Welcome! Before we get started, join poll everywhere using the QR code at right and tell me: What is the best fun fact that you know?

Nobody has responded yet.

Hang tight! Responses are coming in.

Wake Forest®
School of Medicine

Responsible Conduct of Research

Ellen Quillen, PhD

Internal Medicine – Molecular Medicine

Introduction to the Responsible Conduct of Research and Case Study

Today's Format

- There are 4 segments to today's case study. Each segment contains a short set of slides followed by part of a progressive case, including questions for consideration.
- All the details of this case are true, except for the animal research portion.
- You will respond to questions throughout using Poll Everywhere.

Research Misconduct - Definition

- “Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or reporting research results”
  - **Fabrication** - making up data or results and recording or reporting them
  - **Falsification** - manipulating research materials, equipment, or processes, or changing, hiding or omitting data or results such that the research is not accurately representing the research record
  - **Plagiarism** - appropriation of another person’s ideas, processes, results, or words without giving appropriate credit

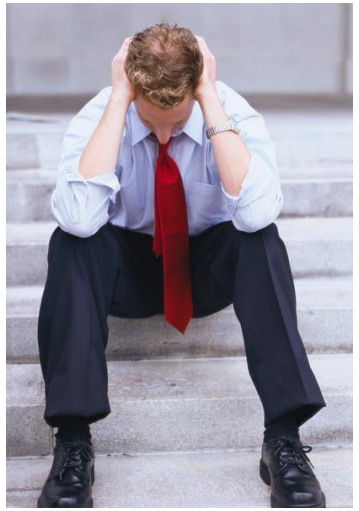
Ethics vs. Integrity

- Research Integrity deals with misconduct
- Misconduct = Unethical
- Unethical ≠ Misconduct (could avoid misconduct activities but still be unethical)
  - Study design
  - Subject selection is not representative or appropriate
  - Protocol is not followed and thus results are unreliable
  - Risk benefit ratio changes, but study continues with no change

Why does misconduct occur?

- Pressure to produce
- Time crunch
- Poor mentoring
- Inadequate expertise in research methods
- Other reasons?

Misconduct - Consequences



- Damaged reputations
- Loss of public trust
- Fines to individuals and institutions
- Long term consequences – inability to receive federal funds for a period of time or life
- Loss of privileges – barred from conducting research

Case Study: Introduction

Anil Potti, born and raised in India, arrived in the US in 1995 with a medical degree. He trained in Internal Medicine at the University of North Dakota, was invited to join the faculty, and quickly became a productive scholar. He became passionate about oncology and published more than 60 papers during a 5-year period on cancer detection and treatment.

Anil Potti, Duke University

Case Study: Introduction

This led to an offer from the renowned Institute for Genomic Sciences at Duke University to work with a group headed by Dr. Joseph Nevins to apply his investigation of cancer treatments to small molecules, such as DNA sequences (genomics) and proteins (proteomics), often shortened to “omics.”

Nevins was researching individualizing chemotherapy based on genetic profiles, and Potti brought some statistical models that he claimed would do just this.

Case Study: Introduction

The manuscript parade continued: 12 in only 2 years, culminating with reports in Nature Medicine and the New England Journal of Medicine on using omic signatures to identify the likely best chemotherapy.

Both papers, and many others from this work, have since been retracted, because the supporting evidence for the computational model could not be replicated or substantiated.

NEWS RELEASE 9-AUG-2006

First-ever genomic test predicts which lung cancer patients need chemotherapy to live

Peer-Reviewed Publication

DUKE UNIVERSITY MEDICAL CENTER

IMAGE: JOSEPH NEVINS, PH.D., ANIL POTTI, M.D., AND DAVID HARPOLE, M.D. view more ›

CREDIT: DUKE UNIVERSITY MEDICAL CENTER

Falsification, Fabrication and Plagiarism is essentially lying, cheating and stealing. It is uncovered only rarely but at a consistent rate in the U.S. Why might a scientist do this when it is so obviously unethical?

Nobody has responded yet.

Hang tight! Responses are coming in.

Case Study: The Whistleblower

One day, Dr. Nevins introduced Potti to Bradford Perez, a 3rd-year medical student at Duke with a 1-year Howard Hughes fellowship. In his fellowship application, Perez was recommended as “top 1%” in computer programing. He seemed perfect for working on statistical modeling of genomic signatures.

Perez was assigned to assist Potti, but he soon had trouble understanding some of the statistical methods. Worse, he couldn’t get straight answers about it from Potti. He was unsure whether Potti was just uncommunicative, or if he was unable to perform the computations correctly.

Case Study: The Whistleblower

Numerous discussions with Nevins were also unsuccessful, because Nevins ultimately told Perez that Potti was “the trusted expert.” Finally, a frustrated Perez submitted a memo to Duke administration under the title “Research Concerns.” He described his problems with the data sets: repeated strings of numbers that he initially suspected might be inadvertent errors. However, when removed, the correlations no longer held up.

'Whistleblowers' point out wrong actions, like research misconduct. Although schools protect whistleblowers, there is still a price to pay for calling out colleagues. What would it be like to be a whistleblower against a more powerful colleague?

Nobody has responded yet.

Hang tight! Responses are coming in.

Animal Welfare

- Refers to the physical and mental state of an animal
  - How is an animal coping with the conditions it lives in?
- Use of animals in research is heavily regulated by the government and overseen by Institutional Animal Care and Use Committees (IACUCs)
- Criteria has been established for animal housing, treatment, veterinary care, pain management and environmental enrichment.

Animal Welfare – The 3Rs

- **Replacement** – replacing experiments with animals for a non-animal alternative techniques
- **Reduction** – scientists must reduce the number of animals used in experimentation whenever possible, if possible
- **Refinement** - research must be arranged so that animal distress is minimal

(Russell and Burch 1959)

Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

- Relevant to human or animal health, or the good of society
- Species & numbers
- Avoids pain & distress
- Analgesics & anesthesia
- Painless death
- Proper husbandry
- Trained researchers
- Minimize risk and maximize benefits

"*Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals*."

Case Study: Animal Subjects

Note: This scenario is not drawn from truth and is included only for illustrative purposes.

Imagine Dr. Potti had a neighbor, Dr. Stacy Hinton, a local veterinarian at a nearby clinic for pet animals. While discussing his computational models with Hinton, Potti complained he needed to strengthen his correlations but lacked high numbers of patient tissue samples of specific tumor types.

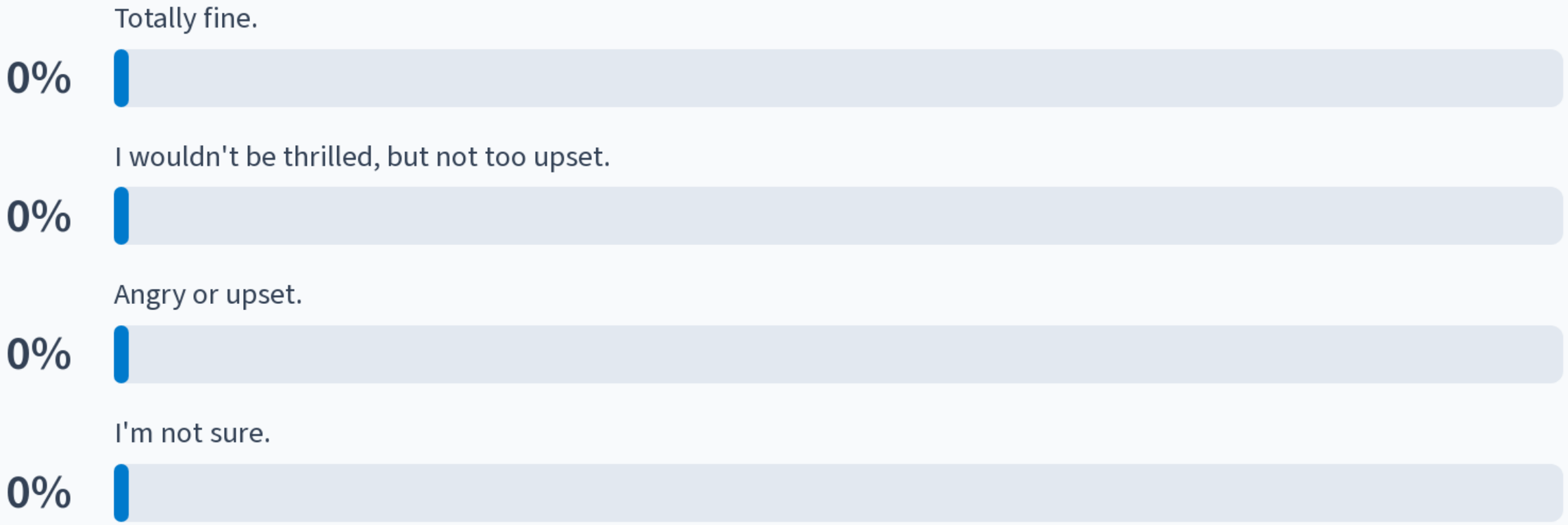
Hinton saw many dogs with a variety tumors that he was describing. She said, “You know, the canine genome was assembled more than a decade ago, and numerous genetic models of canine disease are well-identified.”

Case Study: Animal Subjects

Potti was impressed, so Hinton supplied him with excess tissue from more than 150 cancer biopsies over several months. Potti then gave Hinton a supply of various chemotherapeutic agents to try on the canine patients, saying “People bring you those sick pets for euthanasia. Maybe one of the drugs will work; you don’t need to kill the animals right away.”

Results with one drug showed a beneficial action of mammary tumor regression in dogs. Potti and Hinton quickly composed a manuscript but the journal’s editorial office suspended review until the authors could establish that university-approved animal care protocols were followed.

How would you feel if tissue from your pet was used for research without your consent?



What would your most important concerns be about Dr. Potti's study if you were on the IACUC committee?

Nobody has responded yet.

Hang tight! Responses are coming in.

Case Study: Rigor and External Review

K.A. Baggerly and K.R. Coombes, at the M.D. Anderson Center in Houston, had their own concerns with Potti's publications. They were unable to replicate the same statistical results when using Potti and Nevin's own methodology and publicly disclosed data.

Potti and Nevins acknowledged some clerical errors in their papers and provided additional information to Baggerly and Coombs, who still claimed the work could not be verified. Nevins continued to fend off criticism while Duke took legal steps to make the prediction algorithms proprietary and patent the technology for commercial use ahead of clinical trials.

Research with Humans Participants

- **Research** - A systemic investigation that intends to produce generalizable knowledge

Human Subjects Research

Research involving a living individual about whom data or biospecimens are obtained/used/studied/analyzed through interaction/intervention, or identifiable, private information is used/studied/analyzed/generated

Examples of human subjects research include:

- Collecting blood
- Conducting a survey
- Changing participants' environment
- Administering medicine
- Interviewing
- Administering a psychological test
- Collecting data
- Conducting a focus group
- Testing a new educational technique

01

Basic Principles of the Belmont Report

1. Respect for Persons

   Individuals should be treated as autonomous, and those without autonomy (such as children, prisoners, etc.) need special protections.

2. Beneficence

   Efforts much be made to reduce harm and maximize benefits for participants in research. Kindness is seen as obligatory, not optional.

3. Justice

   Benefits of research should be evenly distributed between all involved parties, especially those participating directly in the research.

02

Application of Principles

1. Risk/Benefits Assessment

Research should be justified in that expected benefits far outweigh the potential risk of harm (physical, mental, financial, etc.) to participants.

2. Selection of Participants

There must be clear principles for inclusion/exclusion in a study. Persons who are eligible or desired for research must be decided with the principle of Justice in mind.

3. Informed Consent

To the full degree which they are capable, research participants must be informed about the nature of the research they are taking part in, and must consent to the collection and use of data they generate as part of any study. Research participants are volunteers, and thus can stop participating at any point, free of any consequence.

Infographic: What are the basic principles of ethical research in humans? Credit: Lana Ruck

Institutional Review Board (IRB)

- Before study, IRB reviews:
  - Informed Consent document(s)
  - IRB application (regulatory info),
  - Research protocol (study description)
- Ongoingly, IRB reviews:
  - Safety events (local patient injury and deviation from the protocol)
  - Data Safety Monitoring Board reports (summaries of all safety events and new information re premise).

Case Study: Human Subjects

Because of excitement over Potti's original findings, Duke quickly began clinical trials on patients selected for certain chemotherapies based on their genetic signatures. Trials were momentarily suspended following Perez' "Research Concerns" memo. After deciding that the investigators had only "a difference of scientific opinion," Perez' concerns and those of external scientists at MD Anderson and the National Cancer Institute (NCI) were essentially disregarded and treatment trials were resumed.

Case Study: Human Subjects

The funder, NCI, began to question the clinical trials and asked Duke to conduct an independent review of the data and Potti's paradigm to address the controversy. The Duke Institutional Review Board (IRB) stopped the trials, and an independent panel was assembled.

The panel was given some relevant information to assess; however, key details about the statistical method and the most recent public criticisms were held back from the panel at Nevins' request to avoid biasing the panel.

In the end, the panel was only able to examine data handed over by Potti and concluded in support of him, stating "we believe the predictors are scientifically valid." Trials resumed.

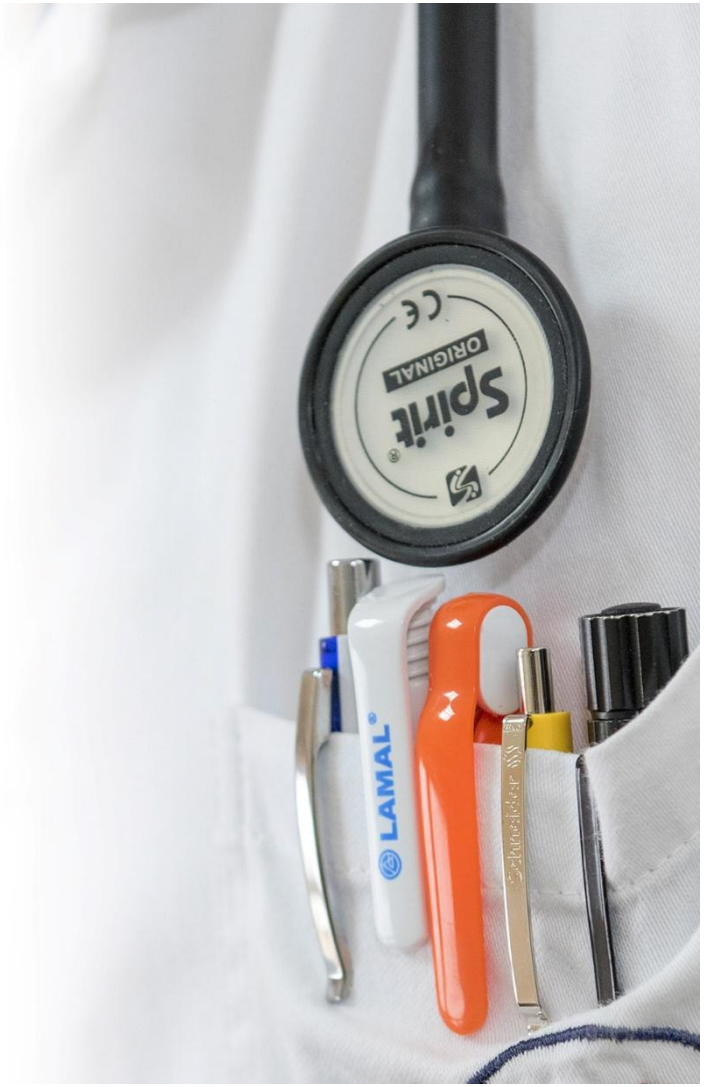
NCI expressed concerns based on dissent within the scientific community about the trial. What issues would make you want to halt a trial early?

Nobody has responded yet.

Hang tight! Responses are coming in.

What is a Conflict of Interest (COI) in Research?

- Competing professional or personal interests that make it difficult to conduct research impartially
- Applies to individuals and institutions
- The appearance or perception of impropriety can undermine public confidence in scientific results, when it looks like bribery or self-promotion



Examples of Financial COI in Research

Research team member conducts research sponsored by a company, and…

- Remuneration for Services
- Consulting
- Speaking
- Advisory board member
- Expert opinion or testimony
- Relationship
- Family ties
- Ownership
- Owner/partner of start-up company
- Owner/partner on patent or license for company's product
- Stock ownership in company
- Member of company's board of directors

How is a financial CoI in research managed?

- The institution reviews, monitors, and manages the research process to minimize or eliminate bias or the appearance of bias
- Formal, written management plan
- Remove the interested party from crucial activities in the conduct of the research and/or provide oversight by non-conflicted individuals in key decision-making:
  - Data acquisition and interpretation; Subject enrollment; Informed Consent process of human subjects; Supervision of students/trainees; financial decisions

Case Study: Conflict of Interest

There were several financial stakeholders involved. Potti had already applied for patent protection to market his computational prediction models. Nevins and their employer, Duke University, also had plans for a financial tie-in. In addition, Nevins had close relations with pharmaceutical firms as a consultant and speaker. Three clinical trials were started at Duke using the computational model to predict the best chemotherapeutic treatment for a given cancer patient. These trials were funded by the National Cancer Institute.

Case Study: Commercial Collaborations

Academia traditionally values open sharing of research results via timely publication to hasten overall progress. Commercial research and development enterprises share much less information in order to profit from intellectual property. In practice, these lines are often less clear.

What are the benefits of collaborations and financial ties between academics and commercial entities (e.g. pharmaceutical companies)?

Nobody has responded yet.

Hang tight! Responses are coming in.

What are the potential harms of collaborations between academic researchers and commercial entities?

Nobody has responded yet.

Hang tight! Responses are coming in.

Case Study: External and Internal Criticism

Scrutiny of Potti himself was fairly low until an anonymous tip in 2010 pointed out that Potti lied on his resume by falsely claiming to be a Rhodes Scholar.

In addition, a groundswell of concern in the research community outside Duke led several prominent biostaticians to write a letter to then NCI director, Harold Varmus, calling for the trials to be suspended until their concerns could be fully addressed.

Case Study: Research Misconduct

A second, much more detailed, peer review revealed several crucial problems:

(1) Data repeats initially identified by Bradford Perez,

(2) Data exclusion, e.g. potentially valid information that wasn't added to the tables presumably because it weakened the correlations,

(3) Data "overfitting", e.g. using too little data establish a pattern,

(4) Failure of the methodology to yield significance when applied to other clinical populations of the same disease process.

Case Study: Finding

Eventually, NIH's Office of Research Integrity concluded these data manipulations were deliberate on Potti's part, which constituted research misconduct. All clinical trials were permanently closed once the scientific premise for the work was discredited.

Out and out research misconduct like this is ultimately rare. Why isn't trust enough even when persons are honest?

Nobody has responded yet.

Hang tight! Responses are coming in.

End of Case

The North Carolina Medical Board reprimanded Dr. Potti but did not suspend his license to practice medicine. Potti left Duke under a cloud and secured a position with a private cancer treatment group in South Carolina. He left there following a critical piece broadcast on 60 Minutes and returned to North Dakota to practice medicine.

Nevins admitted to not having robust checks and balances for the data collected and analyzed in his laboratory and to trusting Potti too much. Professor Nevins retired from Duke in 2013.

Bradford Perez finished medical school and residency at Duke, and is an oncologist in Florida. Potti and Nevins published >40 papers in only 5 years at Duke, and at least 10 were retracted

End of Case

Duke reimbursed the National Cancer Institute $729,000 for the work they had sponsored. The North Carolina Medical Board currently lists 11 settled lawsuits with patients or their families arising from the Potti-Nevins clinical trials at Duke University.

Furthermore, the handling of this case by officials at Duke University has been widely criticized, resulting in a promotion of better practices nationally. Duke University has promoted the use of this case for you use in courses like this.

For your private consideration:

- Under what circumstances might you seriously consider research misconduct? Does it seem impossible now, or could you be tempted by…
  - landing that perfect job?
  - Needing that first big grant?
  - The threat of losing your job/career?
  - Continuing to pay your staff who depend on you?
  - Or do you have personal triggers that you should work on today, so they won't be set off in the future?