the responsible leader of the investigational team. Indeed, you were present when prospective subjects' cases were discussed, and when protocol modifications were considered at the OTCD team meetings."[45]

Following investigations by the Office of Criminal Investigations at the FDA and the Office of Inspector General at the DHHS, the Department of Justice brought civil charges against the University of Pennsylvania, the Children's National Medical Center, Wilson, Batshaw, and Raper. The government alleged that the investigators and their institutions violated the federal False Claims Act by making false statements and claims in connection with grant applications and progress reports to the NIH, submissions to the FDA, information supplied to the IRBs that had oversight over the research, and by failing to obtain proper informed consent.

In February 2005, the government reached civil settlements with the investigators and institutions.[40] The institutions and investigators did not acknowledge the government's allegations and maintained that they acted appropriately and within the law at all times. The investigators did not take responsibility for Gelsinger's death. The University of Pennsylvania agreed to pay a fine of $517,496 and to increase IRB oversight of clinical research and training for investigators and clinical coordinators. The settlement agreement outlined the steps the university had taken to promote safety in clinical research. For example, between fiscal years 1998 and 2005, the number of full-time employees of the University's Office of Regulatory Affairs, which is responsible for staffing the IRBs, increased from 5 to 23. In a written statement, the university said, "Out of this tragedy has come a renewed national effort to protect the safety of those who help to advance new treatments and cure through clinical research." The Children's National Medical Center agreed to pay $514,622 and to increase its IRB budget and staff.

Wilson continued to work at the University of Pennsylvania. The agreement terminated the FDA's administrative proceedings against him. Wilson agreed not to serve as a sponsor of a clinical trial regulated by the FDA or to participate without restriction in research with humans until February 2010. (He already had not been involved with human research participants since January 2000.) Wilson also agreed to meet specified educational, training, and monitoring requirements related to his research and to lecture and write an article on the lessons of human research participants protections learned from the OTC deficiency trial. In a written statement released by Penn, Wilson said, "In the last few years, I have focused my research on the discovery and design of new gene-transfer vectors for gene therapy and genetic vaccines. Reaching this agreement means that I may continue to devote myself fully and without restriction to my laboratory and that I may conduct clinical research when it would be appropriate for scientific advancement." Batshaw and Raper agreed to lesser restrictions.

Enduring Legacy

More than eight years after Gelsinger's death, the case remained sensitive for the University of Pennsylvania. Despite repeated requests, neither Wilson nor any of the university officials with

extensive knowledge of the case were willing to speak about it; Wilson has granted no interviews for many years.

According to Donna Shalala, Secretary of DHHS during the Clinton administration, "The tragic death of Jesse Gelsinger focused national attention on the inadequacies in the current system of protections for human research subjects."[46] In a better world, improved protection for research subjects would be less dependent on responses to tragedy. Nonetheless, the protection of research subjects has often improved after crises, such as the Tuskegee syphilis experiment in the 1970s (see Chapter 8). In an article in the *New England Journal of Medicine* in 2000, Shalala wrote that "the American people expect that clinical researchers will never compromise or neglect the safety of human subjects." She also cited practical considerations: "To put it simply, if we cannot guarantee sound research in general—and patients' safety in particular—public support for gene therapy and other potentially lifesaving treatments will evaporate."[46]

Reports from the DHHS Office of Inspector General, some of which were completed before Gelsinger's death, documented problems with IRBs in the United States. The review boards have been criticized for reviewing too many protocols, working too quickly, having insufficient expertise, and providing too little training for investigators and board members.[47] The National Bioethics Advisory Commission and the Institute of Medicine examined these and additional problems with assuring the safety of subjects.[48,49] A common theme was that broader and more effective federal oversight of clinical research was needed.

In 2000, DHHS established the Office for Human Research Protections. The office replaced the NIH Office for Protection from Research Risks, which had less visibility and stature. In 2001, the FDA established the Office for Good Clinical Practice to coordinate its efforts to protect research subjects. As indicated above, in 2004, the NIH and the FDA launched the GeMCRIS to provide information about clinical gene-transfer trials and allow prompt reporting of adverse events. Institutions that have corrected serious problems with their programs for protecting subjects, such as Johns Hopkins University and Duke University as well as Penn, have markedly increased their spending for these programs, and have increased the number of review boards.[47]

Lawsuits against investigators, IRBs, and academic institutions are increasingly common.[50] Traditionally, litigation in clinical research was based on allegations about failure to obtain informed consent. For example, investigators may not have given research participants sufficient information to permit meaningful consent. In the Gelsinger case and other recent actions, new types of claims have been made. These include product liability claims against a drug manufacturer and fraud claims against investigators for not revealing their financial ties or problems encountered by previous subjects. The number and types of defendants have also expanded.

The allegations in the civil lawsuit filed by Gelsinger's family included wrongful death, product liability, lack of informed consent, and fraud. The initial defendants included William N. Kelly, the former dean of the School of Medicine and the chief executive of its health system, who had recruited Wilson to Penn and had patent interests related to gene transfer research. They also included Caplan, who had been consulted about the trial, the trustees of the University, the main investigators, and Genovo, the company that Wilson had helped to found.[38] When the lawsuit was settled, Kelly and Caplan were dismissed from the suit.[40] According to an analysis of these trends by Mello, Studdert, and Brennan, litigation may help injured subjects obtain compensation. However, it is also likely to lead IRBs to adopt "a more legalistic, mechanistic approach to ethical review that does not further the interests of human subjects or scientific progress."[50]

In response to the Gelsinger case, the American Society of Gene Therapy revised its conflict of interest policies.[51] The Association of American Medical Colleges issued guidelines for oversight of both individual and institutional financial interests in human subjects research.[52,53] In 2004, after years of consideration, DHHS issued guidance on financial relationships and interests and human subject protection.[54] The department recommended that "IRBs, institutions, and investigators consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare of subjects." Among the questions to be addressed were, "What financial relationships and resulting financial interests could cause potential or actual conflicts of interest?" and "At what levels should those potential or actual financial conflicts of interest be managed or eliminated?"[54]

Despite the various reports and institutional changes following Gelsinger's death, it can be argued that nothing has really changed. Review boards and other oversight mechanisms can do only so much. As of 2007, Congress had enacted no legislation to make the system for protecting research participants more efficient and effective. There had been no new federal regulations. For example, according to David Blumenthal, the guidance from DHHS about financial relationships is "notable for the qualified nature of its recommendations, which are not backed by any regulatory authority."[55] In addition, improvements in the federal oversight of research primarily affect federally funded programs. With the exception of research involving new drugs and medical devices that is under the jurisdiction of the FDA, there is no requirement that participants in privately sponsored research receive the same protection that federal regulations provide.[47] The National Bioethics Advisory Commission concluded in 2001 that the difference in protection was "ethically indefensible" and "a fundamental flaw in the current oversight system."[48] This situation remains unchanged. Although it might seem that that research subjects should be safer than they were before Gelsinger's death, there is no way to know for sure.

Ethical Issues

The issues raised by the Gelsinger case have a common theme. In their zeal to help patients with a life-threatening disease, leading researchers at one of the premier academic medical centers in the United States lost their focus. They overlooked warning signals that the experimental intervention was not safe, with tragic, fatal consequences. The ethical issues relate to the selection of the research subjects, informed consent, adherence to the research protocol, and financial conflicts of interest.

The concerns about the selection of research subjects are discussed earlier in this chapter. Although adults with mild OTC deficiency and no mental impairment could provide informed consent, participation in the trial may have placed them at unnecessary risk. New treatments for OTC deficiency were urgently needed for patients with severe disease, not mild disease. Both the enrollment of adults with mild disease or newborns with the lethal form of the disease can be justified, and both positions can be

criticized. As a Phase I study of dosage and safety, the Penn experiment was not intended to evaluate the therapeutic effectiveness of gene transfer for OTC deficiency. It is easy to criticize decisions after a tragedy. There was a rationale for the enrollment criteria, and many oversight groups approved the protocol.

The case underscores the responsibilities of investigators to properly obtain informed consent, to clearly disclose all the risks of research, to adhere to the research protocol, to keep good records, and to communicate promptly and completely with IRBs and regulatory agencies.[13] It also underscores the obligations of review boards and regulatory agencies to provide effective oversight of research.

There is no evidence that the financial interests of the University of Pennsylvania and Wilson in the success of the research had any relation to Gelsinger's death. Nonetheless, the existence of their financial interests inherently created uncertainty about their motives. Even if their motives had nothing to do with making money and their financial incentives had nothing to do with the conduct of the study, there was no way that either Penn or Wilson could effectively respond to the charge that the research was pursued for financial gain. The informed consent document included a statement about the financial interests of Penn, Wilson, and Genovo "in a successful outcome from the research involved in this study," although it did not indicate what the financial interests were, or their magnitude.[10] It can be argued that although disclosing this information to subjects was preferable to not disclosing it, the conflicts did not have to exist in the first place. A key question is whether Penn or Wilson should have been allowed to have these financial interests at all, or if the clinical trial should have been conducted by other investigators or at another institution. An IRB or a conflict of interest committee could require that financial conflicts be eliminated.

Cooperation between academic medical centers and industry can advance medical knowledge and speed the development of new treatments and technologies. Financial relations, however, complicate this cooperation. Some experts consider a presumption that financial conflicts should be eliminated, not managed, to be too draconian because it will impede vital research. Others argue that less radical approaches are doomed to fail. According to Marcia Angell, a former editor-in-chief of the *New England Journal of Medicine,*

> [O]ur society is now so drenched in market ideology that any resistance is considered quixotic. But medicine and clinical research are special, and I believe we have to protect their timeless values of service and disinterestedness. Patients should not have to wonder whether an investigator is motivated by financial gain, and the public should not have to wonder whether medical research can be believed. The only way to deal with the problem is to eliminate it as much as possible. [56]

Gene transfer is still in its infancy. It continues to hold great promise, but the risks and benefits are still being discovered. For example, encouraging results with gene transfer in the treatment of X-linked severe combined immunodeficiency (X-SCID), a devastating disease of young children, were followed by reports of a leukemia-like disorder in some of the research participants. One of these children died in 2004. According to Philip Noguchi of the FDA, the developments are a reminder that "the manipulations needed to create gene therapy add enormous complexity to considerations of safety and preclinical toxicity testing, and for every intended consequence of a complex biological product, there are unintended consequences."[57] In March 2005, an advisory committee to the FDA recommended that gene transfer for X-SCID be restricted to children who have no alternative. As of that month, the FDA had received 472 investigational new drug applications for gene transfer; 123 had been withdrawn, 92 were inactive, 14 had been terminated, and 243 remained active. As of October 18, 2007, the FDA had received 562 applications; 150 had been withdrawn, 101 were inactive, 15 had been terminated, and 296 remained active. The agency had approved no gene therapies.

The death of Jesse Gelsinger has taught the medical community and society about how to make clinical research safer. Research, however, is still research. Only a minority of clinical trials will show benefit. Adverse events are inevitable. Some will continue to be unexpected, and tragic.

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