Conflicts of Interest

Research Misconduct: Error and Negligence

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MIT RCR Course
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Conflicts of Interest

• Legal term that can vary by specific situation

• Many arise due to government encouragement for agreements between universities and private businesses (e.g. Bayh-Dole Act)

• Macrina: “A conflict of interest (COI) exists when an individual exploits, or appears to exploit, his or her position for personal gain or for the profit of a member of his or her immediate family or household.”

• Wikipedia: “A conflict of interest (COI) is a situation in which a person or organization is involved in multiple interests (financial, emotional, or otherwise), one of which could possibly corrupt the motivation of the individual or organization.”

Another view of COIs

• “A conflict of interest is a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest.”

• Primary interest: “the principal goals of the profession or activity, such as the protection of clients, the health of patients, the integrity of research, and the duties of public office.”

• Secondary interest: “financial gain…the desire for professional advancement and the wish to do favours for family and friends.”

  “Financial relationships…are relatively more objective, fungible, and quantifiable.”

• “The secondary interests are not treated as wrong in themselves, but become objectionable when they are believed to have greater weight than the primary interests.”

MIT policy on COIs

• A conflict of interest (COI) can be any situation in which financial or other personal considerations have the potential to compromise a researcher’s professional judgment and objectivity in the design, conduct or reporting of research.

• MIT policy requires that researchers disclose certain financial interests, which disclosure enables MIT to determine if a financial interest creates a conflict of interest or the appearance of a conflict of interest. The existence of a conflict or the appearance of one does not imply wrongdoing on anyone's part and does not necessarily mean that a researcher may not retain his or her financial interest and undertake the affected research. Some conflicts must be eliminated, but often MIT can work with the researcher to manage a conflict or the appearance of a conflict so that the research can continue in a way that minimizes the possibility of bias in the research and preserves the objectivity of the research. Proper management of a conflict depends on full and prompt disclosure.

• **When in doubt-disclose.**

http://coi.mit.edu/policy
Examples of COIs

- **Gifts and gratuities**
  - Textbook example: gifts from vendors
  - Where do we draw the line? A magnet, a book, a lunch, a Red Sox game…
  - MIT policy: Institute and federal policies prohibit the acceptance of personal gifts or gratuities from vendors, subcontractors, and contractors

- **Compensation**
  - Example: consultantships
  - “A scientist-consultant must not transmit to a private business any information, records, or materials generated as a result of research sponsored by philanthropic foundations or government agencies unless the same information, records, or materials are made readily available to the scientific community in general.”
Examples of COIs

• Multiple pay for one job

• Courseware

• Nepotism
  • Motivation: to ensure equal opportunity to employment
  • Scenario: Dr. Ami and Dr. Eros were independently recruited to Superior University. Dr. Ami and Dr. Eros, after several years of professional association, develop a romantic relationship that leads to marriage. Subsequently, Dr. Eros becomes the head of Dr. Ami’s department. What COI considerations apply to this scenario? What options are available to this two-career family?
Examples of COIs

- **Scientific conflict of interest**
  - How can the following be prevented?
    - Member of an editorial board delays publication by a competitor
    - Reviewer is unfairly critical of a competitor’s manuscript or grant application
    - Scientist who serves as expert witness for pay is accused of a COI and giving misleading information

- **Academic conflict of interest**
  - Example: Wealthy donor wants to influence research directions

- **Institutional conflict of interest**
  - Generally relate to financial interests in the private sector
Examples of COIs

• **Insider trading**
  • Confidentiality agreements attempt to eliminate

• **Equity interests**
  • Companies often started to commercialize research discoveries
  • Early and comprehensive disclosure can help avoid COIs.

• **Institutional prerogatives**
  • “Universities have a strong sense of self-preservation or self-protection when confronted with issues that are likely to have major adverse effects on them.”
How to manage COIs

- MIT requires that COI disclosures (mainly significant financial interests, SFIs) must be created in an online system by each investigator. New disclosures should be added in a timely fashion, and disclosures should be reviewed annually.

- MIT is required to report an SFI to the NIH and include a management plan, if appropriate.
ACS policy on COIs

- The corresponding author must reveal to the editor and to the readers of the journal any potential and/or relevant competing financial or other interest (of all authors) that might be affected by publication of the results contained in the authors’ manuscript. Conflicts of interest and sources of funding of the research reported must be clearly stated at the time of manuscript submission and will be included in the published article. In addition, all authors must declare (1) the existence of any significant financial interest (>5,000 or >5% equity interest) in corporate or commercial entities dealing with the subject of the manuscript; (2) any employment or other relationship (within the past three years) with entities that have a financial or other interest in the results of the manuscript (to include paid consulting, expert testimony, honoraria, and membership of advisory boards or committees of the entity). The corresponding author must advise the editor at the time of submission either that there is no conflict of interest to declare, or should disclose potential conflicts of interest that will be acknowledged in the published article.

http://pubs.acs.org/page/policy/ethics/index.html
Case study

- Ms. Jobs is completing her degree at Research University. She has conducted some successful and exciting research in the laboratory of Dr. Keene. Dr. Keene’s project was supported in part by a research contract with Innovations, Inc. Dr. Keene and the members of his laboratory developed new, rapid, accurate assays that can be adapted to kits for direct sale to the public. Innovations, Inc., is considering developing and marketing these kits but has not made a definite decision. Leaper Enterprises offers Ms. Jobs a position in a new unit of the company to apply her training to develop kits based on the technology that she learned and helped develop in Dr. Keene’s laboratory. Discuss any conflict Ms. Jobs may have in accepting a position in a company that competes with Dr. Keene’s sponsor. How is the situation altered if Ms. Jobs was paid or not paid by funds from Innovations, Inc., while a student?
Case study

• Dr. Zhang is funded by a federal research grant to study the effect of physical tension on the production of hormones by endocrine cells in culture. She is assisted in this project by her research assistant, Mr. Singh. Dr. Zhang and Mr. Singh design a culture dish with a flexible bottom. After the endocrine cells have attached to the flexible bottom of the culture vessel, it is possible to stretch the cells, subjecting them to physical tension. Dr. Zhang wants to purchase 100 of these custom-designed vessels, with immediate delivery. Mr. Singh tells Dr. Zhang that he has two brothers who own a small plastics fabrication business, and they could produce the customized dishes quickly. Dr. Zhang prepares a sole-source purchase request for the custom dishes, at a cost of $7500, charged to her federal grant. The fiscal administrator denies the requisition on the grounds that this purchase constitutes a conflict of interest. Dr. Zhang argues that the selection of this supplier is justified because they are getting a special rate and rapid delivery because of Mr. Singh’s relationship with the company. The issue is brought to you for resolution. Who is affected by this action and how? What are the potential benefits or negative consequences of this transaction?
Conclusion on COIs

• Everyone has numerous discrete interests and responsibilities that are often complicated to manage.

• Conflicts of interest (or the appearance of a COI) should be identified, avoided when possible, and properly managed otherwise.

• Communication with administration is necessary to avoid problems when conflicts of interest occur.
Research Misconduct

- **NIH definition**: Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
- **Research misconduct does NOT include honest error or differences of opinion**.
- **Fabrication**: Making up data or results and recording or reporting them
- **Falsification**: Manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record
- **Plagiarism**: The appropriation of another person's ideas, processes, results, or words without giving appropriate credit
Findings of Research Misconduct

- To make a finding of research misconduct:
  - There be a significant departure from accepted practices of the relevant research community
  - The misconduct be committed intentionally, knowingly, or recklessly; and
  - The allegation be proven by a preponderance of the evidence.
- A 6-year statute of limitations exists.
- Punishments (from NIH or institution) include: inability to apply for grants, prohibition from serving on NIH committees, corrections and retractions of publications, termination of a grant, recovery of funds, loss of employment
- An appeals process exists.

http://grants.nih.gov/grants/research_integrity/research_misconduct.htm
Motivations Behind Misconduct

• David Goodstein (Caltech): “In the cases of scientific fraud that I have looked at, three motives, or risk factors have always been present. In all cases, the perpetrators,
  • were under career pressure;
  • knew, or thought they knew what the answer would turn out to be if they went to all the trouble of doing the work properly, and
  • were working in a field where individual experiments are not expected to be precisely reproducible.”

• Usually, motives are self-interested.

http://www.its.caltech.edu/~dg/conduct_art.html
How Common is Research Misconduct?

- 2005 survey of thousands of NIH-funded scientists:

<table>
<thead>
<tr>
<th>Top ten behaviours</th>
<th>All</th>
<th>Mid-career</th>
<th>Early-career</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Falsifying or ‘cooking’ research data</td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>2. Ignoring major aspects of human-subject requirements</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
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<td>3. Not properly disclosing involvement in firms whose products are based on one's own research</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
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<tr>
<td>4. Relationships with students, research subjects or clients that may be interpreted as questionable</td>
<td>1.4</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>5. Using another’s ideas without obtaining permission or giving due credit</td>
<td>1.4</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>6. Unauthorized use of confidential information in connection with one’s own research</td>
<td>1.7</td>
<td>2.4</td>
<td>0.8 ***</td>
</tr>
<tr>
<td>7. Failing to present data that contradict one’s own previous research</td>
<td>6.0</td>
<td>6.5</td>
<td>5.3</td>
</tr>
<tr>
<td>8. Circumventing certain minor aspects of human-subject requirements</td>
<td>7.6</td>
<td>9.0</td>
<td>6.0 **</td>
</tr>
<tr>
<td>9. Overlooking others’ use of flawed aspects or questionable interpretation of data</td>
<td>12.5</td>
<td>12.2</td>
<td>12.8</td>
</tr>
<tr>
<td>10. Changing the design, methodology or results of a study in response to pressure from a funding source</td>
<td>15.5</td>
<td>20.6</td>
<td>9.5 ***</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other behaviours</th>
<th>All</th>
<th>Mid-career</th>
<th>Early-career</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Publishing the same data or results in two or more publications</td>
<td>4.7</td>
<td>5.9</td>
<td>3.4 **</td>
</tr>
<tr>
<td>12. Inappropriately assigning authorship credit</td>
<td>10.0</td>
<td>12.3</td>
<td>7.4 ***</td>
</tr>
<tr>
<td>13. Withholding details of methodology or results in papers or proposals</td>
<td>10.8</td>
<td>12.4</td>
<td>8.9 **</td>
</tr>
<tr>
<td>14. Using inadequate or inappropriate research designs</td>
<td>13.5</td>
<td>14.6</td>
<td>12.2</td>
</tr>
<tr>
<td>15. Dropping observations or data points from analyses based on a gut feeling that they were inaccurate</td>
<td>15.3</td>
<td>14.3</td>
<td>16.5</td>
</tr>
<tr>
<td>16. Inadequate record keeping related to research projects</td>
<td>27.5</td>
<td>27.7</td>
<td>27.3</td>
</tr>
</tbody>
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Note: significance of $\chi^2$ tests of differences between mid- and early-career scientists are noted by ** $(P<0.01)$ and *** $(P<0.001)$.

Fabrication: Marc Hauser

- Evolutionary biologist Marc Hauser resigned from Harvard in 2011 after being found guilty of scientific misconduct. He had been considered a leader in his field.
- A federal report alleged that:
  - “Hauser fabricated data in a 2002 *Cognition* paper that was later retracted, which examined monkeys’ ability to learn patterns of syllables. He never exposed monkeys to a particular sound pattern described in the experiment, despite reporting the results in a graph.”
  - “In two experiments, researchers measured monkeys’ responses to patterns of consonants and vowels, a process called “coding” their behavior. Hauser falsified the coding, causing the results to pass a statistical test used to ensure that a particular finding was not just a chance result. Colleagues coding the same experiments came up with different results. Hauser “acknowledged to his collaborators that he miscoded some of the trials and that the study failed to provide support for the initial hypothesis,” the report said.”

Fabrication: Marc Hauser

• “[Cognition editor Gerry] Altmann said that Hauser had made positive contributions to his field, but that the shortcuts described in his experiments were unacceptable. Informally, he said, the field now recognizes some of his findings—such as the one that was retracted from the journal Cognition in 2010—as unlikely to be successfully repeated, but no formal investigation is planned of his vast body of work.”

• How does fabrication affect a researcher’s reputation?

• Hauser has neither denied nor admitted to research misconduct, only “mistakes.” What responsibilities should researchers have in the wake of misconduct allegations?
Falsification: Duke Cancer Study

• In 2006, Anil Potti and Joseph Nevins published a paper in *Nature Medicine* (doi:10.1038/nm1491) describing “gene expression signatures that predict sensitivity to individual chemotherapeutic drugs.”

• In 2009, Keith Baggerly and Kevin Coombes published a paper in *The Annals of Applied Statistics* (doi:10.1214/09-AOAS291) that described errors in several of Potti Nevins’s studies:
  • “Poor documentation hid an off-by-one indexing error affecting all genes reported, the inclusion of genes from other sources, including other arrays (the outliers), and a sensitive/resistant label reversal.”
  • “Poor documentation led a report on drug A to include a heatmap for drug B and a gene list for drug C.”
  • Conclusion: “The most common problems are simple.”

• In 2010, *The Cancer Letter* reported that Anil Potti falsely claimed to be a Rhodes Scholar. This report prompted an investigation by Duke that eventually leads to Potti’s resignation, numerous retractions, and an active legal case by patients against Duke.

http://www.cancerletter.com/downloads/20100803_9
Falsification: Duke Cancer Study


• How should such a report be handled by administrators? How can a culture in which whistleblowing is encouraged be fostered?

• When scientific misconduct directly impacts human subjects, how quickly should they be informed?

• What motivations did Potti, Nevins, and Duke have to continue the studies?
Plagiarism: ACS definition

- ACS journals adhere to the U.S. National Science Foundation definition of plagiarism as “the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit” (45 Code of Federal Regulations, Section 689.1). Authors should not engage in plagiarism - verbatim or near-verbatim copying, or very close paraphrasing, of text or results from another’s work. Authors should not engage in self-plagiarism (also known as duplicate publication) - unacceptably close replication of the author’s own previously published text or results without acknowledgement of the source. ACS applies a “reasonable person” standard when deciding whether a submission constitutes self-plagiarism/duplicate publication. If one or two identical sentences previously published by an author appear in a subsequent work by the same author, this is unlikely to be regarded as duplicate publication. Material quoted verbatim from the author’s previously published work must be placed in quotation marks. In contrast, it is unacceptable for an author to include significant verbatim or near-verbatim portions of his/her own work, or to depict his/her previously published results or methodology as new, without acknowledging the source.

http://pubs.acs.org/page/policy/ethics/index.html
Euphemisms for Plagiarism

• From *Critical Reviews in Environmental Science and Technology*, “contains language from already published sources without using proper citation methods”.
• From the *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, “unattributed overlap”.
• From *International Cardiology*, “a duplicate of a paper that has already been published” – by other authors.
• From *Landslides*, a “significant originality issue”.
• From *Chemistry – A European Journal*, “the paper was constructed by copying a number of passages from the paper entitled…The authors apologize for this approach.”
• From *Plant Physiology and Biochemistry*, “Some sentences…are directly taken from other papers, which could be viewed as a form of plagiarism.”
Plagiarism: quotations

- **PNAS paper (May 2012):** Structural basis for substrate specificity and catalysis of human histone acetyltransferase 1

- **Correction (Nov. 2013):**

  The authors note that the review article by M. R. Parthun (ref. 11) provided an excellent summary of the structure and biochemical function of HAT1 as a histone acetyltransferase, and served as background introduction for our study. As such, description of some of the specific biochemical functions of HAT1 was not appropriately noted in our article and should be cited and quoted in the following sections:

  On page 8925, left column, second paragraph, lines 11–15, “In vitro, HAT1 specifically acetylates Lys5 and Lys12 of free (nonnucleosomal) histone H4, and “this specificity is entirely consistent with the pattern of acetylation found on newly synthesized histone H4” from many organisms (11).”

  On page 8925, left column, second paragraph, lines 18–22, “The p46/48 protein “is a WD40 repeat protein” involved in “a wide variety of chromatin-modifying complexes” (11). In yeast, “the association of HAT2 with HAT1 increases the catalytic activity of” HAT1 “by a factor of 10 and appears to function by increasing” HAT1 binding to histone H4 (2, 11).”

  On page 8925, right column, first full paragraph, lines 8–10, “Once in the nucleus, the HAT1–HAT2 H3–H4 complex becomes associated with the histone chaperone/chromatin assembly factor HIF1 to form the NuB4 complex” (11).”

  On page 8930, left column, first full paragraph, lines 1–9, “Because of the important role of HAT1 in chromatin assembly, “a number of studies have begun to link HAT1 to” different types of human cancer (11). “The levels of HAT1” have been found “to increase substantially in liver tumors” (11, 29). Also, “HAT1 mKNA and protein levels are elevated in primary and metastatic human colon cancer tissues” (11, 30). In addition, immunohistochemical studies show that HAT1 is primarily nuclear in normal cells, but the localization of HAT1 largely shifted to cytoplasm in the tumor tissues (11, 30).”

  Additionally, Campos, et al. (ref. 12) should be quoted in the following section:

  On page 8925, right column, first full paragraph, lines 10–16, “In human cells, “the sNASP chaperone binds H3.1–H4 heterodimers and presents the H4 carboxyl domain to RbAp46,” which “recruits HAT1 activity. After acetylation of histone H4, the complex is stabilized and the histones” are transferred to the ASF1B chaperone. “ASF1B associates with importin-4, and the histones are then transported into the nucleus” (12).”

Plagiarism: quotations

• Mark Parthun: “I brought this plagiarism to the attention of the editors at PNAS and suggested that this manuscript be retracted. After more than a year, PNAS published a correction (http://www.pnas.org/content/110/45/18339.full). This correction lists all of the passages that were plagiarized and simply says that they should have had quotation marks around them. This seems like a woefully inadequate response. PNAS has essentially made plagiarism irrelevant because if you are caught, all you have to do is retroactively say that you should have used quotations. Is this a common practice with journals. I hope not because I think this represents a serious step in the erosion of scientific ethics.”

• PNAS: “In light of recent concerns from the author of the plagiarized text, we are following up with the PNAS authors’ institution.”

• Parthun: “My problem with his response [is] that they are simply passing the buck. I would have thought that PNAS had the ultimate responsibility for the manuscripts that it publishes. I don’t understand why they need Mount Sinai to tell them when something is improper.”

Plagiarism: quotations

• Another correction (Jan. 2015):

Several readers raised allegations of plagiarism concerning the work noted above. The authors note: “The review of this matter was conducted by a subcommittee of the Research Integrity Committee at Icahn School of Medicine at Mount Sinai (New York). The subcommittee did not find that there was plagiarism, but there were findings of inadequate and improper citation of the work of others. Accordingly, we would like to respond and provide corrections to these specific citations as listed below. As this matter was addressed in a previously published correction (1) we will only address newly found issues here.

“On page 8925, right column, lines 2–6, the following section should be quoted: ‘combined with specific mutations in the N terminus of histone H3, caused defects in both telomeric gene silencing and resistance to DNA-damaging agents (7–9). Such defects are reproduced by the substitution of Lys for Arg at position 12 of histone H4, but not at position 5,’ and the article by Poveda and Sendra (2) should be cited.

“We wish to apologize for any confusion caused by these citations. Please be assured that interpretation of the experiments and the conclusions of this PNAS article are not affected by these clarifications.”

• Why was this not considered plagiarism? Should it have been?
• Should the paper have been retracted rather than corrected?

Baltimore/Imanishi-Kari/O’Toole Saga

• David Baltimore: Nobel-prize winning biologist who, while at MIT, co-published article in *Cell* in 1986 with…
• Thereza Imanishi-Kari: Assistant professor focusing on immunology who discovered method for determining the origin of antibodies.
• Margot O’Toole: Postdoc in Imanishi-Kari’s lab who could not reproduce results in *Cell* paper and initiated investigation by discussion with outside scientists. This eventually led to a correction by Baltimore and Imanishi-Kari. Unsatisfied with this outcome, she eventually got in touch with…
• Walter Stewart and Ned Feder: NIH scientists who had participated in misconduct investigations and alerted…
• Rep. John Dingell: Congressman who chaired committee that determined NIH budget. Convinced of scientific misconduct, he enlisted…

Baltimore/Imanishi-Kari/O’Toole Saga

• The secret service: Analyzed lab notebooks and other documents to determine that some notes were misdated and out-of-sequence.

• OSI (Office of Scientific Integrity): Newly-established NIH office that began investigating case simultaneously. Report was leaked in 1991 that discredited Baltimore (now president of Rockefeller University) and Imanishi-Kari.

• Imanishi-Kari refused to retract Cell paper and appealed decision to ORI (Office of Research Integrity, now separate from NIH). She would be unable to apply for government funding if found guilty.

• In 1996, government panel found that no misconduct had been committed.

Baltimore/Imanishi-Kari/O’Toole Saga

• How could the situation have been avoided?

• At what point did the situation get out of control?

• How should/does the public view of science influence our research and how we report it?