Case Studies for Small Group Discussion

April 2020: Conflicts of Interest
Collaboration
Mentoring
The Scientist and Social Responsibility
(Including DURC/Export Control)

Instructions:
Two or more of these case studies (fictional or real or video) may be discussed in your session.
Please read/view them in advance and come prepared to analyze and discuss with the group.

Keep in mind that reality is often far more complex than fiction.
There may be several RCR-related concerns interwoven throughout the case.
Do you see others not listed below?

“Fictional” Case Studies – Could these happen to you?
“Real” Case Studies in Alphabetical Order:
- Gelsinger - Conflicts of Interest and Use of Human Subjects
- He - Fabrication, Use of Human Subjects, Mentoring, Collaboration, The Scientist and Social Responsibility, DURC
- Hwang - Conflicts of Interest, Use of Human Subjects, Falsification, Collaboration, Mentoring, Responsible Publication, The Scientist and Social Responsibility
- McClellan - Conflicts of Interest
- Olivieri - Conflicts of Interest, Collaboration, Responsible Publication
- Roth - The Scientist and Social Responsibility - Export Control, Research Misconduct
- Stanford v. Roche - Conflicts of Interest, Collaboration, Technology Transfer
- Wakefield - Conflicts of Interest, Use of Human Subjects, Falsification, Responsible Publication
- UMass Lowell - Export Control
Fictional Cases – Could These Happen to You?

Age-old Conflict (Conflict of Interest and Commitment, Intellectual Property Rights)

Dr. Bobby Bill was an undergraduate in the lab of one of the first researchers to successfully demonstrate the existence of a “longevity gene” in *c. elegans*, and since then his passion has been the search for the expression of genes uniquely present in genetic variants of organisms that live significantly longer than the mean. He has turned the attention of his NIH-funded lab to drosophila as a model organism, and his research group at a very good Midwestern school in the US has successfully isolated a handful of genes that are highly expressed in fruit flies that live significantly longer than typical.

Dr. Bill was contacted by a large pharmaceutical company, also interested in longevity, to be a professional consultant. Initially, they were interested in establishing a drosophila colony that would include an aged population, and asked Dr. Bill’s help in the husbandry of the aged fruit flies. They invited Dr. Bill to their corporate research labs about three times a year, each time paying his travel and a $2,000 honorarium. However, the relationship has evolved and now Dr. Bill is serving a role more like a scientific collaborator than a consultant. He has now been asked to serve on their Scientific Advisory Board and as compensation will be getting some shares in the company stock currently worth about $12,000. Furthermore, they have “gifted” $180,000 to his lab to cover a postdoctoral fellow for three years to work on a few collaborative projects. Dr. Bill now spends about 15% of his effort on the collaboration and 60% of his effort on his NIH project. The remainder of his time is spent on teaching and committee service. The trips to the company have increased, and sometimes Dr. Bill has to get other faculty members to cover his lectures because of his travel schedule.

At a recent research meeting at the company, Dr. Bill and the Board could clearly see a potentially patentable product emerging from their joint line of inquiry. This product, which stimulates expression of the longevity genes, has the potential of providing a therapy to slow the onset of aging in humans, which is extremely exciting and could be quite lucrative. However, the Scientific Advisory Board would need to decide whether or not to publish their findings, and how to protect the intellectual property rights emerging from this research. The Board asks which parties need to be represented legally as the push to commercialize the product moves forward: Dr. Bill, his postdoctoral fellow, his institution? Dr. Bill feels that, while his research group contributed to the success of the project, direct experiments related to the product were not performed by any NIH-funded personnel. And, he has spent much effort at night and on weekends on the company’s project. Therefore, he feels that it is fair that his intellectual property (IP) interests be represented, but not necessarily the school’s interests. Dr. Bill feels as though, since he fulfilled his teaching, service, and research efforts at the school during this time period, all additional efforts he may have made were on his own behalf. Further, Dr. Bill feels that since the postdoctoral fellow was getting his training on this project, he has not really earned any additional benefit for his participation in the project.

Additional Questions to Consider:

- Does Dr. Bill have either a perceived or real conflict of interest in participating in this project? At what point in this scenario did that happen?
- Does Dr. Bill have a conflict of commitment? How does this concept differ from the concept of a conflict of interest?
- Under NIH Financial Conflict of Interest (FCOI) guidelines, must he report any or all of his travel reimbursements, stocks or direct payments from the company? Does the company have to report their compensation to Dr. Bill?
- When should IP/patent rights be discussed and determined in a collaborative project? By what mechanism does that occur at academic institutions?
- In your opinion, does the school have any IP/patent rights? Why might this be important to the school?
- Are faculty sometimes allowed to serve as outside consultants? If the school has a policy on faculty consultation activities, might that affect their rights in this situation?
- Is collaboration between academia and industry a good thing? What are the pros and cons?
- Has Dr. Bill done anything “wrong” in this scenario? Has the company?
- What special issues might arise for the postdoctoral fellow whose stipend is paid through a gift from a company, such as in this case?
- Should this research be subjected to peer review through publication, or is the push to help humanity better served by allowing the company to continue along these research lines without the added competition that publication would certainly bring?
- Does the NIH have any IP/patent rights in this scenario? In any scenario?
- Debate Question: Must we avoid all conflicts of interest, or can some be managed?

From: http://www.oridhhs.gov/case-one-age-old-conflicts
A Commercial Opportunity? (Conflict of Interest – Intellectual Property)
Shen was always interested in bioinformatics and decided to use some of his free time to write a program that others in his microbial genetics laboratory would find useful. Starting with a popular spreadsheet program on his university-provided computer, he wrote the program over the summer and posted it on his personal Web page as a bundle that combined the spreadsheet program and his own program. Over the next academic year, he improved his program several times based partly on the feedback he got from the people in his laboratory who were using it. At national meetings, he discovered that researchers in other laboratories had begun to download and use his program package, and friends told him that they knew of researchers who were using it in industry. When the issue arose in a faculty meeting, Shen's faculty adviser told him that he should talk with the university's technology transfer office about commercializing it. "After all," his adviser said, "if you don't, a company will probably copy it and sell it and benefit from your hard work." The director of the technology transfer office was much more concerned about another issue: the fact that Shen had been redistributing the spreadsheet in violation of its license. "You do have rights to what you created, but the company that sells this spreadsheet also has rights," he said. "We need to talk about this before we talk about commercialization."

Additional Questions to Consider:
- What obligations does Shen have to the developer of the original spreadsheet program? To the university that provided the spreadsheet and computer?
- What are the pros and cons of trying to commercialize a program that is based on another's product?
- What conflicts and practical difficulties might Shen encounter if he tries to operate a business while working on his dissertation?

A Conflict of Commitment (Conflict of Interest – Mentoring)
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.

Additional Questions to Consider:
- Has Dr. Frederick done anything wrong in giving Sandra this assignment?
- What potential conflicts in terms of data collection, data interpretation, and publishing might Sandra encounter as she continues with her research?

Mentoring
Milton France, a senior level graduate student, is seen less and less during the day by his mentor and other members of the laboratory. It becomes apparent to the mentor, Dr. Wise, that Milton is working very long hours evenings and nights at times when most of the other laboratory workers are not there. This persists for several weeks and Dr. Wise does not think the pattern is a good one. Dr. Wise approaches Milton and requests that he spend more time during "standard working hours" in the lab. Dr. Wise argues that interaction with him and with other members of the laboratory is important and that it is best for all to talk about science regularly. Milton argues that he can work much more efficiently when fewer people are around. He cites the fact that a piece of equipment he was using in his research was continually busy throughout the daytime hours and this was not conducive to him performing needed experiments in a timely fashion. Milton discloses that this was the "straw that broke the camel's back", forcing him into working unconventional hours. Both the faculty advisor and the student hold tight to their arguments and over the next several days the situation between them grows tense.
Additional questions to consider:

- What are the problems or issues in this case? Who or what is affected?
- What might have been done differently to prevent the situation from escalating?
- What avenues might be pursued to bring about resolution of this conflict?
- Whose responsibility is it to initiate a dispute resolution process?

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Collaboration

Drs. Sterling and Crystal at Research University have been collaborators for a number of years. Each is funded as a principal investigator, with the other as co-investigator, from federal agencies. Drs. Sterling and Crystal develop strong differences, largely of a personal nature. Dr. Sterling, who is more senior, believes that she owns the data and experimental materials derived from the collaboration. Dr. Sterling takes steps to deprive Dr. Crystal of access to the materials. Dr. Crystal appeals to Dr. Bluff, the research administrator of Research University, to intervene. Dr. Bluff calls Dr. Sterling and Dr. Crystal together and asks them to work it out. Dr. Sterling and Dr. Crystal cannot reach agreement, and Dr. Crystal decides to leave Research University. Dr. Sterling charges Dr. Crystal with intent to remove research materials from Research University without authorization. These accusations are brought to the attention of the federal funding agencies.

Additional Questions to Consider:

- What are the problems or issues in this case? Who or what is affected?
- You are asked to conduct an inquiry. How do you proceed?
- What regulations exist at your institution regarding removal of data and research materials?
- Have any institutional regulations been compromised? Federal regulations?
- Who owns the data?
- What could have been done to prevent this situation from escalating?

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The Scientist and Social Responsibility - Dual Use Research, Safe Laboratory Practices, Animal Welfare, Responsible Publication

Cell-matrix Interaction and Tumor Growth & Metastasis

Dr. Gray is an NIH postdoc interested in cell-matrix interaction and its role in tumor growth and metastasis. She finds that membrane protein X is over-expressed in tumor cells and thinks that it may regulate cell adhesion and invasion. She hypothesizes that the N-terminal domain would make a good dominant-negative inhibitor and discovers that expressing this domain inhibits adhesion and kills tumor cells. To produce pure protein to use as a drug to treat cancer, Dr. Gray and her colleague Dr. White develop a bacterial expression-secretion system and are able to isolate the recombinant N-terminal domain from bacterial culture medium. They are excited to find that it kills tumor cells at remarkably low concentrations (0.1 μg/ml), and they name the recombinant fragment "N-statin." They show that it does not kill normal cells until they use 20-fold higher doses. They do a tumor survival study using three doses of N-statin or control buffer administered to mice by intraperitoneal injection. The lowest concentration has minimal effect, the medium dose effectively prolongs survival though the mice look lethargic for a week, and the highest dose kills the treated mice.

After repeating these experiments, the lab rushes to try to publish their exciting results in a prominent journal. They decide to publish the identification of protein X, the purification and characterization of N-statin, and only the medium-dose survival curve. In the manuscript, they emphasize that exceptionally low doses are needed, and they decide to leave out the toxicity findings to keep the story simple because they feel that any drug – even aspirin – has side effects at very high doses. They submit the paper immediately after two days of intense writing.

Is this approach acceptable?

While Dr. Gray tries to identify how N-statin works before her fellowship ends in one month, Dr. White wonders if the new drug candidate will work if taken orally. Worried about possible toxicity, he obtains some leftover mice from a neighboring lab and puts N-statin into their drinking water. They all die immediately. Believing that you should "make lemonade if life gives you lemons," he realizes that it might make a good and very cheap rat/mouse poison, because the bacterial expression-secretion system provides an easy source of the material. He is delighted to find that putting just a single drop of the bacterial culture medium on mouse food kills all of another cage of leftover mice. For his own safety with this potent agent, he begins wearing gloves and sometimes even a
lab coat – he is complimented by a secretary on his fashionable purple vinyl gloves when he returns some paperwork to the office. He also takes home a flask of bacterial medium after spinning out the cells to be tested by his brother, who runs a pest exterminator business. **What problems do you see with what he has done?**

Dr. Gray has to return to her home country, and Dr. Green – the head of the lab – agrees that Dr. Gray can take the plasmids and bacteria with her to continue the work. As she is leaving the U.S. at Dulles airport, vials of these materials are found in her carry-on bag and she is detained by TSA. They ask her about if the contents are nonhazardous and whether they are valuable research materials stolen from the lab she has left. **What could have been done to avoid this problem?**

Dr. Gray and Dr. Green manage to talk their way out of the problem with TSA. Dr. Gray returns home, establishes multiple collaborations, and mails her plasmid to several colleagues to help her determine N-statin’s mechanism of action, with warnings to handle it carefully. **Is there anything wrong with this?**

Meanwhile, one reviewer of the submitted paper had been so excited about this powerful new potential drug that he gave a copy of the paper to a grad student in his lab. The student quickly generates an N-statin plasmid by PCR and produces N-statin using the same bacterial expression-secretion system. While purifying the molecule without using gloves, she grabs a quick sandwich at her desk. She is found unconscious and is hospitalized in critical condition – her doctors are baffled. **What went wrong here?**

Another reviewer is also impressed by the potency of the biological drug candidate, but wonders in passing whether toxicity might be a concern. The journal returns the paper to the authors for minor revisions. Dr. Green resubmits the paper after adding their toxicity data. After seeing the new results, the Editor begins to worry about the safety of this agent and tells that authors that the journal will probably have to have the paper reviewed further concerning “Dual Use” technology because of the "Patriot Act." Drs. Green, Gray, and White are quite baffled by this action. **What is the editor’s concern?**

Dr. White tries to continue working with N-statin, but he drops a shaker flask containing N-statin and cuts his foot because he is wearing sandals. He falls unconscious and is hospitalized. Dr. Green cleans up all the mess and puts the materials into MPW waste for disposal. **What should have been done?**

Dr. Green goes to bed worried about Dr. White and dreams that he dies, and dreams further that some terrorist thanks him for providing a new tool to kill Americans. The next day, he reads more about the Patriot Act and Dual Use research and realizes that he and his colleagues might even be prosecuted and potentially sent to prison.

Dr. Gray begins worrying that her paper might not be accepted, that her N-statin might somehow be connected with Dr. White’s coma, and that she should have been more careful about distributing her materials. And all just because she wanted to cure cancer!

After information about what has happened starts to leak out, several people besides friends and family members become alarmed or angry at the research team, including the Scientific and Institute Director, safety officers, Chair of the animal care and use committee, the Institute’s technology transfer office, the FBI, and Department of Homeland Security. **Why did each react so negatively, and what should have been done instead?**

**Additional Questions to Consider:**

- Could you have avoided these problems if N-statin was your discovery?
- What should you do in this case?
- Should you alert the researchers? The Institutional Biosafety Committee (IBC)? Someone else?
- Do you know who to go to at MSK or at RU for help?
- Should the method and the findings be shared with others working in this area? And if so, should they be notified of the potential dual use of this research?

Case Study: Gelsinger – Use of Human Subjects, Conflicts of Interest


Gene therapy was the embryonic stem cell research of the 1990s. Its promise to cure was both therapeutic and financial: billions of dollars stood to be made from curing diseases as rare as OTCD and as common as cancer, leading several companies to invest millions in the technology. Jesse Gelsinger, an 18-year-old boy, suffered from ornithine transcarbamylase deficiency (OTCD), a rare metabolic disorder that prevents the body from breaking down ammonia. Many children with OTCD die at a young age, but Gelsinger had a mild version and led a fairly normal life through medicine and a special non-protein diet.

In 1999, Gelsinger enrolled in an OTCD clinical trial at the University of Pennsylvania at the age of 18. He knew that participants were not expected to benefit directly from the trial, but wanted to help others with this disorder.

The researchers sold the clinical trial to Gelsinger and his family as a relatively safe experimental treatment that would attempt to replace defective genes with normal ones. An adenovirus vector (carrying the normal OTCD gene) would be injected into patients' livers.

However, shortly after the researchers injected Gelsinger with the replacement genes, his ammonia levels skyrocketed. Within a few days, he suffered brain damage and organ failure and was comatose. His family then removed him from life support.

The Gelsinger family initially took Jesse's death as an unfortunate and unforeseeable event, held no grudge against the Penn researchers and continued to support their efforts. But a series of revelations in the following weeks quickly eroded this goodwill - and threw the gene therapy field into a whirlwind. At the center of this turmoil was the information gap between researchers and patients and lack of true informed consent.

The researchers did not disclose concerning safety data from animal studies - Two rhesus monkeys had died of liver failure when given higher doses of the vector. In addition, human volunteers in other similar gene transfer trials had suffered adverse reactions that were not reported to the NIH and FDA - side effects serious enough to have halted the trials had they been properly reported. In addition, the study protocol and consent form had been changed without notifying the FDA.

Lastly, one of the lead researchers, James Wilson, MD, PhD, did not disclose the magnitude of his direct financial interest in the trial's successful outcome. His company had attracted significant investments. If Wilson could devise a way to deliver good versions of the OTC gene to Gelsinger and others like him, his company could then patent the gene delivery system and use it to try to cure other, more common genetically linked disorders, such as cancer. Wilson stood to make millions.

Jesse may have thought twice about participating in the clinical trial if any these issues had been disclosed. These failures to disclose important information - along with other violations of clinical ethics and standard research protocols - led the Food and Drug Administration to sanction and repudiate the Penn researchers. Gelsinger's family sued Wilson and others at Penn involved in the study, leading to an out-of-court settlement.

Jesse Gelsinger did not die in vain. He remains a powerful symbol of why researchers must do right by the very subjects they depend upon and, moreover, why greater federal oversight of human research subjects is needed. But the 10-year anniversary of Jesse's death is a sober reminder that much work remains if we are to prevent similar tragedies in the future.

Additional Questions to Consider:
- How might knowing about the investigator's and the institution's potential financial interests in this project prior to Jesse's participation have potentially affected the outcome? Would this have become as “infamous” a case had they consented with prior full disclosure of all commercial/financial interests?
- As asked by the author: What constitutes informed consent? And what's relevant to a patient's decision to participate in a clinical trial? Whose obligation is it to see that what is reported to the regulators is what is reported to the patient and his/her family?
- Do you agree with the author's comment: “oversight has flattened, profit motives have become more entrenched in medical research and the pool of potential human subjects has come to focus on the vulnerable, both at home and abroad.”? Why, or why not?
- If there are certain standards of care and consent for US human subject protections, do we have the right to impose or disregard these standards when working in other countries that do not mandate the same level of protection? Are the
research results any less valid when “tainted” by suspect or misunderstood compliance controls? Do the end results justify the means in obtaining them?

- Because of this tragedy, “gene therapy” research was severely criticized and curtailed. Do you think this tragedy was a result of the experimental, new age science that was being tested, or a result of the failure of the “system” that did not develop or adhere to proper controls, policies and procedures to safeguard human subjects? As this author suggests – is “greater federal oversight needed”? Whose responsibility is the protection of human research subjects?


Excerpt from Jesse's Intent [emphasis added]:

My own son has shown me the way to lead my own life and for that I am so very grateful. I have watched our system struggle to come to grips with what is wrong with the protection of human beings in medical research. What is wrong is that a growing, ambitious minority of researchers and institutions have compromised their ethics for profits and prestige, mostly as a result of industry’s inappropriate financial influence over them and our government. I still support our need for clinical trials, but with this caution: **Informed consent is only possible if all facets of the research endeavor are ethical and in the open. Because of the secretive and conflicting influences on clinical research, the average research subject has little hope of understanding and giving truly informed consent.** All research subjects **really want is to be able to trust the system.** If we can somehow get that system to apply Jesse’s Intent... not for recognition and not for money, but only to help... then research will get **all it wants and more; they’ll get research right and have a real prosperity, one they never imagined possible. Until that happens I am so very grateful that we had a legal recourse that enabled us to draw attention to the problems currently inherent in clinical research.**
Case Study: He – Fabrication, Use of Human Subjects, Mentoring, Collaboration, The Scientist and Social Responsibility, DURC


Jiankui He, a Chinese researcher, used CRISPR-Cas9 on human embryos to disable the CCR5 gene. He altered the genes of twin girls to help them resist possible future infection with HIV, the Aids virus. He claims that the two embryos were subsequently implanted, and infant twin girls have been born. A third baby is expected to be born later this year.

He made his work public at the second International Summit on Human Genome Editing in Hong Kong in November 2018. He was expecting to be lauded for his historic scientific effort and medical breakthrough, but instead, he was greeted with world-wide scorn for flouting all accepted research integrity regulations and practices.

According to the NIH, his work represents a deeply disturbing willingness to flout international ethical norms. The project was largely carried out in secret, the medical necessity for inactivation of CCR5 in these infants was utterly unconvincing, the informed consent process appears highly questionable, no supporting data was shared/published, and the possibility of damaging off-target effects has not been satisfactorily explored.

Long before the claim of the world’s first gene-edited babies became public, He shared the news with a US Nobel laureate who objected to the experiment yet remained an adviser to He’s biotech company. The revelation that another prominent scientist knew of the work, which was widely condemned when it was revealed, comes as scientists debate whether and how to alert the public about troubling research, and the need for clearer guidelines.

Emails obtained under a public records request show that Craig Mello of the University of Massachusetts, who won the Nobel Prize for medicine in 2006 for his genetics research, learned about the pregnancy in April from He in a message titled “Success!”

“I’m glad for you, but I’d rather not be kept in the loop on this,” Mello replied. “You are risking the health of the child you are editing ... I just don’t see why you are doing this. I wish your patient the best of luck for a healthy pregnancy.”

Mello stayed on as a scientific adviser for He’s Direct Genomics company for eight more months, until December, just after news of the births became public and drew international scorn. The Chinese scientist’s gene-editing work was not a company experiment.

Several Stanford professors including He’s former adviser, Stephen Quake; bioethicist Dr. William Hurlbut, and genetics expert Dr. Matthew Porteus have said they were in contact with He over the last year. His disclosure to Mello in April is notable because it specified the pregnancy had been achieved and came on the day He himself said he learned of it.

The senior researcher with the most intimate knowledge of the work seems to be Michael Deem, a biophysicist at Rice University in Houston, Texas. Deem was once He’s adviser and is a member of the scientific advisory board of a Shenzhen-based genome-sequencing company that He founded. Deem was reportedly also a senior author on a paper — which remains unpublished — describing He’s experiments and is said to have been present during the recruitment of participants. What role he had is not clear. Deem’s lawyers acknowledge that Deem sometimes comments on He’s papers. But they insist that Deem does not do human research and did not do so for this project. They say that he did not attend recruitment or informed-consent meetings, did not authorize the use of his name as an author on any human-gene-editing paper and was not a senior author on the paper. Rice University is investigating Deem’s involvement.

Editing embryos intended for a pregnancy is not allowed in the US and many other places because of the risk of harming other genes and concerns that these DNA changes can be passed to future generations.

But there is no certain way to stop a rogue scientist from experimenting, no matter what rules are in place, because the gene-editing technology is cheap and easy to use. It was not clear how someone would have raised concerns about He’s project, said
University of Wisconsin bioethicist Alta Charo, who was one of the leaders of the Hong Kong gene-editing conference where He gave details of the experiment. He’s work has not been published in a scientific journal.

University of Minnesota bioethicist Leigh Turner said the lack of action by scientists who learned of He’s intentions indicated a broader culture of silence. “There seems to have been multiple lost opportunities,” Turner said.

China’s state media reported that He could face consequences after investigators determined he acted alone and fabricated an ethics review by others.

**Additional Questions to Consider**

- What do you believe is the most significant ethical breach in this case and why?
- Why do you think He did not share or publish his data?
- Do you agree that “there is no way to stop a rogue scientist” from experimenting? Is world-wide criticism enough to change behavior?
- What role (if any) did He’s mentors and collaborators play in allowing He to believe what he was doing was acceptable?
In 2009, cloning pioneer Woo Suk Hwang was sentenced to two years in prison at the Seoul Central District Court, after being found guilty of embezzlement and bioethical violations, but cleared of fraud.

Hwang was once celebrated for creating human stem-cell lines using cloned embryos derived from patients suffering from spinal-cord injury and other disorders. The accomplishment, which promised an endless supply of stem cells genetically matched to patients, turned out to be bogus.

Hwang admitted in January 2006 to falsifying data, while maintaining that he had the ability to do what he had claimed. In South Korea, scientific fraud would be illegal only if Hwang had used fraudulent data to gain grants. Prosecutors argued that he duped two companies into supplying research funds. But the court rejected the allegations on the grounds that the firms provided money without expecting to benefit. The court did, however, find Hwang guilty of buying human eggs in violation of the country’s bioethics law and of embezzling 830 million won (US $700,000) of government money.

The events began to unfold in October 2005, with news of ethical misconduct and legal violations in obtaining eggs from South Korean women. Over subsequent weeks, Hwang first lied and then confessed about ethical breaches in collecting eggs for his research; an international stem cell consortium that he had announced collapsed; a member of his research team was investigated for illegally buying women's eggs; and Hwang reportedly asked Science to retract his article. In early November, Gerald Schatten, a University of Pittsburgh-based research collaborator, withdrew from the consortium, saying he believed Hwang had engaged in ethical misconduct obtaining eggs. The Pacific Fertility Center, which had been planning on providing eggs for the San Francisco satellite, pulled out of the deal two days later. Shortly thereafter, Hwang resigned as head of the foundation. He admitted that two of his junior researchers had provided eggs for the research, and that he had denied it a year earlier in order, he said, to protect their privacy. In addition, a prominent member of Hwang’s research team conceded that he had paid 16 women $1,443 each out of his own pocket for their eggs. The consent form the women signed said they had received “no financial payment.” Only a few days earlier, he had admitted to using illegally traded eggs in his fertility clinic, despite a newly-enacted Korean bioethics law prohibiting the commercial sale of eggs and sperm. Three of the women interviewed said that they agreed to provide eggs because they were in dire financial straits; two of them said they had not been fully informed about the potential risks.

A co-author of the Science paper admitted that Hwang pressured the researchers to falsify the data, and that at least nine of the eleven stem cell lines were fakes. Eventually Schatten wrote a letter to Science, requesting that his name be removed as principal investigator of the article because it had come to his attention that some of the results may be fraudulent.

Additional Questions to Consider (some adapted from questions posed by The Center for Genetics and Society):

- Who in Hwang's lab and among the co-authors of the Science article knew about the faked data and the ethical breaches in obtaining eggs, and when? As part of the responsibility of being a co-author – is it reasonable that Dr. Schatten did not know about the “fraud” prior to publication? By definition, isn’t an author “responsible” for all he data presented? Did he have the right to request his name be removed, after the fact?
- What role did the mentoring relationship between Hwang and his subordinates play in the events that transpired? Could this relationship have been what prevented those who knew from coming forward sooner?
- Do you believe that exaggerations and over-promising about stem cell and cloning research at the time of this incident, and competition based on the prospect of celebrity and commercial returns from it, played into this situation? If so, how?
- Does a scandal such as this demonstrate the need for strong and enforceable regulations to protect both the health of women who provide eggs for research and the integrity of the scientific endeavor itself? Or should institutions be given the latitude to determine policy? Do you know where to find information on MSKCC policy on human embryonic stem cell research?
- Do you think the outcome would have been different if this case was tried in the US court system? If so, how?
Case Study: McClellan - Conflict of Interest

The Food and Drug (FDA) Administration reversed a decision to award a no-bid $4.2 million grant to a policy center at Duke University headed by former FDA commissioner and current paid board member for Johnson & Johnson - Mark McClellan.

The funding opportunity was posted in late April (2018) as a five-year grant for which only a single institution, the Duke- Robert J. Margolis Center for Health Policy, was eligible to apply. The grant's purpose was to "to help advance regulatory science to promote the increased availability of safe and effective drugs to the public." FDA said that it is in the process of opening the grant application to other institutions.

Several health policy experts had expressed favoritism concerns about the initial no-bid proposal, raising questions about what made the Duke center uniquely qualified to do the work, which involves convening discussions with drug companies, health-care providers, and patient groups to discuss key issues in the drug approval process.

They also raised concerns about McClellan's role as a paid board member for Johnson & Johnson, one of the largest drug makers in the world, given the pharmaceutical industry's deep interest in drug approvals. "It is not like there's one laboratory on the planet that knows how to clone these particular genes — there's a substantial number of groups out there that work on these issues. It frankly makes no sense that the only place you could go for this is the Duke center run by a drug company advocate," said Jerry Avorn, a professor of medicine at Harvard Medical School, which has a center that conducts similar work. "The very fact that they could have thought this was a good idea, even to the point of publishing the request for proposals, is important because of what it reflects about the decision-making process within FDA and the administration.” Ellen de Graffenreid, a spokeswoman for the Duke-Margolis Center, directed inquiries about the grant to the FDA and stressed that Gregory Daniel, the deputy director of the center, is the Principal Investigator on its current agreements with the agency — not McClellan.

The FDA, after initially defending the no-bid proposal, said in a statement that the agency had “become aware of other organizations who believe that they can submit a competitive proposal to conduct the needed research and related activities. As a result, FDA has decided to change the announcement from a sole source award to an open competitive grant.”

FDA made a sole-source award of a similar grant in 2013 to the Brookings Institution's Engelberg Center for Health Care Reform, which McClellan led from 2007 to 2013. McClellan took a paid position on the Johnson & Johnson board in fall of 2013. He received $285,000 last year for his work, according to company filings. De Graffenreid said that McClellan was no longer affiliated with the Engelberg Center when he joined the corporate board, saying in an email he had stepped down in 2012 to spearhead a major initiative. Documents posted by Brookings Institution described the initiative as “within the Engelberg Center." De Graffenreid later said that he continued to be affiliated with the Center through 2015. The Principal Investigator of that grant was also Daniel, McClellan's current deputy at the Duke-Margolis Center.

Additional Questions to Consider:
- Should “sole-source” contracts be publicly advertised? Why or why not?
- Should McClellan have disclosed his financial relationships in publications – even if it wasn't University policy to do so?
- Does the fact the deputy director was named as PI make a difference?
- Do you think the conflicts cited by others were real or perceived? Why?
- What type of conflict management plan could have been put into place to manage or mitigate these possible conflicts?
In November 2002, Dr. Nancy Olivieri's six-year nightmare finally came to an end. During those years, she lost her job four times, was sued for $10 million, and her scientific reputation was dragged through the mud. What had she done wrong? She had told the truth.

Olivieri is a professor of Medicine at the University of Toronto and a physician at the Hospital for Sick Children, where she is an award-winning specialist in the treatment of hereditary blood disorders, especially thalassemia, a hemoglobin disorder. Patients who receive treatment for thalassemia must endure regular blood transfusions and run the risk of chronic toxicity from too much iron in the blood, called "iron loading." This can affect major organs such as the heart and liver. An effective drug that prevents iron loading would therefore offer substantial benefits to the thousands who suffer from the disease.

In the early 1990s, Olivieri wanted to continue studying a promising drug called deferiprone, which appeared to reduce iron loading in transfusion-dependent patients. To fund the research, Olivieri and her co-workers obtained corporate sponsorship from Apotex, Canada's largest domestically-owned pharmaceutical company. This in turn brought matching funding from the Canadian Medical Research Council. At the time, Apotex also happened to be in the middle of complex negotiations with the Olivieri's university about a $30 million financial donation, the largest in the university's history.

Olivieri signed two contracts continuing an already existing trial and starting a completely new one. However, Apotex had the right to withdraw funding at any time, and the contract for continuation of the existing trial also gave Apotex the right to control communication of the drug trial data for a year after the trial finished. By 1995 Olivieri and her co-collaborator, Dr. Gideon Koren had identified an unexpected risk: in six of 21 patients studied, tissue iron burdens were higher than expected. Crucially this meant that the drug lost effectiveness over time. By early 1996, the number of patients with high iron burdens had doubled to 12.

This was not the outcome Olivieri had wanted. To the contrary, she had spent years hoping the drug would work. Nevertheless, she felt an obligation to inform patients in the clinical trials that there was a problem. In accordance with the Hospital's Ethics Board, she told Apotex of this decision. Apotex disagreed. The company did "agree that some patients [were] responding inadequately," but stated that the trials should continue and wanted "no further action."

When Olivieri went ahead and informed her patients in May 1996, the company reacted swiftly and severely. An investigation by the Canadian Association of University Teachers (CAUT) found that, in response, Apotex, showed "disregard for the interests and concerns of patients when without notice, it terminated both trials and stopped supplying the drug." Apotex also warned that it would "vigorously pursue all legal remedies," if Olivieri spoke to her patients or published anything.

According to the CAUT: "Apostex acted against the public interest in issuing legal warnings to Dr. Olivieri to deter her from communicating about risks" of the drug trials. The company would subsequently deny ever having written any threat.

Showing just how intertwined corporate and public research had become, the person who terminated the trials was Apotex Vice President Dr. Michael Spino, who had been a full-time member of the University of Toronto Faculty of Pharmacy from 1975-1992, at which time he left to join Apotex. However, Spino still held a "status" professorship at the University.

By February 1997, Olivieri was worried that she had discovered a further unexpected, but potentially far more serious problem with the drug. She became concerned that it might cause liver fibrosis, findings that were backed up by other scientists working in England. Working with colleagues she drafted a report for regulators warning of this "severe adverse reaction."

Meanwhile, the drug company began efforts to convince the regulatory authorities, patients, the hospital and the wider scientific community that the drug was safe, while privately proposing to change the testing procedure to remove vital tests. They wrote to Olivieri warning that her results were "not scientifically valid" and threatened their "business."

Throughout this three-year ordeal, Olivieri received no support from the Hospital for Sick Children or the University of Toronto. At the beginning of 1999, she was dismissed from her post as director of its hemoglobinopathy program. She and some of her close colleagues were later gagged by the Hospital for Sick Children. After mediation, she was reinstated and allowed to continue research in late January 1999. The hospital also belatedly promised to support her financially if Apotex sued her.
By 2000, the increasingly bitter feud had reached the courts. Olivieri sued Apotex for libel after the company accused her of making "false" statements. Apotex filed a counterclaim against Olivieri, asking for $10 million damages.

In January 2002, the CAUT published a supplement to its investigation, concluding that Dr. Olivieri had been exonerated by their inquiry and three others, including an inquiry conducted by the Dean of the Faculty of Medicine of the University of Toronto. "Unless the lessons are learned," wrote the CAUT, "everyone will lose. It is important to recognize that the circumstances that gave rise to this case are not isolated--they illustrate a system-wide problem."

In November 2002, a settlement was reached that "resolved all outstanding litigation and arbitrations pending between all the parties." But Olivieri's case may only be the tip of the iceberg.

The British Medical Journal (BMJ) has warned about the "proliferation of stories of companies suppressing publication." A month before the Olivieri settlement, a paper in the New England Journal of Medicine concluded that universities "routinely" engage in lucrative industry-sponsored research that restricts academic freedom.

Dr. Kevin Schulman from Duke University Medical Center found that "academic institutions rarely ensure that their investigators have full participation in design of trials, unimpeded access to trial data, and the right to publish their findings." Schulman's team surveyed more than 100 medical centers in the US and found that only one percent involved in multi-center studies had independent access to all trial data.

In March 2001, the BMJ revelations that the Wyeth pharmaceutical company had "shelved" a study of its contraceptive pills that indicated "clear increases in the risk of developing deep venous thrombosis." Although Wyeth provided the data to regulatory authorities, it did not submit it for publication as "the study did not offer any new scientific information."

Six months later the BMJ editorialized about problems that have arisen due to the "entanglement" of academia with industry, noting that "control lies in the commercial rather than in the academic or public sector." Methods used by industry included designing "studies likely to favor their products" and analyzing data "providing the spin--that favors them."

This entanglement worried Olivieri deeply. "Commercialization of university research," she says "benefits companies at the expense of the public good."

Additional Questions to Consider:
- What role, if any, did institutional conflicts of interest play in this case?
- How "routinely" do you think universities and other institutions "engage in lucrative industry-sponsored research that restricts academic freedom?"
- Do you agree with Olivieri’s statement: "Commercialization of university research benefits companies at the expense of the public good"? Why, or why not?
- Do you agree with the BMJ comment: “control lies in the commercial rather than in the academic or public sector”? Why, or why not? If so, is this a good situation?
- Do you know who to contact at your Institution before entering into, or signing an industry-sponsored contract or other commercial venture?
Case Study: Roth - The Scientist and Social Responsibility, Research Misconduct – Export Controls

Retired University of Tennessee Professor Convicted of Arms Export Violations
On January 18, 2012, John Reece Roth, a former professor of electrical engineering at the University of Tennessee (UT) in Knoxville, began serving a four-year prison sentence for his September 2008 convictions. Roth had been on bond pending his appeals, all of which were unsuccessful. He self-surrendered to the federal correctional facility in Ashland, Kentucky.

Roth was convicted after a jury trial in U.S. District Court in Knoxville, of conspiracy, wire fraud, and 15 counts of exporting “defense articles and services” without a license. As a UT professor, Roth obtained an U.S. Air Force (USAF) contract to develop plasma actuators to control the flight of small, subsonic, unmanned, military drone aircraft. During the course of that contract, he allowed two foreign national students (from China and Iran) to access export controlled data and equipment, and export some of the data from the contract on a trip to China. The Arms Export Control Act prohibits the export of defense-related materials, including the technical data, to a foreign national or a foreign nation. This case was a first-of-its-kind prosecution of a university professor for the transfer of controlled defense technology to foreign national graduate students. Roth was also accused of taking reports and related studies in his laptop to China during a lecture tour in 2006 and having one report e-mailed to him there through a Chinese professor's Internet connection.

The case marked the first time the government used the export control act to crack down on the distribution of restricted data, not hardware, to foreigners in a university setting. Roth, 71, testified at trial that he didn't believe he broke the law because the research had yet to produce anything tangible. He said he received only about $6,000 from the contract.

The Federal Bureau of Investigation led the investigation and was joined in its efforts by Immigration and Customs Enforcement, USAF Office of Special Investigations, and Department of Commerce Office of Export Enforcement. U.S. Attorney Bill Killian said, “This sentence communicates the importance of export compliance to academia and industry, especially in the research and development communities. It underscores the criminal consequences of noncompliance and what happens to those who knowingly and willfully violate export control laws.”

Additional Questions to Consider:
- What responsibility does the scientific community have regarding national security? Is this an ethical dilemma or strictly a legal question?
- Should it have made a difference whether the research in question had produced any tangible results?
- How concerned should you be about possible violations of export control regulations?
- What are the implications for data sharing and material transfer agreements considering these regulations?
- How can you ensure that equipment and biologics that are purchased are clear of federal export control restrictions?
- What are the risks of traveling abroad with laptops and other electronic devices that may contain your research data?
- What are the risks of shipping data and/or research materials to another country? How can you ensure that you are following prevailing rules and regulations?
Case Study: Stanford v. Roche - Conflicts of Interest, Collaboration, Technology Transfer

The US Supreme Court, in a decision concerning the patent rights of research universities, ruled in favor of Roche in a patent-dispute case between the pharmaceutical company and Stanford University. In a 7–2 vote, the Court upheld a lower court’s decision that Stanford did not have a claim to patents for technology to detect HIV blood levels using polymerase chain reaction (PCR) technology - a Nobel Prize winning technique.

The issues surrounding the patent-dispute case date back to 1988, when a California-based research company, Cetus, began to collaborate with scientists at Stanford University’s Department of Infectious Diseases to test the efficacy of new AIDS drugs. Mark Holodniy, a research fellow at Stanford at the time, was assigned to Cetus to conduct research and developed a PCR-based procedure for measuring the amount of HIV in a patient’s blood. Upon returning to Stanford, he and other Stanford employees tested the procedure, and Stanford secured three patents relating to the measurement process. Roche later acquired Cetus’s PCR-related assets, and after conducting clinical trials on the HIV quantification method developed at Cetus, commercialized the procedure. At Stanford, Holodniy had signed an agreement assigning his interests to the university for inventions that resulted from his employment there and also signed an agreement with Cetus, as part of gaining access for his research at Cetus that assigned his interests to Cetus. At Stanford Holodniy undertook to develop an improved method for quantifying HIV levels in patient blood samples, using PCR. Because Holodniy was largely unfamiliar with PCR, his supervisor arranged for him to conduct research at Cetus. As a condition of gaining access to Cetus, Holodniy signed a Visitor’s Confidentiality Agreement (VCA). That agreement stated that Holodniy would assign and did presently assign to Cetus any right, title and interest in each of the inventions and improvements made as a consequence of his access to Cetus. Thus, Holodniy entered into two separate assignments, giving rights to both Stanford and Roche (via Cetus). It was this duality of assignment that directly lead to the dispute requiring resolution of this novel legal question, first by the Federal Circuit and then ultimately by the Supreme Court.

The crux of the case centered on whether Holodniy had the right to assign his interest to Cetus or whether the rights belonged to Stanford under the University and Small Business Patent Procedures Act of 1980 (i.e., Bayh-Dole Act), which established a framework for determining ownership interest in federally funded research. Stanford first sued Roche in 2005, and in 2009, a federal appeals court ruled that Stanford did not have grounds for patent infringement. The US Supreme Court ruling later affirmed the lower court’s decision. The court stated: “The Bayh-Dole Act does not automatically vest title to federally funded inventions in federal contractors or authorize contractors to unilaterally take title to such inventions.”

In commenting on the ruling, Stanford University issued a statement, saying that it “respectfully disagrees” with the court’s ruling. “We are disappointed with the ruling by the Supreme Court in this case, but will move forward to protect the interests of all parties in inventions created with federal funding, including the interests of the federal government and companies that license technology from Stanford,” said Stanford General Counsel. Stanford also raised concerns over the potential implications of the ruling on federally funded research. “For example, the federal government could lose its many rights in the inventions, could lose the assurance that the royalties that would have gone to the university are used to further scientific research and education, and could lose the requirement that exclusive licensees will manufacture any products substantially in the United States.”

Additional Questions to Consider:

- What conflicts exist for each of the affected parties?
- What if anything, could each have done differently to avoid this dispute?
- Do you agree or disagree with the court’s ruling and why?
- Do you agree or disagree about Stanford’s concerns over future rulings when federally funded research is involved? Why or why not?
Case Study: Wakefield - Conflicts of Interest, Use of Human Subjects, Falsification, and Responsible Publication

Source: Scientific Misconduct and the Autism-MMR Vaccine Link Posted on: February 7, 2009 9:12 PM, by Mike Dunford

The *Sunday Times* reported extensively that Andrew Wakefield falsified much of the data that was used in the 1998 *Lancet* article that first identified the MMR vaccine as a potential cause of autism.

In the original journal article, Wakefield and his co-authors reported on a series of 12 children who presented to the hospital exhibiting symptoms of what the authors referred to a "syndrome" of combined gastrointestinal disorders and developmental setbacks. According to Wakefield, these symptoms presented in these patients developed shortly after the children received the MMR vaccine.

Specifically, the paper reports that evidence of developmental problems did not first show up soon after MMR vaccination in at least seven of the twelve cases discussed in the Lancet study. In one case, the symptoms were first noted 3-5 months after vaccine administration. In six cases, evidence of developmental difficulties was present prior to the first administration of the vaccine.

Wakefield did not report the presence of any confirmed or even possible neurological or behavioral issues in any of the cases detailed in the paper. In fact, he explicitly reported that, "[in] eight children the average interval from exposure to first behavioral symptoms was 6.3 days (range 1–14)." The statement that eight of the twelve children exhibited their first symptoms during the first two weeks after receiving the vaccine is clearly incompatible with the paper's claim that earlier symptoms were present in six cases.

Wakefield and his colleagues reported that colonoscopy findings for 11 of the 12 children showed abnormalities. The *Sunday Times* reports that in at least seven of these cases, the hospital's initial pathology reports showed no abnormalities, and that these findings were changed after Wakefield's team undertook a "research review" of the results.

In the Lancet article, Wakefield and his colleagues do not mention any initial disagreement about the pathology reports. Instead, they talk about "the uniformity of the intestinal pathological changes" and refer to "consistent gastrointestinal findings."

Wakefield also described his patients as a "self-referred group". According to the *Sunday Times*, this is also untrue: The mothers of Child Two and Child Three reported what others said in medical records: they had heard of Wakefield through the MMR vaccine campaign, Jabs. Thus, when they arrived on Malcolm ward, and produced the "finding" about MMR, it was by no means a random sample of cases.

What parents did not know was that, two years before, Wakefield had been hired by Jabs' lawyer, Richard Barr, a high-street solicitor in King's Lynn, Norfolk. Barr had obtained legal aid to probe MMR for any evidence that could be used against the manufacturers. He is adamant that at all times he acted professionally, and diligently represented his clients.

Over the last several years, the *Sunday Times* has published a series of articles detailing a number of undisclosed financial conflicts of interest involving Wakefield and this paper. The conflicts include almost half a million pounds Wakefield collected as a result of his MMR work, in addition to the funds that were used for his research. The new report includes another massive conflict of interest bombshell:

In June 1996 - the month before Child One's arrival at the hospital - Wakefield and Barr filed a confidential document with the government's Legal Aid Board, appearing already to know of a "new syndrome". Referring to inflammatory bowel disease and then bowel problems with autism, Wakefield and Barr wrote to the board, successfully seeking money.

"The objective," they wrote, "is to seek evidence which will be acceptable in a court of law of the causative
connection between either the mumps, measles and rubella vaccine or the measles/rubella vaccine and certain conditions which have been reported with considerable frequency by families who are seeking compensation.” Wakefield did not mention his work with or funding from the Legal Aid Board when he submitted his article to the *Lancet*.

Taken individually, it's possible - if only barely - that any one of these things could be an innocent mistake. However, the combination of all these circumstances - the failure to report the prior developmental symptoms, the failure to report the initial negative pathology findings, the failure to report the Legal Aid conflict of interest, and the document that described the existence of the syndrome to Legal Aid prior to the commencement of the research project - cannot reasonably be explained away so easily. Simply put, this is a pattern that is very strongly suggestive of outright fraud, with possible associated financial gain.

After the publication of the article, and the publicity that ensued as a result of both the article and Wakefield’s press conference, vaccination rates plummeted sharply, because parents were too frightened of the possible side effects to vaccinate their children. Predictably, measles rates shot through the roof, and in 2006 the UK saw its first measles fatality in over a decade.

**Additional Questions to Consider:**

- Should physician/researchers be allowed to refer their own patients into studies that they are leading, even if, there are no commercial or financial interests?
- Does it make a difference whether the alleged conflicts of interest were real or inferred?
- What role does “public perception” play in this case? What role do the media play in its influence over public perception?
Case Study: UMass Lowell - Export Control – To ship, or not to ship?!

As a result of export control violations, the Center for Atmospheric Research at UMass Lowell entered into a settlement agreement in 2013 with the Bureau of Industry and Security (BIS) of the US Department of Commerce. The institution agreed to pay a fine of $100,000 that may be waived if no further violations occur during a two-year probationary period. UMass Lowell also agreed to make the details of the violations and the terms of the settlement agreement public information, as an example for others to learn from.

In 2007, the UMass Lowell center exported two instruments to the Pakistan Space and Upper Atmosphere Research Commission (SUPARCO) in violation of export control laws. These two instruments are designated as EAR99 on the US Commerce Control List (CCL). EAR99 items generally do NOT require an export license. However, if the proposed shipment is to an embargoed country, to an end-user of concern, or in support of a prohibited end use, then an export license may be required and could be denied. In this case, the foreign recipient was an end-user of concern. This transaction required a license because SUPARCO has been on the Bureau of Industry and Security Entity List since 1998 when it was “determined to be involved in nuclear missile activities.”

Additional Questions to Consider:

• What responsibility does the scientific community have regarding national security? Is this an ethical dilemma or strictly a legal compliance question?
• How concerned should you as a researcher, be about possible violations of export control regulations?
• What are the implications for data sharing and material transfer agreements considering these regulations?
• How can you ensure that equipment and biologics that are purchased are clear of federal export control restrictions?
• What are the risks of traveling abroad with laptops and other electronic devices that may contain your research data?
• What are the risks of shipping data and/or research materials to another country? How can you ensure that you follow prevailing rules and regulations? Do you know who in your Institution to contact for help or guidance?