Case Studies for Small Group Discussion

March 2020: Authorship and Responsible Publication
Practices Peer Review
Use of Human Subjects

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:
- Amsterdam, UPENN - Authorship, Ghostwriting, Conflicts of Interest
- COPE - Responsible Publication, Peer Review, Use of Human Subjects
- Fujii - Data Management, Fabrication, Authorship, Responsible Publication, Use of Human Subjects
- Guatemalan STD Case - Use of Human Subjects - Vulnerable Populations, Informed Consent
- Henrietta Lacks - Use of Human Subjects, Responsible Publication Practices, Conflicts of Interest
- Narayanan - Fabrication and Falsification
- Neumeister - Use of Human Subjects, Falsification, Conflicts of Interest
- Obokata - Fabrication, Responsible Publication, Plagiarism, Reproducibility, Mentoring
- Pavuluri - Human Subjects, Fabrication, Falsification
- Poisson - Data Management, Falsification, Whistleblowing, Authorship, and Collaboration
- Roche - Use of Human Subjects, Conflicts of Interest, Responsible Publication Conflicts of Interest
- Schön - Authorship, Responsible Publication, Peer Review, Data Management, Fabrication and Conflicts of Interest
- Stanford Prison Experiment - Use of Human Subjects and Whistleblowing
Fictional Cases – Could These Happen to You?

Authorship and Responsible Publication Practices
An assistant professor in the genetics department, Pam, is working on a project looking at colon cancer tissue specimens. After five years at the institution, she is hoping to advance to associate professor when she goes up for tenure review in the next year.

One day, Pam approaches you, a senior colleague, and asks to meet for advice on one of her research projects. Eager to help a promising young faculty member, you chat about her project and encourage her. You also provide her with a polymerase reagent for genetic analysis that has been on back order. Pam is delighted at the way professors in the department collaborate and share lab supplies and equipment, no questions asked. You think nothing of it; are glad to help out and want to ensure the progress of the study when necessary.

A year later, you are on your department’s Tenure Committee and see that Pam is coming up for promotion to associate professor. As you look through her dossier, you see that Pam has published a number of articles on her genetic analysis of colon cancer. However, one of the articles that was recently submitted to an eminent journal in her field has listed you as a co-author. You are astounded. You knew nothing of this, and certainly did not review and approve the final manuscript with your name on it.

Additional Questions to Consider:
- Do you think you qualify for co-authorship or is this a case of “gift” or “courtesy” authorship?
- If you are unsure, where can you go to find out the criteria of authorship?
- What if a reader suspected that the data had been “cooked” and you were asked to explain “your data”, what would you say? What are other negative outcomes connected with accepting such an authorship?
- Why do you suppose there are professional ethical standards regarding who qualifies as an author?
- Do different fields of science have different standards of authorship?
- How are standards for assigning authorship likely to evolve in years to come? Why or why not? *
- Are there other ways to acknowledge people who have helped without naming them as a co-author?
- Has Pam done something unethical? Do you think it was intentional or done out of generosity and naïveté?
- What might be her possible motives?

From: http://www.ori.dhhs.gov/case-three-should-i-be-listed-author

Authorship and Responsible Publication Practices
Ana holds a PhD from a prestigious American state university and specializes in the study of pain, its pathways and pain reduction interventions. Though trained in Taiwan, Ana thinks in English, which is her third language after the Khalkha dialect of Mongyol kele and Mandarin. However, she has some difficulty writing scientific papers inappropriate and nuanced English; hence, she typically asks colleagues to review and help edit her writing.

Ana has taken a postdoctoral fellowship at a famous institution with a strong publish or perish culture. Researchers flaunt their publication record and look down on anyone who does not have as many published papers as they do. Ana enjoys giving people ideas and supporting them. In return, she sometimes asks for help with her writing and is happy to acknowledge their assistance in her papers. But when colleagues return her manuscripts with their names included in the list of authors, Ana is stunned. It seems they feel entitled to do this.

Although she feels that others are taking advantage of her, Ana refuses to change. She gains satisfaction by thinking that she is helping to improve science. She says her goal is to be a good scientist, not to fight over who gets to be an author of her work. She feels blessed with an opportunity to work on some of the most
intellectually exciting projects and places in the world. She would never do anything to jeopardize this opportunity.

Yet Ana is upset when her lab boss not only puts his name on her work, but also takes a proposal she has prepared for funding by NIH and sends it off under his name—without even discussing that with her. She mentions it to him, and he just looks at her as though she were crazy. However, some administrators within the research institution

Ana is unsure what recourse she has. She values the opportunity to share ideas with others and get their responses, and is unwilling to do anything that will cut off that rich intellectual interaction. The theft of her ideas seems a minor price to pay for her scholarly environment. What should Ana do?

Additional Questions to Consider:

• What are the standards that apply in this situation?
• What are effective ways in which you could ensure that intellectual property rights are respected?
• What factors may motivate peers and superiors to exploit someone in this way? What kinds of power differentials are operating here?
• What factors are likely to result in persons “stealing” authorship that does not legitimately accrue to them?
• Do authorship practices vary depending on the national culture of the researchers involved?
• What would be a responsible role for a mentor in guiding this postdoc? How might she find supportive mentors?
• How could this postdoc arrange her writing and her collaboration with others to better control what happens to the designation of authorship of her papers?
• What risks do exploiters take when they claim authorship that they do not deserve?
• Have you ever had something similar happen to you? How did you deal with it, and what lessons did you learn?


Authorship vs. Acknowledgment

Dr. Colleen May is a participating neurologist in a clinical trial to assess the efficacy and toxicity of a new anticonvulsant medication. For the duration of the two-year study, each neurologist is to meet with each of his or her patients for an average of 30 minutes each month. In Dr. May's case, this amounts to an average of 20 hrs./month. During each visit, the physicians administer a variety of specialized tests, requiring judgments dependent on their experience and training in neurology. At the completion of the study, the results are to be unblinded and analyzed by the project leaders. It is anticipated that at least two publications will be prepared for the New England Journal of Medicine. Dr. May has just learned that she will be listed in the acknowledgments, but not as an author of the manuscript. Dr. May argues that she has provided nearly 500 hours of her expert time, far more than needed to complete a publishable study in her experimental laboratory.

Additional Questions to Consider:

• Does Dr. May have a case for authorship?
• At what point in the research should the issue of authorship have been discussed and/or decided?
• What recourse (if any) does Dr. May have at this point in time?

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Peer Review
Dr. George Adams receives a manuscript for ad hoc review from the editor of a scientific journal. George gives the manuscript to Al Nance, his senior postdoctoral fellow. He asks Al to read the manuscript and prepare some written comments critiquing it. One week later, Al provides to Dr. Adams one page of comments. Al also provides Dr. Adams with an extensive verbal critique of the paper. Dr. Adams then prepares a written review which is submitted to the editor of the scientific journal. A few weeks later, Dr. Adams learns that Al made photocopies of the entire literature citation section of the manuscript because it contained “some useful references.” Dr. Adams proceeds to verbally reprimand Al, telling him that no part of a manuscript received for review should be copied.

Additional Questions to Consider:
- What are the problems or issues in this case? Who or what is affected?
- Comment on the behavior of both the faculty member and the postdoctoral fellow in this scenario.
- Could this behavior be considered conflict of interest? If so, in what way?

Peer Review
Dr. Baylor, an expert in the area of aging and mental health, agreed to review an unpublished manuscript for a leading journal. Although Dr. Baylor has limited time outside of her teaching and research activities, she found the article so interesting that she gathered some of her colleagues together to share the findings with them.

Additional Questions to Consider:
- What are the problems or issues in this case? Who or what is affected?
- Could this behavior be considered conflict of interest? If so, in what way?
- What action might the journal editor take in this case?
A University of Pennsylvania psychiatry professor has accused his department chairman and four colleagues of publishing an article that was ghostwritten on behalf of a pharmaceutical company and made unsupported claims for one of its bestselling drugs.

The medical-journal article, published in 2001, "was biased in its conclusions" and "made unsubstantiated efficacy claims and downplayed" negative side effects of the antidepressant drug Paxil, according to a complaint filed by lawyers for Jay D. Amsterdam, a professor of psychiatry at Penn.

Dr. Amsterdam's complaint was filed with the Office of Research Integrity of the U.S. Department of Health and Human Services, which investigates allegations of misconduct in federally financed medical research. The research cited by Dr. Amsterdam was supported both by the National Institutes of Health and by the maker of Paxil, now known as GlaxoSmithKline.

An article reporting the research appeared in the June 2001 issue of the American Journal of Psychiatry with eight listed authors. The complaint accuses five of them: Dwight L. Evans, a professor and chairman of psychiatry at Penn; Laszlo Gyulai, an associate professor of psychiatry at Penn; Charles B. Nemeroff, a professor and chairman of psychiatry at the University of Miami; Gary S. Sachs, an associate clinical professor of psychiatry at Harvard University; and Charles L. Bowden, a professor and chairman of psychiatry at the University of Texas Health Sciences Center at San Antonio.

The other three authors—Ivan P. Gergel, Rosemary Oakes, and Cornelius D. Pitts—are not identified by any affiliation in the published article. They are GlaxoSmithKline employees, said Paul D. Thacker, an investigator with the Project on Government Oversight, a nonpartisan watchdog group.

Penn, in a written statement of response, said it took the allegations seriously and would investigate them. "Both Penn faculty members have been advised of the allegations in the complaint and, while they believe them to be unfounded, have made clear to the university that they will fully cooperate with the investigation, which they hope will be resolved expeditiously," the university said.

The allegations by Dr. Amsterdam, who has been on leave from the Penn medical faculty since August 2010, represent the latest incident in a series of cases in which GlaxoSmithKline has been accused of overstating the benefits and understating the risks of Paxil, and university researchers, including Dr. Nemeroff, have been accused of helping them.

It's also the second recent case involving the University of Pennsylvania. The Project on Government Oversight, or POGO, last November produced evidence of four instances of federally financed researchers' signing their names to journal articles favorable to Paxil that were written by a company paid by GlaxoSmithKline.

One of the four cases concerned an editorial in a 2003 issue of Biological Psychiatry that listed its authors as Dr. Evans and Dennis S. Charney, then an NIH official and now dean of the Mount Sinai School of Medicine, in New York. POGO obtained e-mail correspondence in which Sally K. Laden, an author affiliated with the medical-writing company Scientific Therapeutics Information, pressed a GlaxoSmithKline official for payment for having written the article for Dr. Evans. The published article had credited Ms. Laden with providing only "editorial support."

**Sharply Worded E-Mails**

POGO, in a letter to President Obama, asked that he remove Amy Gutmann, president of the University of Pennsylvania, from her position as chairman of the Presidential Commission for the Study of Bioethical Issues, until the two cases involving Dr. Evans are fully investigated and resolved.
A spokesman for the Department of Health and Human Services declined to comment directly on the future of the bioethics panel, but said in a written statement that the Office of Research Integrity would review the complaint submitted by Dr. Amsterdam.

The University of Pennsylvania also promised a review. "We take allegations of research misconduct seriously," Penn said in its statement, "and will investigate the matter thoroughly under the university's and the School of Medicine's well-defined processes and procedures."

Documents obtained by POGO show that Dr. Amsterdam, in a series of sharply worded e-mails with his colleagues at Penn in 2001, repeatedly complained about being omitted from the list of authors of the article that appeared in the American Journal of Psychiatry. In the complaint filed this month by his lawyers, he contends that "data from his study was effectively stolen from him, manipulated, and used in a ghostwritten article designed "to advance a marketing scheme by GlaxoSmithKline to increase sales of Paxil."

A university official, speaking on the condition of anonymity, cast doubt on the primacy of Dr. Amsterdam's role in the study. Dr. Amsterdam did enroll the largest number of patients in the study, but only in a supporting role after other researchers in charge of the trial had had trouble finding enough recruits, the official said. The published article, which noted Dr. Amsterdam only as a contributor, "was biased in its conclusions, made unsubstantiated efficacy claims, and downplayed the adverse event profile of Paxil," he said in his complaint to the Office of Research Integrity.

Karl Rickels, a professor of psychiatry at Penn who at the time headed the department's Mood and Anxiety Disorders Section, said in one 2001 e-mail to Dr. Amsterdam that the university researchers listed as participants apparently "never had a chance to review or even just see the manuscript" prepared by GlaxoSmithKline. Dr. Nemeroff declined to comment. Dr. Bowden said he was traveling and couldn't immediately discuss the matter, though he said all authors listed on the 2001 study had roles that would warrant their inclusion. Dr. Amsterdam and the other researchers he named in his complaint did not immediately respond to requests for comment.

A spokeswoman for GlaxoSmithKline, Sarah Alspach, said the cases cited by POGO were too old for the company to have significant information on the circumstances of its participation. GlaxoSmithKline's financial support for the 2001 article was noted in the publication, even though the company affiliation of three of its authors was not, Ms. Alspach said. "This article, of course, was published 10 years ago," she said. "Under current standards, their affiliation with GSK would be noted."

The article's findings, suggesting that Paxil may be beneficial in the treatment of bipolar depression, have now been cited in "hundreds of medical-journal articles, textbooks, and practice guidelines," Dr. Amsterdam's complaint says.

**Additional Questions to Consider:**

- Could this situation occur at your Institution? What is your Institutional policy about Ghostwriting?
- Should authorship be granted based on how many subjects/patients one can enroll in a study?
- Should the President of the University be removed from the Presidential Commission for the Study of Bioethical Issues because of issues being investigated at her institution? Why, or why not?
Case Study: COPE - Responsible Publication, Peer Review, Use of Human Subjects

A paper was submitted reporting results of a randomized trial. The trial seemed to look at immune responses in lung fluid in participants receiving either a particular vaccine or placebo. We got a copy of the trial protocol before going to peer review as per our normal editorial policy, and made sure the trial was registered.

One reviewer pointed out major discrepancies (principally in sample size and outcome measures) between the trial report, and the protocol document and registration record. We asked the authors to revise and to explain why these discrepancies had happened. The authors explained that that the protocol and registry record originally sent were actually for a totally different study, and they had now separately registered the trial reported here. They also sent a new protocol document apparently now corresponding to the study in question.

This revised paper then went to re-review and the reviewers were happy. However in-house journal staff was still worried about differences between the new protocol and the study reported in the paper. The new protocol did not seem to describe the conduct of a trial but rather a case-control study. There were also differences in the number and timing of invasive procedures being used to assess outcomes in the study, and there seemed to be more of these in the study report than in the protocol.

We went back to the authors to say we were very concerned about this and would need their explanation. If they couldn't provide an explanation then we would alert their ethics committee.

The authors wrote back to us, cc'ing the heads of their two research ethics committees, to say that indeed, the manuscript did not match the two different protocols they sent us. They explained that there was a fault in the manuscript and not in the work carried out. They explained that the paper they sent us did not describe a single study but rather parts of 4 different approved studies taking place over the same time frame and being carried out on overlapping study populations. They then detailed aspects of these studies and explained that the different interventions, assessment of outcomes, etc, that were reported in the paper indeed corresponded to sections of approved protocols. (Although, no single protocol explained all of the aspects reported in the paper).

At this point we are very concerned about the following things:

Individual participants being recruited into many different ongoing studies - were the ethics committees aware of this and is it wise?

Selective reporting of findings. Presumably the main outcomes for the protocol describing a trial (i.e., the one involving randomization to vaccine or placebo) have gone unreported. Why? We are also very worried about validity of the data and analyses (even to the point of suspecting fabrication, of a sort), because of this level of selectivity.

Misrepresentation in the original manuscript. Our assumption when we see the report of a trial is that, unless it is presented as a secondary, follow up, or other type of ancillary or nested analysis, then the report describes all the main aspects outlined in the approved protocol. This wasn't the case here, but how serious is this? Is it a form of scientific misconduct and if so who should we report it to? (The ethics committee may not care - are there any "rules" that a trial, once approved, has to be published in the form it's approved?)

At this point we are considering rejecting the paper essentially on the grounds of protocol deviations, and sending all relevant documents and correspondence to the ethics committees (who are already aware of the issues raised).
Advice:
The committee warned that the ethics committees could be part of the problem, and so seeking help from them (who are already aware of the issues raised) may not be very useful. The editor provided the update that the paper has now been rejected and that the author has made a formal complaint about the editor because the paper was mishandled. The committee was unanimous in its support for the editor who they said should remain firm in the face of the authors’ allegations. Further advice was to contact the authors’ institutions and inform them of the issues. The committee cautioned that this case highlights the need for trial registration for all studies.

Follow up:
The paper was rejected. The editor wrote to the chairs of both ethics committees enclosing a copy of the paper and protocol documents. The Director of Publishing dealt with the author’s complaint about the editor, and wrote back to the author to uphold the editor’s handling of the paper. We did not hear back from one of the chairs of the ethics committees but the editor did speak to the other chair, who felt that we had not understood the realities of conducting clinical research, in which protocols may change. We decided not to go to the authors’ institution to pursue this case further.

Additional Questions to Consider:
- Did the reviewers and/or editors act responsibly in this case or did they over-step their bounds?
- How important is it for peer reviewers to be familiar with policies and processes of the author’s institution when reviewing a manuscript?
- Do different disciplines have different standard operating procedures when it comes to reporting on clinical trials? Should there be different standards for review and acceptance?
After more than a decade of suspicion about the work of anesthesiologist Yoshitaka Fujii, formerly of Toho University in Tokyo, investigations by journals and universities have concluded that he fabricated data on an epic scale. At least half of the roughly 200 papers he authored on responses to drugs after surgery are in line for retraction in the coming months.

Like many cases of fraud, this one has raised questions about how the misconduct went undetected for so long. But the scope and duration of Fujii’s deception have shaken multiple journals and the entire field of anesthesiology, which has seen other high-profile frauds in the past few years.

Fujii was dismissed from Toho University in February 2012 because he lacked proper ethics approval for clinical studies that were detailed in eight papers. But suspicions about his entire 20-year publication record had been growing since 2000, when Peter Kranke, an anesthesiologist at University Hospital Würzburg in Germany, first started to question Fujii’s superhuman publication rate.

Fujii’s data were also “too perfect.” Kranke analyzed 47 of Fujii’s articles on Granisetron, published between 1994 and 1999, and found that the frequency of headaches — a common side effect of the drug — was identical or nearly identical in a suspiciously high number of groups involved in the trials.

In the following years, similar doubts emerged about Fujii’s studies of other drugs. Yet the deception began to unravel only in September 2011, after growing doubts among anesthesiologists prompted Toho University to begin an investigation into Fujii’s lack of approval from institutional review boards for several clinical trials.

Fujii’s subsequent dismissal was soon followed by a flood of damning evidence about his work. Late last month, Steven Shafer, editor-in-chief of Anesthesia & Analgesia — who has led the campaign to examine Fujii’s papers, posted online the responses from the institutions, along with a notice of retraction for three papers in his own journal. Shafer expects other editors to begin retracting the remaining fraudulent papers, probably including those being considered by Tsukuba, in the forthcoming issues of their journals.

Meanwhile, an investigation begun in March by the Japanese Society of Anesthesiologists reported in June that 172 of Fujii’s papers were probably fraudulent, in some cases because there was no evidence that the data had actually been collected. In late August, the society announced that Fujii, who had already left the society of his own volition, would be permanently barred. All of Fujii’s co-authors have denied knowledge of his wrongdoing, according to Koji Sumikawa, a member of the society’s board of directors who was involved in the investigation, and an anesthesiologist at Japan’s Nagasaki University School of Medicine.

Sumikawa says that Fujii’s work has had little impact on clinical practice, because the anti-emetics he studied are rarely used in Japan. But it has embarrassed the field of anesthesiology, which was already reeling from two high-profile fraud cases. In 2009, 21 publications by Scott Reuben, who was based at Tufts University School of Medicine in Boston, Massachusetts, were retracted because they contained fabricated data. The following year, around 90 papers by Joachim Boldt, formerly of the Ludwigshafen Hospital in Germany, were retracted from 11 journals, because of fabrication and because Boldt did not have proper ethics approval for the trials.

Ample opportunities
Most anesthesiologists insist that there is no evidence that their field is more prone to fraud than any other. But Carlisle says that anesthesiology does offer many opportunities to generate large sets of clinical data very quickly. Millions of anesthetic procedures are performed every year during surgeries, and patient outcomes are
immediate and easy to measure. There are “frequent opportunities for anesthetists to conduct clinical studies very quickly, potentially by themselves, without overview from other people”, he says. How did Fujii get away with his deception for so long? One reason could be that he spread his publications over a wide range of journals, in fields as diverse as gynecology and ophthalmology, suggests Sumikawa. “No one is looking at all of these,” he says.

Fujii’s peripatetic career may have also provided a smokescreen for his fraudulent behavior. Over two decades, he held posts at five institutions, and adjunct positions at two more, making it easy for him to claim that data had been generated or ethics approval had been granted while he was in a previous post. If any of Fujii’s colleagues were suspicious, they did not come forward at the time, says Sumikawa, who plans to set up a mechanism for whistleblowers to report concerns about colleagues.

**Additional Questions to Consider:**
- Do you believe that some disciplines are more prone to “fraud” or misconduct than others? If so, which ones and why?
- What situations or environmental elements do you believe contribute to this tendency and what controls could be implemented to prevent this type of research misconduct?
- What lessons about proper data retention can be learned from a case like this?
- What culpability does the institution have for allowing work to proceed without proper institutional review boards/ethical oversight?
- What responsibilities and/or culpability do the co-authors have in this situation? Is it acceptable for them to just claim ignorance of the wrong-doing of another?
- How do you explain how a deception such as this could continue for so long? Are you aware of systems at your Institution for reporting concerns about research misconduct, including protections for whistleblowers?
U.S. government researchers who purposely infected unwitting subjects with sexually transmitted diseases in Guatemala in the 1940s had obtained consent a few years earlier before conducting similar experiments in Indiana. The stark contrast between how the U.S. Public Health Service scientists experimented with Americans and Guatemalans clearly shows that researchers knew their conduct was unethical, according to members of the Presidential Commission for the Study of Bioethical Issues.

At least 5,500 prisoners, mental patients, soldiers and children were drafted into the experiments, including at least 1,300 who were exposed to the sexually transmitted diseases syphilis, gonorrhea and chancroid. At least 83 subjects died, although the commission could not determine how many of the deaths were directly caused by the experiments.

“This is a dark chapter in our history. It is important to shine the light of day on it. We owe it to the people of Guatemala who were experimented on, and we owe it to ourselves to recognize what a dark chapter it was,” said Amy Gutmann of the University of Pennsylvania, the commission’s chairwoman.

The revelations came on the opening day of a two-day hearing to review the findings of its investigation. President Obama ordered the probe when the experiments were revealed. Investigators reviewed more than 125,000 documents from public and private archives around the country and conducted a fact-finding trip to the Central American nation.

The Guatemalan government is conducting its own investigation. The experiments were approved by some Guatemalan officials. “Actually cruel and inhuman conduct took place,” said Anita L. Allen of the University of Pennsylvania. “These are very grave human rights violations.”

In one case, a woman who was infected with syphilis was clearly dying from the disease. Instead of treating her, the researchers poured gonorrhea-infected pus into her eyes and other orifices and infected her again with syphilis. She died six months later.

The ultimate goal of the Guatemalan research was to determine whether taking penicillin after sex would protect against syphilis, gonorrhea and chancroid. The question was a medical priority at the time, especially in the military. The Guatemalan experiments, carried out between 1946 and 1948, aimed to find a reliable way of infecting subjects for future studies.

The research included infecting prisoners by bringing them prostitutes who were either already carrying the diseases or were purposely infected by the researchers. Doctors also poured bacteria onto wounds they had opened with needles on prisoners’ penises, faces and arms. In some cases, infectious material was injected into their spines, the commission reported.

The researchers conducted similar experiments on soldiers in an army barracks and on men and women in the National Mental Health Hospital. The researchers took blood samples from children at the National Orphanage, although they did not purposely infect them.

In the studies conducted in Indiana, researchers exposed 241 inmates in Terre Haute to gonorrhea in 1943 and 1944. But there, the researchers explained the experiments in advance in detail and experimented only on the prisoners who volunteered. In contrast, many of the same researchers who began experimenting on Guatemalans a few years later actively hid what they were doing and never tried to obtain permission, the commission found.
About 700 of the Guatemalan subjects were treated for the sexually transmitted diseases, but it remains unclear whether they were treated adequately or what became of them. Gonorrhea can cause a variety of complications, including infertility. Chancroid can cause painful ulcers. Syphilis can cause blindness, major organ damage, paralysis, dementia and death.

Susan M. Reverby, a historian at Wellesley College in Massachusetts, discovered the Guatemalan experiments while doing research for a book on the infamous Tuskegee studies in Alabama. Reverby found papers from John C. Cutler, a doctor with the federal government’s Public Health Service. Cutler had participated in the Tuskegee experiment, in which hundreds of African American men with late-stage syphilis were left untreated to study the disease between 1932 and 1972. Cutler died in 2003.

Additional Questions to Consider:

• What is the value in acknowledging any wrong doing so long after-the-fact?
• Should these experiments have been performed on human subjects even with so-called informed consent? Can prisoners truly give informed consent of their own free will?
• Should there be different standards for informed consent based on population, cultural norms, and/or local regulation?
• Should these standards vary depending on research funding sources?
Case Study: Henrietta Lacks - Use of Human Subjects, Responsible Publication Practices, Conflicts of Interest


Medical researchers use laboratory-grown human cells to learn the intricacies of how cells work and test theories about the causes and treatment of diseases. The cell lines they need are “immortal”—they can grow indefinitely, be frozen for decades, divided into different batches and shared among scientists. In 1951, a scientist at Johns Hopkins Hospital in Baltimore, Maryland, created the first immortal human cell line with a tissue sample taken from a young black woman with cervical cancer. Those cells, called HeLa cells, quickly became invaluable to medical research—though their donor remained a mystery for decades. In her book, The Immortal Life of Henrietta Lacks, journalist Rebecca Skloot tracks down the story of the source of the amazing HeLa cells, Henrietta Lacks, and documents the cell line’s impact on both modern medicine and the Lacks family.

Henrietta was a black tobacco farmer from southern Virginia who got cervical cancer when she was 30. A doctor at Johns Hopkins took a piece of her tumor without telling her and sent it down the hall to scientists there who had been trying to grow tissues in culture for decades without success. No one knows why, but her cells never died.

Henrietta’s cells were the first immortal human cells ever grown in culture. They were essential to developing the polio vaccine. They went up in the first space missions to see what would happen to cells in zero gravity. Many scientific landmarks since then have used her cells, including cloning, gene mapping and in vitro fertilization.

When the cells were taken, they were given the code name HeLa, for the first two letters in Henrietta and Lacks. Today, anonymizing samples is a very important part of doing research on cells. But that wasn’t something doctors worried about much in the 1950s, so they weren’t terribly careful about her identity. When some members of the press got close to finding Henrietta’s family, the researcher who’d grown the cells made up a pseudonym—Helen Lane—to throw the media off track. Other pseudonyms, like Helen Larsen, eventually showed up, too. Her real name didn’t really leak out into the world until the 1970s.

Twenty-five years after Henrietta died, a scientist discovered that many cell cultures thought to be from other tissue types, including breast and prostate cells, were in fact HeLa cells. It turned out that HeLa cells could float on dust particles in the air and travel on unwashed hands and contaminate other cultures. It became an enormous controversy. In the midst of that, one group of scientists tracked down Henrietta’s relatives to take some samples with hopes that they could use the family’s DNA to make a map of Henrietta’s genes so they could tell which cell cultures were HeLa and which weren’t, to begin straightening out the contamination problem.

So, a postdoc called Henrietta’s husband, but he had a third-grade education and didn’t even know what a cell was. The way he understood the phone call was: “We’ve got your wife. She’s alive in a laboratory. We’ve been doing research on her for the last 25 years and now we have to test your kids to see if they have cancer.” This wasn’t what the researcher said at all. The scientists didn’t know that the family didn’t understand. From that point on, though, the family got sucked into this world of research they didn’t understand, and the cells, in a sense, took over their lives.

This was most true for Henrietta’s daughter. Deborah never knew her mother; she was an infant when Henrietta died. She had always wanted to know who her mother was but no one ever talked about Henrietta. So, when Deborah found out that this part of her mother was still alive she became desperate to understand what that meant: Did it hurt her mother when scientists injected her cells with viruses and toxins? Had scientists cloned her mother? And could those cells help scientists tell her about her mother, like what her favorite color was and if she liked to dance.
Deborah’s brothers, though, didn’t think much about the cells until they found out there was money involved. HeLa cells were the first human biological materials ever bought and sold, which helped launch a multi-billion-dollar industry. When Deborah’s brothers found out that people were selling vials of their mother’s cells, and that the family didn’t get any of the resulting money, they got very angry. Henrietta’s family has lived in poverty most of their lives, and many of them can’t afford health insurance. One of her sons was homeless and living on the streets of Baltimore. So the family launched a campaign to get some of what they felt they were owed financially. It consumed their lives in that way.

**March 2013:**

Scientists sequenced the genome of HeLa cells and uploaded HeLa’s genome to a public Web site called SNPedia, again without the family’s knowledge or consent. Minutes later, it produced a report full of personal information about Henrietta Lacks, and her family. Until recently, few people had the ability to process raw genome data like this.

Francis S. Collins, Director of the National Institutes of Health, said, “This latest HeLa situation really shows us that our policy is lagging years and maybe decades behind the science. It’s time to catch up.” The regulations governing this sort of research were written in the 1970s, long before anyone imagined what you could learn from a bit of DNA. They are largely based on the now outdated belief that if samples are “anonymized” (i.e., your name is removed), there’s no need to get consent before using them in research.

**Additional questions to consider:**

- So much of science today revolves around using human biological tissue of some kind. How much control should individuals have over how their discarded tissue is used? Do donors have the right to “sell” their samples to the highest bidder? Should individuals and/or companies be able to profit from the use of human biologics?
- How does the commercialization of selling tissue affect the nature of science? How do conflicts of interest considerations affect the research?
- The story of HeLa cells and what happened with Henrietta has often been held up as an example of a racist white scientist doing something malicious to a black woman. Do you believe that was the intent? And if it was, does that mitigate the scientific value of the discovery?
- The Lacks’ experiences over the last 60 years foretold nearly every major ethical issue raised by research on human tissues and genetic material. Now they’re raising a new round of ethical questions for science: though their consent is not (yet) required for publishing private genetic information from HeLa, should it be? Should we require consent before anyone’s genome is sequenced and published? And what control should gene-sharing family members have?
Case Study: Narayanan – Fabrication, Falsification
Source: https://www.nyunews.com/2018/04/02/04-02-news-research/
https://ori.hhs.gov/content/case-summary-narayananbhagavathi
https://ori.hhs.gov/content/case-summary-narayanan-bhagavathi

Bhagavathi Narayanan, a former researcher at NYU School of Medicine, falsified data in three papers and grant applications to the National Cancer Institute and National Institute of Health according to the U.S. Office of Research Integrity (ORI).

According to the ORI: [Narayanan] fabricated and/or falsified Western blot data for protein expression levels in cancer tissues and/or cells in fifty-eight (58) blot panels included in twenty-two (22) figures reported in three (3) papers and seven (7) grant applications submitted to NIH. In the absence of valid Western blot images, the quantitative data presented in associated bar graphs and statistical analyses also are false. Specifically, [Narayanan] trimmed and/or copied Western blot images from unrelated sources, manipulated them to obscure their origin, and reused and relabeled them to represent different experimental results.

By the end of 2016, Narayanan retracted papers published in 2003, 2006 and 2011. The papers were cited 69, 25 and 7 times, respectively.

According to Retraction Watch, the retractions were due to missing original data. Along with retracting the papers, Narayanan agreed to not apply for grants for a period of three years.

An NYU School of Medicine professor who knew Narayanan said she was not often around campus. The professor asked to remain anonymous: “Although Dr. Narayanan (and her husband) worked many years in the Department of Environmental Medicine of NYU Langone Medical Center, I really know little about her and her research projects because she rarely reached out and interacted with other researchers in the department,” the professor wrote in an email to Washington Square News (WSN).

According to the professor’s experience, Narayanan did not get along well with researchers at NYU and the American Health Foundation where she previously worked.

ORI found that Narayanan engaged in research misconduct by knowingly and intentionally falsifying and/or fabricating data reported in three (3) published papers and seven (7) grant applications submitted to NIH.

Additional Questions to Consider:
- How did Narayanan fly under the radar for so long? How likely is it that someone suspected wrongdoing?
- How important is it for each lab to have a systematic/detailed record keeping system and policy for recording and storing data? What are some methods for computer-assisted record keeping?
- Does electronic record keeping make it easier to spot misconduct?
Case Study: Neumeister - Use of Human Subjects, Falsification, Conflicts of Interest


New York University’s (NYU) medical school shut down eight studies at its prominent psychiatric research center and parted ways with a top researcher after discovering a series of violations in a study of an experimental, mind-altering drug.

A subsequent federal investigation found lax oversight of study participants, most of whom had serious mental issues. The Food and Drug Administration (FDA) investigators also found that records had been falsified and researchers had failed to keep accurate case histories.

Pfizer said that NYU was responsible for conducting the trial, and that the company had previously tested the same drug, known as an F.A.A.H. inhibitor, for osteoarthritic pain, without significant side effects. Earlier this year, six patients in a French trial of another experimental drug with similar, marijuana-like effects were hospitalized with severe neurological problems; one has reportedly died.

The study was an attempt to extend a small trial that Dr. Alexander Neumeister had done previously, suggesting that cannabis might relieve anxiety in some people with post-traumatic stress disorder. “We know very well that people with PTSD who use marijuana often experience more relief from their symptoms than they do from antidepressants and other psychiatric medications,” Dr. Neumeister said in a 2014 NYU news release after the first trial.

The research team decided to use a drug intended to produce some of marijuana’s effects, made by Pfizer, which financed the trial. Some participants took the drug over a seven-day period; others took a placebo pill. The NYU team performed scans on each person to see whether brain activation patterns correlated with symptom relief.

The study called for recruiting 50 people with PTSD diagnosis, according to study documents. Only 14 enrolled at the NYU site, according to federal documents, and many had participated in previous studies by Dr. Neumeister. One had completed a study of another drug 16 days earlier, when the protocol called for a 30-day window, according to the FDA.

The federal inspection, from July 16 to Aug. 5, 2015, found that the research team had failed to assess at least three subjects 24 hours after they had taken the experimental drug, contrary to study protocol. In several instances, the agency found, Dr. Neumeister had falsified documents by signing a fellow investigator’s name on reports. The violations “jeopardize subject safety and welfare, and raise concerns about the validity and integrity of the data collected at your site,” stated the FDA warning letter to Dr. Neumeister. Dr. Neumeister and NYU continue to disagree over the seriousness of the research violations, but the university has tossed out all of the data as unreliable, and tracked down the study participants to check on their health.

Update (2017): The U.S. Attorney’s Office for the Southern District of New York and the U.S. Department of Health and Human Services’s Office of Inspector General (OIG) announced criminal charges against Neumeister, alleging he used the grant funds on trips and meals for family and friends. The U.S. Attorney has also filed a civil lawsuit against Neumeister under the False Claims Act, also for misuse of grant funding. The charges include one count of theft of government funds, which carries a maximum prison sentence of 10 years, and one count of wire fraud, which carries a maximum sentence of 20 years. In the civil suit, the government can recover three times the alleged damages plus financial penalties for each false claim.
Sentencing (2018): The former prominent neurological researcher at Yale and New York University avoided prison time for stealing research funds, but a judge said he must play piano for indigent elderly people in Connecticut to make amends. The unusual sentence was handed out by US District Judge Analisa Torres.

Additional Questions to Consider:

- What responsibility should the Institution have had for proper oversight of these studies?
- What additional protections/safeguards should have been in place for this vulnerable population?
- What potential conflicts of conscience may have been faced by sub-investigators? What steps could be taken to report potential misconduct?
- What role, if any, did financial conflict of interest play in this case? If this had not been an industry-sponsored trial would the Institution have performed different oversight? How could a potential conflict of interest have been managed?
- Was NYU wise to “toss out” all the existing data? Why or why not?
- What do think about the unusual sentencing? Does this punishment fit the crime?
**Case Study: Obokata - Fabrication, Responsible Publication, Plagiarism, Reproducibility, Mentoring**


Dr. Haruko Obokata, a 30-year-old Japanese stem cell scientist, led a research unit at the Riken Center for Developmental Biology in Kobe. Riken is Japan’s largest comprehensive research institution renowned for high-quality research in a diverse range of scientific disciplines. Obokata published supposedly groundbreaking research in *Nature* showing stem cells could be made quickly and cheaply.

It was soon discovered that there were irregularities in data, no other group in the world could repeat her findings, and her own institution concluded it could not be done. She claimed that stem cells could be produced from normal adult cells by dipping them into acid for a 30-minute shock period. The announcement of the creation of these “STAP” cells (stimulus-triggered acquisition of pluripotency) sent shockwaves around the world.

Of the eight co-authors of the main STAP article, Obokata and Charles Vacanti, an anesthesiology professor at Harvard University, served as lead authors.

During a news conference on April 9, 2014 Obokata emphasized she had no malicious intent, and challenged Riken’s investigation report, released on April 1, that said her papers contained fabrications. “The STAP mechanism is a truth that has been verified on many occasions,” Obokata, told more than 300 reporters. She said she has successfully engineered STAP cells on more than 200 occasions.

In May, she agreed to withdraw a supplementary paper, which also contained erroneous use of illustrations. She tearfully defended her work and said that sending the message to the world that STAP cells have no scientific basis is flat wrong.

Vacanti had also opposed withdrawing the main article, saying the irregularities do not reduce the value of the discoveries. Retracting an academic paper published in *Nature* requires the consent of all its authors. The lead authors must make an application to the journal’s editing team to withdraw the article. *Nature*’s editing team said it reserves the right to withdraw an article after a request is made by the authors.

Riken’s investigation report said one of Obokata’s *Nature* articles contained images that starkly resemble those used in her PhD dissertation on a different subject. The use of those images, Riken said, constitutes “fabrication.” The institute’s report also said the tweaking and combining of images to produce an image of the results of genetic analysis constitutes “doctoring.” Reports questioned the images she used, and allegations of plagiarism were raised concerning her doctoral dissertation at Waseda University.

Obokata’s complaint argued that the “fabrication” was nothing but an innocent “mix-up” of images. It said Riken’s description of “fabrication” was wrong because the correct images exist, and that Obokata never made up data that never existed.

Prof. Yoshiki Sasai, 52, her mentor was cleared of direct misconduct by an investigation, but faced criticism for his oversight and for not spotting inconsistencies in the publications that were ultimately retracted. In August of 2014 the disgraced Sasai was found dead of an apparent suicide. The prominent scientist left a suicide note for his family saying he had grown weary of the media during the scandal over STAP cell research.

By March 2015, Riken announced it will demand that Haruko Obokata, 31, the former Riken employee at the center of the scandal, return 600,000 yen ($5,000 – the cost required to file the articles with *Nature*). The figure represents only a fraction of the funds (20 million yen) that were provided for her research on STAP
cells. It also said it will not pursue the option of filing a criminal complaint and give up patent rights to the method of creating STAP cells.

Additional Questions to Consider:

• What role, if any, did gender/age bias play in this story?
• Could some of these issues have been avoided with more effective oversight and mentoring?
• Should the articles have been retracted for a “mere mix-up” with image processing? Is it valid to claim it is not fabrication because the real images exist, but somehow weren’t the ones published?
• Do you think that the Riken was to blame for rushing to publicize this great achievement, perhaps blinded by patent and Intellectual Property rights?
• Was the journal at fault for rushing to publish these results before they could be vetted further?
Case Study: Pavuluri – Use of Human Subjects, Fabrication, Falsification
Source: https://www.propublica.org/article/university-of-illinois-chicago-response-manipavuluri-research-misconduct

Child psychiatrist, Mani Pavuluri was noted as one of the University of Illinois at Chicago’s (UIC’s) star physician researchers. Her main focus was treating kids with bipolar disorder and was able to secure millions of dollars from the federal government for her research. Through her clinic and research, she propelled UIC’s status as a leader in child psychiatry.

As Pavuluri become more nationally well-known, more and more parents from across the country would come to have their children assessed by her. One particular NIH-funded study, began in 2009. It was uncovered that 89 of the 103 participants (86%) did not meet the study’s eligibility criteria.

Pavuluri:
- Enrolled children younger than 10 years old, although the study was approved only for boys and girls ages 13 to 16 years old.
- Included children who had previously used psychotropic medication, although, under the protocol, that should have made them ineligible;
- Managed the medical care of some of the children involved in her study, although she was told to keep her clinical and research roles separate.
- Failed to give some girls pregnancy tests before they began taking lithium, even though consent forms said they would be tested. The drug can lead to an increased risk of birth defects.
- Pavuluri’s two young sons were amongst the children and teens who participated as healthy control subjects, a violation of university protocol and generally accepted research practices.

NIMH concluded that UIC’s IRB did not provide proper review and oversight of the study and was also at fault. The University reported serious non-compliance of the IRB and reported this to the OHRP in a letter dated March 22, 2013. One of the points was that there was insufficient initial review conducted by the IRB, as no research protocol was provided at the time of review. The University stopped Pavuluri’s lithium research in 2013 and shut down two other federally-funded studies that she was conducting. She returned nearly $800,000 that she had not yet spent on those studies.

However, even after learning of the misconduct, the University named her a “university scholar” later in 2013 which included a $30,000 award, allowed her to keep her position as faculty chair and gave her a base salary of almost $200,000/year with additional bonuses.

In a rare occurrence, the NIMH demanded that the University repay the $3.1 million that funded Pavuluri’s study. The federal government concluded that: Pavuluri’s “serious and continuing noncompliance" with rules to protect human subjects violated the terms of the grant. The NIMH said she had "increased risk to the study subjects" and made any outcomes scientifically meaningless, according to documents obtained by ProPublica Illinois.”

Where is Pavuluri now? Pavuluri resigned from UIC on 6/30/18. She plans to open a treatment center called the Brain and Wellness Institute in Lincoln Park. In addition, she maintains a blog at:
http://www.drmanipavuluri.com/

Additional Questions to Consider:
- Do you feel that Pavuluri’s and the UIC IRB share equal blame in this situation?
- Did the University fail in its responsibilities to support a culture of integrity? If yes, how so?
- What are the motivations for committing blatant misconduct which would jeopardize children’s lives?
- Do you feel the punishment fit the crime? Should there be harsher consequences/punishments (e.g., jailtime)?
Case Study: Poisson - Data Management, Falsification, Whistleblowing, Authorship, and Collaboration

Sources:
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Robinson, A. CMAJ 1994 (151); 831-834, Lowry, F. CMAJ 1994 (151);835-837, Gorman, C. Time 1994 (March 28th); 52-53
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In 1985, the National Surgical Adjuvant Breast Project (NSABP) published findings from a clinical trial suggesting that lumpectomy for certain breast cancers was as effective as mastectomies. These results were published in the New England Journal of Medicine (NEJM).

In June 1990, NSABP became aware that Dr. Roger Poisson, a Montreal surgeon at Hopital St-Luc, had falsified some data. Although one of 89 institutions, he contributed approximately 19% of the cases to the above study and was 3rd and 4th author on the two major papers produced.

The Office of Scientific Integrity was called, initiated an investigation and prohibited public discussion of the case. In April 1993, the final report concluded Poisson was guilty of scientific misconduct and was barred from receiving public funds for 8 years.

After this a reanalysis of the trial data excluding Poisson's contributions was initiated. The conclusions held with respect to the value of lumpectomy in breast cancer treatment and were published in the NEJM. Bernard Fisher, then coordinator of NSABP was forced to resign. He was later cleared of any misconduct after a legal trial. At the time he stated that Poisson altered data on only 6 of the 354 women he enrolled. Poisson failed to report the correct date for a biopsy, which would have resulted in a longer period between biopsy and definitive surgery than that mandated in the protocol. Poisson enrolled patients under his care. In this capacity he argued that it was difficult to tell a woman with breast cancer that she was ineligible to receive the best treatment available because she did not meet 1 criterion out of 22 when he knew that this criterion had little or no oncological importance. His sole concern at all times was the health of his patients.

Prior to the study Poisson was a strong advocate of lumpectomy and opposed to radical mastectomy. After the allegations of fraud were made public, Poisson was not apologetic, “That has no impact on the oncological outcome, so why make such a fuss about it? My patients are very supportive of me.”

Poisson also wanted to advance the field of breast cancer. He lamented, only 2% of all breast-cancer patients in North America enter into clinical trials it slows the studies tremendously. A colleague later described Poisson as a proud man - proud to say that he puts most of his patients in trials, proud to get grants, proud to get his name on research papers.

The FDA disqualified Poisson from receiving further funds after he acknowledged falsifying the results of other studies. In the end, the ORI found 115 well-documented instances of data fabrication. Although data management staff assisted in this deception, Poisson claimed full responsibility, except in the instance where a staff member created progress reports on a dead study patient. The fallout in scientific and lay press was considerable, to the point that Congressional Hearings were held in the US.

Additional Questions to Consider:
• When and how should disclosure of misconduct take place and to whom?
• How can similar cases be prevented?
• Is it “fair” for the PI to accept full responsibility when others definitely assisted and/or knew about the deception and said or did nothing?
• How much does “ego” influence this type of behavior? Is it concern for patients’ welfare or the desire for “fame” that drives one to commit research misconduct? Or is it a combination of many factors?
• Should doctor/researchers be allowed to put their own patients into research studies that they are leading? Why, or why not?
Case Study: Roche - Use of Human Subjects, Conflicts of Interest, Responsible Publication

Conflicts of Interest

Ellen Roche, a 24-year-old technician at Johns Hopkins University's asthma and allergy center, fell ill one day after she inhaled an experimental compound, hexamethonium as part of an NIH-funded study to understand the cause of asthma. Ms. Roche spent several weeks in an intensive care unit. Her air sacs collapsed, her lungs became stiff, air began to leak out of them, her organs began to fail, and, finally, her family decided to remove her life supports.

The fatal illness probably was precipitated, university officials said, when Ms. Roche took a drug in the study. The study was conducted at the center where she worked, but not by the researcher she worked for. She was healthy, and the study was not intended to help her personally. Volunteers were paid up to $365 for their time and effort.

The university suspended all ten studies being conducted by the principal investigator, Dr. Alakis Togias, an associate professor of clinical immunology.

This tragedy raises questions of what is required to assure the utmost safety for volunteers in research. The study was investigating why healthy people and people with asthma responded so differently to substances that constricted their airways. When the constriction occurs, people without asthma can breathe deeply and make their airways relax, but those with asthma cannot get their airways to relax.

The researchers hypothesized that nerves in the lungs controlled this relaxation. They proposed constricting the airways of volunteers with one drug and then giving them a second drug, hexamethonium. That drug temporarily blocks the nerves in their lungs from responding normally. The combination of drugs can simulate an asthma attack.

Hexamethonium, however, was not approved by the Food and Drug Administration (FDA). Dr. Togias reported to the Institutional Review Board (IRB), an ethics group overseeing his work that had concluded that the drug's main risk was in causing a temporary drop in blood pressure. His conclusions were reflected in a consent form signed by Ms. Roche and the other study volunteers.

That form "should not have been approved" by the IRB, the Hopkins investigating committee concluded. The form did not mention that hexamethonium was not approved by the FDA, and it did not say that the drug's safety was uncertain or that the only data on the safety of inhaling it came from the experience of just 20 people.

In addition, the committee found that Dr. Togias had apparently missed some papers suggesting that the drug might injure the lungs. Many believe that this was indeed a contributing factor to this tragedy. Dr. Togias limited his literature search by relying on a limited number of resources, including PubMed, which at the time was only searchable back to 1966. It was found after the fact, that previous articles published in the 1950's warned of lung damage associated with hexamethonium.

Ms. Roche was the third subject in the study to inhale hexamethonium. The first subject developed a cough and shortness of breath upon exertion. Those effects lasted for a week. But Dr. Togias did not report that subject's symptoms to the IRB, reasoning that they were not serious and that they were probably due to a cold that was going around in the research unit, or to the acidity of the hexamethonium solution.

A few days after the first subject recovered, Ms. Roche took the drug, became ill and went to the hospital. Dr. Lewis Becker, the chairman of the internal committee, said he did not blame Dr. Togias for not recognizing the possible significance of the first volunteer's reaction to the drug. "I can completely understand how he could have attributed it to a cold or the high acidity of the solution," he said. But, the committee said, Dr. Togias should have reported the first subject's experience to the IRB.
The committee said the university would redouble its efforts to ensure safety in its clinical research. And that raised questions of whether the FDA should have been involved. The committee said in its report that the IRB should have asked Dr. Togias to find out whether he needed the FDA's approval to do the study. The agency, Dr. Miller said, often has information from drug company studies that can address safety questions. It could also have required the Hopkins researchers to do additional studies of their own, perhaps giving the drug to animals, before giving it to people.

Drug companies are required to get FDA permission before doing a study like the one at Johns Hopkins, said Dr. Bert Spilker, senior vice president for scientific and regulatory affairs for Pharmaceutical Research and Manufacturers of America. Complying with the agency's requirements typically would take one to two years and cost $1 million to $5 million.

The FDA used to exempt most academic research from this process, said William Vodra, a former FDA lawyer. But, he said, with recent problems, including the death of a subject in a gene therapy study at the University of Pennsylvania, that policy "was shaken to the core." But if the FDA did require universities to adhere to the same standards for research studies as industry, it was not clear where the money would come from, he said. "I don't think society will be comfortable with industry picking up the tab," Mr. Vodra said. "And I don't think George Bush wants to repeal his tax cut to pay for this."

Roche's death on June 2, 2001, the first death ever of a healthy volunteer at Johns Hopkins, stunned Hopkins researchers. They were stunned again on July 19 when the U.S. Office for Human Research Protections (OHRP) suspended all federally funded research involving human subjects at nearly all Hopkins divisions. The shutdown halted some 2,400 protocols. The initial response from the university was anger: A media release on the day of the suspension called OHRP's action "unwarranted, unnecessary, paralyzing, and precipitous," and you can still find researchers who-- not for attribution--use the words "excessive" and "disproportionate" and "bordering on unethical." Hopkins nonetheless accepted responsibility and moved forward immediately with a corrective action plan. OHRP partially lifted its suspension after five days, and in the weeks following the suspension, Hopkins cooperated with government regulators and committed to an arduous re-review of every current research protocol. A faculty committee conducted an internal review of the circumstances surrounding Roche's death, and Hopkins administrators commissioned an external review. The findings from both committees forced Johns Hopkins to confront inadequacies in its protection of human research subjects. Hopkins administrators and faculty began a long, painful process of institutional soul searching.

Additional Questions to Consider:
- Is there an issue with an institutional employee participating in a research study at that same institution? Does this present any potential conflicts of interest, commitment and/or conscience? If so, why?
- Do you think that monetary considerations played a significant role in this tragedy? If so, how and by whom – individuals, the institution, the federal agency, etc.
- Given the year of this study (2001), does $365 seem like a reasonable amount of compensation? Is it too much (coercive), or too little?
- What role did responsible publication practices play in this tragedy? Did the principal investigator do enough to search the literature?
- These questions were raised in 2001... Are they still valid questions today? Have significant improvements been made to protect research volunteer and the integrity of the research enterprise?
  - Does the national system of regulatory oversight and IRBs adequately protect research volunteers, or is it outmoded and overwhelmed by profound changes in the research environment?
  - Was the system inherently flawed from the beginning?
  - What must change to enable vital research to continue, but with better assurance of volunteer safety?
Case Study: Schön - Authorship, Responsible Publication, Peer Review, Data Management, Fabrication and Conflicts of Interest

http://www.americanscientist.org/bookshelf/pub/physicsandpixie-dust
This is a review of a book about Schön:

Between 2000 and 2002, Jan Hendrik Schön, a researcher at Bell Laboratories, published more than 20 articles on electrical properties of unusual materials. He shot to the very top of the booming field of “molecular electronics”—a wonder field in which researchers aim to shrink computer chips down to single-molecule components. At Schön’s peak, he was submitting 4 or 5 articles per month, most of them going to top journals like Science and Nature. He hit his record in autumn 2001, turning out 7 articles that November alone. The output was staggering. It’s rare for a scientist—even a string theorist, beholden neither to instruments nor to data—to submit 7 articles in an entire year, let alone one month. And Schön’s papers were no run-of-the-mill exercises. In them, he announced one unbelievable discovery after another: He had created organic plastics that became superconductors or lasers; he had fashioned nanoscale transistors; and more. The editors of Science hailed one of his many contributions as a “breakthrough of the year” in 2001. The CEO of Lucent Technologies (parent company of Bell Labs) likewise touted Schön’s work when courting investors. Everything Schön touched seemed to turn to research gold.

Following a formal investigation in 2002, Bell Labs dismissed Schön. The investigating committee, chaired by Stanford professor Malcolm Beasley, considered serious allegations against 24 papers by Schön and his coauthors, including 8 published in Science and 5 in Nature. The committee concluded that at least 16 of the papers showed clear evidence of scientific misconduct. Another 6 struck the committee as “troubling,” even if they were not indisputably the result of intentional fraud.

According to the Beasley committee, Schön’s misconduct fell into three basic categories: “substitution of data,” “unrealistic precision of data” and “results that contradict known physics.” The “substitution” charge was that Schön recycled graphs representing data from one type of material, changed axes or labels, and passed them off as coming from different materials. The second two charges involved either heavy-handed manipulation of data—such as replacing raw data with averaged, filtered or smoothed curves—or the fabrication of entire data sets out of thin air. Some graphs in the suspect articles, for example, appeared to have been generated by matching a known equation, with no experimental input whatsoever.

He conducted nearly all of his experiments at his former laboratory in Germany, where he had completed his doctorate, rather than on site at Bell Labs. When colleagues occasionally expressed curiosity about how he prepared his samples or undertook his measurements, Schön could throw up his hands and explain that the apparatus was several thousand miles away. Schön also maintained that he was in the habit of deleting all computer files of raw data—he later claimed that his computers lacked adequate storage space to keep the original data files—saving instead only the results after data had passed through various layers of analysis.

Most interesting is that Schön’s frauds actually benefited from rigorous peer review at elite journals. The critiques and suggestions that Schön received in referee reports told him exactly what it would take to convince skeptics about new findings. If his amazing plastics really did show evidence of superconductivity, reviewers pressed, had Schön checked for such and such effects or measured this or that parameter? Schön could then deliver those results right back, in perfect keeping with expectations.

The official inquiry, chaired by Beasley, exonerated all of Schön’s coauthors and colleagues of any wrongdoing. Some of Schön’s former managers even won awards for their handling of the allegations. Yet is it plausible that “one bad apple” was responsible?

Those managers had reasons to welcome Schön’s alluring offerings. The dot-com stock bubble had burst, sending the finances of Bell Labs into free fall. The laboratory began to hemorrhage researchers; its Physical
Research Laboratory lost half its staff between 1997 (the year before Schön arrived as a postdoc) and 2001. A wave of corporate restructuring brought in more middle managers with less lab-bench experience. The fast-changing organization charts led to a management vacuum: Over the course of just a few months in 2001, Schön answered to three different managers in succession. The managers, in turn, were all too happy to see their star researcher churn out stupendous results at very low cost. They began to tell other staff scientists to stop asking for expensive equipment and act more like Schön.

Nor were the managers at Bell Labs alone in wishing upon a star. A pattern of solicitous editors—both Nature and Science were eager at just that time to increase their publications in areas such as materials science and nanotechnology, so as to counter the journals’ heavy concentration on biomedical topics. Editors often fast-tracked Schön’s articles, sending them out for fewer rounds of peer review than usual. Schön’s papers in Science, for example, made it into print more than 25 percent faster than the journal’s average.

The excesses of the Schön case throw light onto habits and practices that have come to seem normal. The relentless rat race to produce new results quickly in order to secure the next round of funding or promotion is not without consequences. The cozy relationship between prestigious scientific journals like Science and Nature and journalists—who receive prepublication copies of “hot” articles under special embargo, allowing them to prepare accompanying news coverage—entangles scientists, laboratories’ press relations staff, journal editors, investors and others in dizzying webs of potential conflicts of interest.

Additional Questions to Consider:

- In what ways did the peer review system fail in this case? How could this have been avoided? What responsibility do editors have, to ensure that the work is authentic?
- Could that many published papers have gone unnoticed and/or unchallenged by colleagues in a university or academic medical center setting vs. private industry?
- By exonerating all the co-authors and collaborators, what message was sent about author responsibilities?
- Was the fact that Lucent Technologies was “courting investors” a factor in allowing the deception to grow?
- What role did the interwoven and possibly competing conflicts of interest play in keeping Schön’s success at a fever pitch?
- How would rules about data management (acquisition, storage, ownership, sharing, reproducibility, etc.) have helped to prevent this deception? Do you know where to find your Institution's Data Management Policies?
Case Study: Stanford Prison Experiment - Use of Human Subjects and Whistleblowing

The Menace Within
What happened in the basement of the psych building 40 years ago shocked the world. How do the guards, prisoners and researchers in the Stanford Prison Experiment feel about it now?


IT BEGAN with an ad in the classifieds.
Male college students needed for psychological study of prison life. $15 per day for 1-2 weeks.
More than 70 people volunteered to take part in the study, to be conducted in a fake prison housed inside Jordan Hall, on Stanford's Main Quad. The leader of the study was 38-year-old psychology professor Philip Zimbardo. He and his fellow researchers selected 24 applicants and randomly assigned each to be a prisoner or a guard. Zimbardo encouraged the guards to think of themselves as actual guards in a real prison. He made clear that prisoners could not be physically harmed, but said the guards should try to create an atmosphere in which the prisoners felt "powerless."

The study began on Sunday, August 17, 1971. But no one knew what, exactly, they were getting into.

Forty-four years later, the Stanford Prison Experiment remains among the most notable—and notorious—research projects ever carried out at the University. For six days, half the study's participants endured cruel and dehumanizing abuse at the hands of their peers. At various times, they were taunted, stripped naked, deprived of sleep and forced to use plastic buckets as toilets. Some of them rebelled violently; others became hysterical or withdrew into despair. As the situation descended into chaos, the researchers stood by and watched—until one of their colleagues finally spoke out. The public's fascination with the SPE and its implications—the notion, as Zimbardo says, "that these ordinary college students could do such terrible things when caught in that situation"—brought Zimbardo international renown. It also provoked criticism from other researchers, who questioned the ethics of subjecting student volunteers to such extreme emotional trauma. The study had been approved by Stanford's Human Subjects Research Committee, and Zimbardo says that "neither they nor we could have imagined" that the guards would treat the prisoners so inhumanely.

In 1973, an investigation by the American Psychological Association concluded that the prison study had satisfied the profession's existing ethical standards. But in subsequent years, those guidelines were revised to prohibit human-subject simulations modeled on the SPE. "No behavioral research that puts people in that kind of setting can ever be done again in America," Zimbardo says.

The Stanford Prison Experiment became the subject of numerous books and documentaries, a feature film (2015) and the name of at least one punk band. In the last decade, after the revelations of abuses committed by U.S. military and intelligence personnel at prisons in Iraq and Afghanistan, the SPE provided lessons in how good people placed in adverse conditions can act barbarically.

The experiment is still a source of controversy and contention—even among those who took part in it.

Additional Questions to Consider:

- Forty years ago, could payment of $15 per day for 1-2 weeks to a college student seem “coercive?”
  Would it be considered so today? If not, what amount would be coercive? What factors need to be considered before making that determination?
- Would a study that “subjects student volunteers to such extreme emotional trauma” ever be approved today? What safeguards are in place to prevent such harmful situations?
- Are there rules about using students or employees in clinical trials at your Institution? Is this acceptable under any circumstances? What are the rules of informed consent – would this statement be allowed: "You can't quit—you agreed to be here for the full experiment."