Study Case 1. Gelsinger, OTC and Risks of Gene Therapy

Ornithine transcarbamylase (OTC) deficiency is a genetic disease which prevents the body from breaking down ammonia (a metabolic waste product). In OTC patients, the excessive build-up of ammonia often causes death soon after birth, unless the patient's diet is immediately adjusted and monitored throughout their entire life.

A 17-year-old boy named Jesse Gelsinger with OTC deficiency was fairly well controlled on a strict non-protein diet. In 1999, Jesse volunteered for an experimental gene therapy, at the University of Pennsylvania, designed to test a possible treatment for OTC in which an adenovirus vector carrying a normal OTC gene was injected into his liver. Prior to entering the study, Jesse and his family were informed that other subjects had received adenovirus infusions without serious complications. Following the infusion, Jesse suffered an unusual reaction triggered by the injection of the adenovirus vector, which in turn triggered a fatal hyperactivation of his immune system reaction. On September 17, 1999, four days after the injection, Jesse Gelsinger died.

Following Jesse Gelsinger's tragic death, investigations by a number of different agencies and scientific experts revealed new information and insights about prior research and clinical experiences which had great relevance to current and future gene therapy research and treatment.

Research investigators gave considerable thought to the selection of subjects for these gene therapies: healthy, adult volunteers who had OTC or babies born with OTC whose parents consented. A concern was raised as to whether parents with very sick newborns could really understand that gene therapy experiments were very risky and probably would not help their baby. Ultimately, the research investigators chose adults, who were thought more likely to have better comprehension.

Although initially it was thought that the adenovirus vector system was relatively safe and that Jesse's deadly reaction was random and unforeseeable, the investigations turned up some 700 instances of adverse events among gene therapy subjects (human and animal). Although most of these events had been reported to the FDA, the agency had neglected to set up a formal tracking and information sharing system because of pressure from the gene therapy industry. Consequently, these previous problems had not been communicated adequately to stakeholders in gene therapy community, including volunteer subjects, families, and other members of the research community. Jesse's family said that they were never adequately informed of these past events, and that when Jesse decided to volunteer, he thought the risks were lower than they actually were.

The lead scientist, Dr. James Wilson, held more than 20 patents related to gene therapy, and also held 30% of the stock in a small startup company, Genovo, which was sponsoring the research and clinical testing. In addition, the University of Pennsylvania also held some of the stock in Genovo. Investigators concluded that Gelsinger had not been fully apprised of the financial interests of the research institute and investigators. If the adenovirus vector being used in the OTC gene therapy trial worked correctly and was successful, the investigators and the affiliated institutions stood to earn a large amount of money, and to benefit in many other respects, such as using it to treat people or selling it to other researchers and physicians.

Adapted with modifications from http://highschoolbioethics.med.nyu.edu/briefs/jesse-gelsinger
Questions for Discussion

Describe how their financial stakes in the OTC gene therapy might have influenced some scientific and/or clinical decisions made by Dr. Wilson and associates as he continued with his investigations.

Do you think a researcher can make sound decisions about an experiment when they have a stake in the outcome of those experiments?

Do you think researchers can make ethically sound decisions about clinical investigations when they have financial or intellectual stakes in the outcome of those experiments?

Do you think there are any conflicts of interest in the deliberations about choice of research subjects? Would you make the same decision?

Describe how the various financial arrangements described in this case constituted or led to conflicts of interest.
Case Study 2. Dr. Roberts and a new drug for lupus.

Dr. Linda Roberts has spent the past five years working on a new drug for the treatment of lupus erythematosis. The molecule she designed links a fragment of an anti-inflammatory drug with a protein that binds to the diseased cells. Designing this new drug was made possible by two decades of research in the Immunology Laboratory at Westfield University Medical School, where Dr. Roberts works. Without the basic work in researching the molecular biology of this disease (the early stages of the research were funded by the National Institutes of Health), the highly specific drug would never have been developed.

In the past five years, she has been supported by funds from Arthrid, Inc., a company that markets a number of drugs for arthritis, given a consultant fee of $50,000, and assistance from Arthrid researchers with methods for producing large amounts of the therapeutic molecule. Because Arthrid is a local company and has been generous to the medical school, several members of the Westfield University Hospital Institutional Review Board (IRB) have bought stock in the company. This relationship has led to an agreement that entitles Arthrid to own the patent rights to all discoveries made in the course of the research it funds, and entitles Westfield University to 5% of Arthrid stock and a 5% royalty on sales of all products that result from the research. There also is a non-disclosure agreement which allows Arthrid to review all data and manuscripts at least 30 days prior to their submission for publication, and to block publication or presentation of any data or information which might threaten its rights to any patentable invention.

Extensive use of the experimental drug in animal models of lupus has been highly successful, producing the desired anti-inflammatory effects. Other similar drugs have been used without any serious toxicity. The drug is now ready for Phase I clinical trials. Arthrid offers to pay for a trial at Westfield University Hospital, it is directed by Dr. Roberts. Arthrid also is willing to issue to Dr. Roberts 2% of its common stock, her husband will receive 2% of Arthrid stock and her 14-year-old son will receive 1%. If the trial is successful, this would go a long way toward covering her son's college tuition.

Dr. Roberts asks her postdoc, Dr. Henry Chung, to join her in testing the new drug, but Dr. Chung has been pursuing a different and potentially significant project, cloning a gene for asthma. If Dr. Chung joins the Arthrid project, the company will issue him shares of Arthrid common stock equal to 2% and also pay him a generous consulting fee, in addition to continuing to receive his postdoctoral stipend. Dr. Chung is already somewhat annoyed that Dr. Roberts is spending so much time at the Arthrid labs that he is not receiving adequate supervision for his asthma project.

Westfield University Medical School allows a faculty member to spend 20% of his or her time on outside commitments, and Dr. Roberts is spending about 12-15 hours a week at the Arthrid labs. Since Dr. Roberts works closer to 60 hours a week (she always works on the weekends and takes work home every night), she does not feel that her time away from the medical school is excessive. Furthermore, this time away from her medical-school lab allows her to work on the therapeutic molecule using laboratory equipment at Arthrid which her own lab lacks.

The IRB will meet soon to review Dr. Roberts’ proposal to study the new drug at Westfield University Hospital. The IRB chair has been informed by the dean of the medical school how
Questions for Discussion

1: The medical school, the department, and Dr. Roberts retain their share in the patent and embark on a joint venture with Arthrid to manufacture the drug. If the drug is useful and gains FDA approval, the profits will be used to fund the laboratory, and would include salary support for Dr. Roberts. In this scenario, what problem, if any, would there be if Dr. Roberts organized and participated in the clinical trial?

2: Dr. Roberts is concerned that any connections between the medical school investigators and Arthrid threatens the perceived objectivity of her research and potential for conflicts of interest. What options do Dr. Roberts and the medical school have in minimizing conflicts of interest and potential harms to the patient subjects in this promising research?

3: What difference would it make to any conflicts of interest if there were an internal review committee (scientists and others from the same laboratory and school) or an external review committee (scientists and others from outside the medical school) which would monitor the clinical trial?

4: The IRB is under pressure to approve the proposal so that the clinical trials can begin. What role, if any, should the IRB play in determining whether Dr. Roberts has a conflict? Are there problems if Dr. Rosen, members of her family, the medical school or IRB members have equity interests in Arthrid? If yes, what is the appropriate course of action?

Case 3. Pharmaceutical companies and drug trials.

Cynthia Walsh, M.D., an associate professor of medicine, is a prominent academic cardiologist. Her personal financial investments include significant stock holdings in three publicly traded biotechnology firms. She is approached by one of these firms to be a lead investigator in a therapeutic trial of a novel agent for preventing tissue damage from myocardial infarction (MI). This will be a randomized double-blinded, placebo-controlled clinical trial (neither patient nor physician will know whether the drug under investigation or a placebo is being used in a given patient). Dr. Walsh is quite familiar with the preliminary animal and cell biology work in the area and believes that there is an excellent chance that this new drug will result in a significant improvement in survival and reduce damage to the heart muscle. She even thinks this novel agent may reduce the risk of heart failure and irregular beats. Dr. Walsh's group is one of the few cardiology groups fully prepared to carry out this investigation, which is why she was contacted. She also has a clinical fellow who is capable of managing the study, cares for a large number of patients with MI and believes that she could enroll 19 patients efficiently. The drug will only be available to her patients if her group participates in the trial. The company is offering $5,000 for each patient enrolled and the money would really help both her salary and the division budget. As a lead investigator, she will become much better known and will likely experience an increase in referrals if the trial succeeds.

Questions for Discussion

1. Is Dr. Walsh's participation in this study appropriate? Justify your position.

2. Does Dr. Walsh have a conflict of interest? If so, what is the nature of the conflict?

3. How could it be mitigated? Would the nature of the conflict of interest be different had she not already owned stock, but instead had been offered stock as a form of compensation for conducting the study?

4. If Dr. Walsh already believes the drug is an improvement based on the literature emanating from animal experiments, can she honestly assign patients randomly to treatment or placebo? What if she believes the drug is deleterious because of its adverse effects on the kidney late in the course of treatment?

5. What should the role of the university be in this case?

6. During study of the first few patients, it becomes apparent to Dr. Walsh that she can tell who is on the active drug because the patients get a facial flush. Might that further influence her ability to remain objective? What considerations apply in answering that question?

Case #15 (from Teaching the Responsible Conduct of Research Through a Case Study Approach, Korenman, S.G., and Shipp, A. Eds, © 1994 Association of American Medical Colleges. All rights reserved. Reproduced with permission.)
Case Study 4  A Conflict of Commitment

Sandra was excited about being accepted as a graduate student in the laboratory of Dr. Frederick, a leading scholar in her field, and she embarked on her assigned research project eagerly. But after a few months she began to have misgivings. Though part of Dr. Frederick’s work was supported by federal grants, the project on which she was working was totally supported by a grant from a single company. She had asked Dr. Frederick about this before coming to his lab, and he had assured her that he did not think that the company’s support would conflict with her education.

But the more Sandra worked on the project, the more it seemed skewed toward questions important to the company. For instance, there were so many experiments she needed to carry out for the company’s research that she was unable to explore some of the interesting basic questions raised by her work or to develop her own ideas in other areas. Although she was learning a lot, she worried that her ability to publish her work would be limited and that she would not have a coherent dissertation. Also, she had heard from some of the other graduate students doing company-sponsored work that they had signed confidentiality statements agreeing not to discuss their work with others, which made it difficult to get advice. Dr. Frederick and the company’s researchers were very excited about her results, but she wondered whether the situation was the best for her.

Questions for Discussion

1. Has Dr. Frederick done anything wrong in giving Sandra this assignment?

2. What potential conflicts in terms of data collection, data interpretation, and publishing might Sandra encounter as she continues with her research?

3. Discuss some conflicts of interest which might arise for a student working on an industry-sponsored research project. Can you think of any possible benefits?

4. Does Dr. Frederick’s dual funding arrangements (government grants plus industrial support) carry any risk for conflicts of interest.

5. Do you think Sandra’s work on industrially sponsored work will be beneficial or harmful to her education? Explain your answer.

Case Study 5: Who Owns Research Data?

Jessica Banks, a Ph.D. student working with Professor Brian Hayward, a sociologist studying urban sprawl, has recently defended her dissertation and is now ready to file it and leave for her new job. During her second year, when starting research with Hayward, Banks divided her time among three projects. Then, in her third year, after consultation with Hayward, she decided to continue and expand upon one of the three lines of investigation for her dissertation research. This was also the project most closely related to Hayward's grant at the time. Later, Banks’s experimental plan and early results were included in Hayward's grant renewal. The other two promising lines of research were left incomplete.

Shortly before leaving for her job, Banks comes to Hayward's office to make copies of research data stored only on Hayward's computer using special software, which she also plans to copy. Although her new faculty position will place a heavy emphasis on teaching, she is looking forward to continuing to do some research as well. In particular, she is eager to pick up where she left off with the two incomplete projects she worked on earlier. Hayward comes in as Banks is downloading her material, and asks her what she is doing. She tells him, and he then says to her that she cannot take the data. "They belong to me," he says. Banks is confused. "But I did the work, and I wanted to follow up on it. I can't do that without the data." Hayward is adamant. "I'm sorry, but you should understand this. Our research project was a joint enterprise, and all the work you did was funded by money I brought in via grants. The data do not belong to you or to me; they actually belong to the university, and the work will be continued with other students. I've already talked to one of the new students about working on those projects this fall." Banks, seeing her plans fall apart around her, protests, but Hayward is implacable.

After a few minutes, she stalks away. Later that afternoon, Banks gets together with her classmate Paul Larson, and she tells him about her run-in with Hayward. "Look," Larson says. "Hayward has no right to deny you access to data. You did the work that generated all the data." "I know!" Banks says. "But Hayward wouldn't listen to that argument when I made it." "Here’s my suggestion," Larson says after some reflection. "Just stop by his office and copy it sometime during the weekend. I happen to know Hayward will be out of town, so he'll never know. That's the fair thing to do." Banks seems uncertain, but she says she'll think about Larson’s suggestion and decide before the weekend.

Case Study 5: Who Owns Research Data?

1: Who owns research data? Do you think this policy is fair?

2: How could this problem of access to the research notebooks and manuals have been avoided?

3: Under what conditions should copying of data been done?

4: Are the policies of data ownership clearly defined in research projects in which you are engaged?
Adapted with modifications from RCR Responsible Conduct of Research, Columbia University, http://ccnmtl.columbia.edu/projects/rcr/rcr_data/case/index.html#2
This case was adapted from “The Jessica Banks Case”
Moral Reasoning in Scientific Research: Cases for Teaching and Assessment
Developed by Muriel J. Bebeau, University of Minnesota
With Kenneth D. Pimple, Karen M.T. Muskavitch, Sandra Borden, and David H. Smith, Indiana University
Indiana University, December 1995, pages 21-29
Developed for project entitled “Teaching Research Ethics: A Workshop at Indiana University” (TRE)
Case Study 6: Share and Share Alike?

Jim is a graduate student in the department of genetics. For his thesis research, he is mapping a gene involved in blood-sugar homeostasis. His work is part of a larger, multi-center study of the genetics of obesity, which involves several thousand patients and collects information such as socioeconomic class, self-identified ethnicity, activity level, weight, and other medical data. Blood and DNA samples are maintained in Jim’s lab along with a database that links unique identifiers but not patient names with the data. The study coordinator at each site has access to the encryption key; however, the students and other researchers working on the project do not. Researchers may use the database to retrieve and enter data pertaining to the samples, but they cannot learn the identity of the individuals in the study.

The subject/patients involved in the study were recruited at various study sites. On first contact with a potential participant, a genetic counselor explains the study and arranges for a meeting to begin the informed-consent process. During this meeting, participants learn about the aims of the project, their role as subjects, and the risks and benefits involved in participation. The consent forms state that blood and DNA samples and the resulting data will be anonymized, that subjects may withdraw at any time, and that samples will be used exclusively for this study. If individual samples are to be used in unrelated research, the participants' must be recontacted and go through a second consent process specific to the new study.

Jim’s project involves a subset of several hundred samples from the obesity study. One day, Renee, one of the other graduate students in the lab, approaches Jim and starts asking questions about the samples he’s working with. She explains that her work on sickle-cell anemia and mutations in a hemoglobin gene in African-Americans requires 50 ethnically matched control samples. Since Jim has access to such a large collection of samples, Renee asks if she can take small aliquots of some of his samples from the obesity study. She tells Jim that she will not be looking at disease in these patients and is not really doing a "study" on them. She just needs them as controls, and she doesn't even need that much DNA. "Which box are they in?" Renee asks, as she heads for the freezer. Renee was standing at the freezer with the door open when Jim said, "I'd be happy to tell you more about our samples, Renee, but you had better talk to Jane, the study coordinator, about getting consent from the obesity-study participants if you really want to use them for your study." He went on, "Another option, which might be faster, is to just order a set of anonymous samples from a commercial DNA bank. It would really be a pain to recontact all of those people just for a set of controls."

Case Study 6: Questions for Discussion

1: Why are data held in such a way that certain individuals working on a research study do not have access to personal information about the material?

2:

3: What does it mean to have data anonymized? Why should we protect data collected from human subjects?
3: Why shouldn’t Renee be able to use the samples, since she is not studying any disease associated with the blood samples?

5: What other options does Renee have besides ordering anonymous samples from a DNA bank?

Adapted from RCR Responsible Conduct of Research, Columbia University
http://ccnmtl.columbia.edu/projects/rcr/rcr_data/case/index.html#1
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