

*IRBMED Education Symposium, University of Michigan
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Misconduct & Questionable Research Practices

Goals:

- ✓ Brief history of research misconduct
- ✓ How to think about responsibilities in research
- ✓ Brief summary of important areas

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Case study

When It Comes to Beliefs, Doesn't Believe

Foundation for Lung Cancer: Early Detection, Prevention, and Treatment

- 2006 Study (NEJM)
 - ✓ Cancer early detection study
 - ✓ CT scan vs. X-ray
 - ✓ With CT, 80% of cases could be cured
- Support for research:
 - ✓ Supported in part by the National Institutes of Health (R01-CA-633931, to Dr. Henschke, and R01-CA-78905, to Dr. Yankelevitz); the Department of Energy (DE-FG02-96SF21260, to Dr. Markowitz); the Department of Defense to Dr. Eckman; Department of Health and Mental Hygiene of the City of New York; New York State Office of Science, Technology, and Academic Research; American Cancer Society; Israel Cancer Association; Starr Foundation; New York Community Trust; Rogers Family Fund; Foundation for Lung Cancer: Early Detection, Prevention, and Treatment; Foundation for Early Detection of Lung Cancer; Dorothy R. Cohen Foundation; Research Foundation of Clinic Hirslanden; Clinic Hirslanden; Swedish Hospital; Yad-Hanadiv Foundation; Jacob and Malka Goldfarb Charitable Foundation; Auen-Berger Foundation; Princess Margaret Foundation; Tenet Healthcare Foundation; Ernest E. Stempel Foundation; Academic Medical Development; Empire Blue Cross and Blue Shield; Eastman Kodak; General Electric; Weill Medical College of Cornell University; New York Presbyterian Hospital; Christiana Care Helen F. Graham Cancer Center; Holy Cross Hospital; Eisenhower Hospital; Jackson Memorial Hospital Health System; and Evanston Northwestern Healthcare.
- "No potential conflict of interest relevant to this article was reported."

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Conflicting interests


- March 28, 2008 NY Times*
 - ✓ Did not report study funded by Tobacco company
 - Vector Group (Liggett) → \$\$\$ → Early Screening Foundation
 - ✓ Did not report held patents on CT-scan-related technology
 - Impact/profit: 48M former smokers / 40M current smokers (US)
 - ✓ Did not report others with role in Early Screening Foundation
 - Dean & Vice-Chair Board of Overseers, Weill Cornell Medical College
 - Other researchers
- What decisions could the funding have influenced?
 - ✓ PI and co-PIs interpretation of result—smoking-related lung cancer can be cured
 - ✓ Conflict of Interest Committee, which presumably approved
 - ✓ Financial Office, which oversaw mixing of funds
 - ✓ Dean's agreement to accept
 - ✓ Medical School's policies on accepting grant funds
- Does funding impact research results?

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*see also Paul Goldberg, Cancer Letter Inc. (2008)

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Impact of financial interests



- Bekelman (2003), *JAMA*
 - ✓ Meta-analysis of 37 COI studies (1,000s of trials)
 - ✓ Positive correlation (3.60 OR), industry sponsorship & positive outcomes
- Lexchin (2003), *BMJ*
 - ✓ Meta-analysis of 30 COI studies
 - ✓ Positive correlation (4.05 OR), industry sponsorship & positive outcomes
- Friedman (2004)
 - ✓ 398 publications, *NEJM* and *JAMA*
 - ✓ Correlation (2.35-2.64 OR), industry/positive outcomes
- Conclusion: Funding does affect research findings

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Correcting the record...

- NEJM response (early April):
 - ✓ Two "corrections by authors"
 - COI revision: Vector provided "virtually all of the Foundation's funding"
 - Financial conflict amended to include conflict
- Weill Cornell Medical College statement
 - ✓ WCMC takes seriously the need for transparency and integrity in research and the protection of patients who participate in research studies, and has policies and procedures in place to ensure the highest degree of integrity in the research conducted at WCMC.
- Questions:
 - ✓ Did the policies ensure integrity and protect patients?
 - ✓ Does this case reflect efforts to ensure "highest degree of integrity"?
 - ✓ Are concerns about conflict of interest consistent?


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Case two:



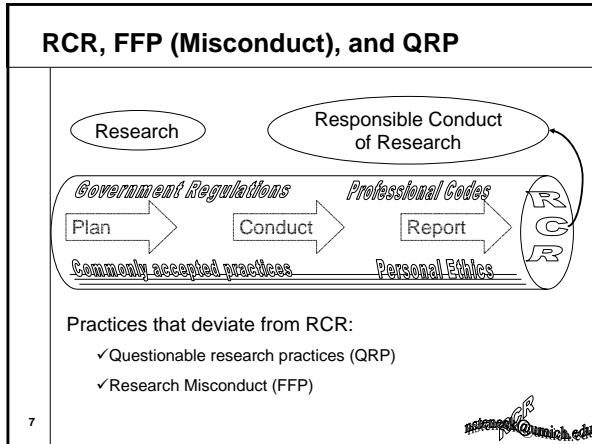
- School drug & alcohol prevention programs
 - ✓ Must be scientifically proven to work to qualify for federal funding
 - ✓ 78% of the "scientific evaluations" included the program developer as an author
 - ✓ 94% of the program developers have a financial relationship with the program distributors
(Source: D Gorman, *Evaluation and Program Planning* 2007)
- Question: what is the difference between these studies and clinical trials?



Professional decisions about responsibility are often inconsistent

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UM sets high standards for integrity

- The University of Michigan is committed to the highest standards of ethical behavior by faculty, staff, and students engaged in the conduct and administration of research and other scholarly activity. As noted in the Policy Statement on Academic Integrity
- **Bad practices (research misconduct) include:**
 - (1) Fabrication of data
 - (2) Plagiarism
 - (3) Abuse of confidentiality
 - (4) Falsification in research
 - (5) Dishonesty in publication
 - (6) Deliberate violation of regulations
 - (7) Property violations
 - (8) Failure to report observed offenses
 - (9) Retaliation

Rules & regulations

- **Must follow**
 - ✓ National regulations
 - ✓ State regulations
 - ✓ Institutional regulations
 - ✓ Journal policies
- **Should follow**
 - ✓ Guidelines
 - ✓ Commonly accepted practices
 - ✓ Laboratory policies

Rules and regulations will not answer all questions

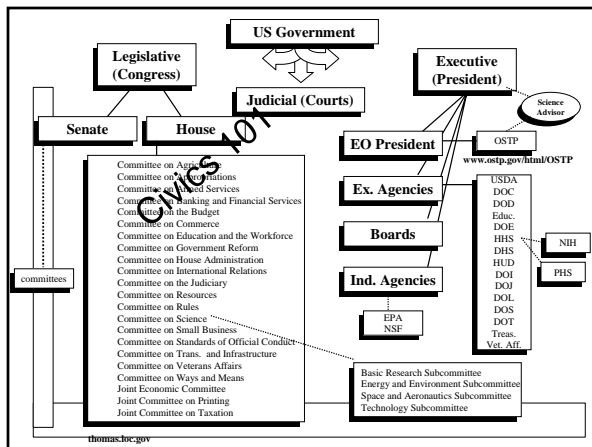
Diverse standards for responsible behavior

- **Nine core areas:**

Misconduct	Collaboration
Human subjects	Mentoring
Animal subjects	Publication
Conflict of Interest	Peer review
Data management	
- **Other areas**

Lab safety	Biohazards
Grant management	Radioactive materials
Workplace rules	Stem cells
IT rules	

Rules are complicated & sometimes conflict



Researchers' approach to misconduct

- Misconduct emerged as issue in late 1970s
- Community reaction to the situation:
 - ☆ Serious misconduct is rare
 - ⊙ Self-regulation keeps in check
 - ⊙ Misconduct is difficult to detect
 - ⊙ Misconduct cannot be prevented
 - ⊙ Apart from misconduct, standards for integrity in research are high
- Reaction based on hypothesis & "experience"
 - ✓ Supporting evidence was weak, absent, or contradictory
 - ✓ Recent research suggests most of the early assumptions were inadequate or wrong


Policy paradox (US)

Definition of misconduct has narrowed

- ✓ Serious deviation from accepted practice ... to
- ✓ FFP that deviates from accepted practice

Evidence of scope of misconduct has broadened

- ✓ 1980s, major cases dominated the news and policy making
- ✓ Today, other "questionable research practices" recognized

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Changing definition of Misconduct

- 1986-HHS:
 - ✓ (1) serious deviation, such as fabrication, falsification, or plagiarism, from accepted practices in carrying out research or in reporting the results of research; or (2) ...
- 1987 NSF:
 - ✓ (1) fabrication, falsification, plagiarism, or other serious deviation from accepted practices in proposing, carrying out, or reporting results from research; (2) ...
- 2000 OSTP
 - ✓ Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results
 - ✓ [must be a] significant departure from accepted practices of the relevant research community

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Shift to proactive approach ~ training

- 1980s, RCR assumed, no special training needed
- 1989, first national recommendation:
 - ✓ IOM, *The Responsible Conduct of Research in the Health Science*
- 1989, first required training:
 - ✓ NIH/ADAMHA Training Grant Requirement
 - ✓ Recommended cover six key areas (1994)
- **Impact**
 - ✓ Increase in number of courses and web programs
 - ✓ Development of an "RCR community"
 - ✓ Increase in resources: textbooks, course outlines...


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Effort peaks in 2000

- NIH, *Required Education in the Protection of Human Research Participants (2000)*
- PHS, *Policy on Instruction in the Responsible Conduct of Research (2000)*
 - ✓ All PHS-funded research
 - ✓ All research staff
 - ✓ 9 core areas
- NSF required RCR on IGERT awards
 - ✓ Must include: "instruction in ethics and the responsible conduct of research"
- 2007 America Competes
 - ✓ NSF must provide RCR and mentoring

Core Areas


1. Data acquisition, management, sharing, and ownership
2. Mentor/trainee responsibilities
3. Publication practices and responsible authorship
4. Peer review
5. Collaborative science
6. Human subjects
7. Research involving animals
8. Research misconduct
9. Conflict of interest and commitment

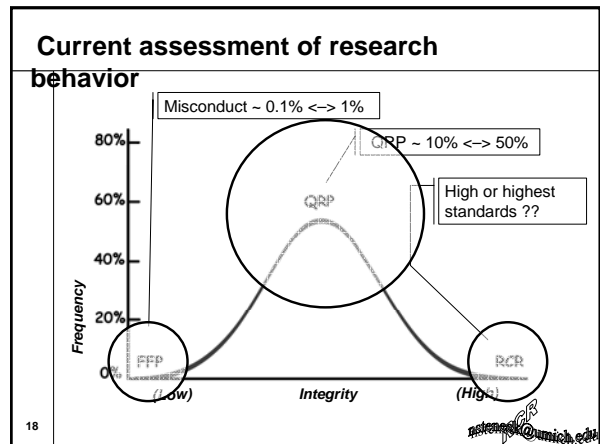
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Institutional Commitment


- **Sentencing guidelines for white collar crime (US):**
 - ✓ ... take reasonable steps to communicate periodically and in a practical manner ... standards and procedures, and other aspects of the compliance and ethics program ... by conducting effective training programs
 - ✓ Organizations must:
 - ensure that the organization's compliance and ethics program is followed, including monitoring and auditing to detect criminal conduct;
 - evaluate periodically the effectiveness of the organization's compliance and ethics program; and
 - have ... a system, ... whereby the organization's employees ... may report ... potential or actual criminal conduct without fear of retaliation.
- **Can university research programs meet these standards?**

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Flagrant cases are well known

- Flagrant misbehavior = misconduct = FFP
 - Fabrication, falsification, & plagiarism
- FFP have significant short-term impacts
 - Damages the image of science/research
 - Waste funds & time (€10s M/case)
 - Undermines validity
- Long-term impact less significant
 - Are caught & the record corrected
 - Occasional fines & penalties
- Covered by both University & Federal regulations
- Some protection for whistleblowers




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What is known about prevalence?

Scientists behaving badly

To protect the integrity of science, we must look beyond falsification, fabrication and plagiarism, to a wider range of questionable research practices, argue Brian C. Martinson, Melissa S. Anderson and Raymond de Vries.


- Martinson, *Nature* (June 2005)
 - Goal: factors that influence research behavior
 - Method:
 - Developed peer-based list of major offenses
 - Survey to 6,000+ researchers (3,000+ response)
 - Major question: "have you done ... in last three years?"
 - Results
 - Major offenses, ca. 0.3%
 - Questionable Research Practices (QRP) ca. 5-15% or higher



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Studies continued

- Gardner, *Contemporary Clinical Trials* (2005)
 - Authors pharmaceutical clinical trials (64% response)
 - 1% reported target article misrepresented the research
 - 5% reported fabrication in a study they had participated in over the last 10 years
 - 17% knew personally of fabrication in a study over the last 10 years
- Rossner, *Journal of Cell Biology*
 - 11 in 1,100 papers had serious improper digital image manipulation



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Three conclusions:

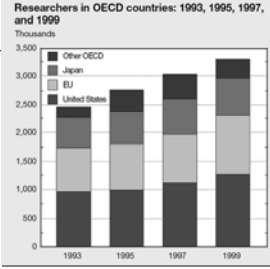


- Research misconduct is not rare:
 - 0.1% - 1% of researchers engage in seriously wrong practices
- Policy makers consistently underestimate the prevalence of misconduct in research
 - Seldom clarify what is meant by "rare"
 - "Rare disease" = 1/250,000 / .0004%
- Most misconduct is not detected / reported
 - Researchers do not report colleagues
 - Journals do not report
 - Institutions are sometimes reluctant to investigate



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Realistic estimates



- Rough approximation:
 - Evidence ~ 1/1,000+
 - Assume ~ 1/10,000
- Cases predicted
 - US ~ 1,500
 - EU ~ 1,000
 - Japan ~ 600
 - Other OECD ~ 400
- Cases seen
 - US ~ 20/year
 - EU ~ 10/year
- Mechanisms for detecting, reporting, investigation and resolving research misconduct need to be improved!

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QRP may be more important

- Can have devastating consequences
 - Improper and unreported conflicts
 - Improper literature review
 - Poor design and/or review
- At a minimum, costly and wasteful
 - Geoffrey Chang retraction
 - Lab did not check work carefully
 - Editors & funders ignored reviewers
 - Who more important than what
- FFP vs. QRP
 - FFP more visible, receives most attention
 - QRP more common / more impact

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Martinson study

Ten Top Behaviors = Federal definition of misconduct

1. Falsifying or 'cooking' research data
2. Ignoring major aspects of human-subject requirements
3. Not properly disclosing involvement in firms whose products are based on one's own research
4. Relationships with students, research subjects or clients that may be interpreted as questionable
5. Using another's ideas without obtaining permission or giving due credit
6. Unauthorized use of confidential information
7. Failing to present data that contradict one's own previous research
8. Circumventing certain minor aspects of human-subject requirements
9. Overlooking others' use of flawed data or questionable practices
10. Changing the design, methodology or results of a study in response to pressure from a funding source

Martinson et al., *Nature* 435 (19 June 2006)

Diagnosis by researchers



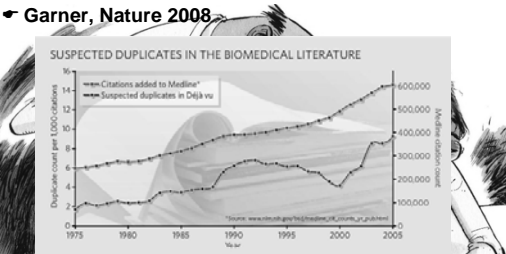
Practices likely to occur & adversely impact research*

83%	Over-interpretation of "significant" findings in small trials
80%	Selective reporting based on p-values
76%	Selective reporting of outcomes in the abstract
75%	Subgroup analyses done without interaction tests
68%	Negative or detrimental studies not published
68%	Putting undue stress on results from subgroup analysis
64%	Inappropriate subgroup analyses
64%	Selective reporting of (i) subgroups (ii) outcomes (iii) time points
60%	Selective reporting of positive results/omission of adverse events
60%	Failure to report results or long delay in reporting
59%	Post-hoc analysis not admitted
56%	Giving incomplete information about analyses with non significant results
54%	Analysis conducted by the sponsor of the trial

*Al-Marsouki, *Contemp Clin Trials* 26(2005)

Duplicate publication

Garner, *Nature* 2008



14/1,000 x 400,000 = 5,600 suspected, 2005
 \$4,000/article x 5,600 duplicates = \$22,400,000

Other problems in publications

- Ghost and honorary authorship
 - Person who wrote the paper is not listed
 - Person who is listed did not contribute to the article
- Bias in abstracts and reviews:
 - Abstracts oversell results, ignore deficiencies
 - Reviews favor reviewer's speciality or country
- Review bias
 - Established researchers get more favorable reviews
 - Institutional importance impacts reviews
- Peer Review Congresses major impetus
 - <http://www.ama-assn.org/public/peer/peerhome.htm#Issues>
 - Article: *JAMA*, June 5, 2002

Citation errors

- Inaccurate information/claim in notes
 - Grouped as major and minor (or)
 - Citational vs. quotational
 - Pre-2000, rates ranged from >10% to <30%
- Recent findings:

Field	All	Major
Otolaryngology (2000)	37.5	11.9
Primary Care/AIDS (2003)		3% / 8%
Manual Therapy (2004)	20 to 59% citational	

Rate appears high & constant

Researchers have mixed views on responsibility

Study of subscription to norms and counternorms*

	Norms	Counternorms
10.8 in principle	Share	Secret
9.1 self	Empirical	Personal
6.5 others	Advance science	Self-interest
5.7 in principle	Skeptical	Dogmatic
6.5 self		
9.2 others		

Researchers...

- Accept both norms & counternorms
- Rate their own acceptance of norms higher than colleagues

* M. Anderson, *JERHRE* 2007

Individual responsibilities?

- Know and understand your responsibilities
- Follow best practices
- Ask if you are not sure something is proper
- Do not ignore problems
- Do not do something just because "everyone does it that way"

Report misconduct and questionable practices

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Reporting is not easy

LESSONS

- Experience of clinical trial coordinators*
 - 18.3%, first-hand knowledge of misconduct prior year
 - 21.9% in academic settings
 - Competitiveness and funding pressures, major cause
 - Perceptions of prevalence
 - Coordinator response?
 - 10.4% do nothing
 - 37.3% object to PI but not report
 - 26.7% ask PI to report if did not
 - 25.7% report to appropriate authority

Failure to take responsibility (to report) is a major problem in research today

Misbehavior	Often	Some
Plagiarism	.2	5.2
Falsifying	.5	4.0
Enrollment violations	1.2	7.5
Procedure violations	1.2	9.1
Selective dropping data	.7	3.7

32 * Pryor, Habermann, Broome, Journal of Medical Ethics 33(2007): 365-369. nsteneck@umich.edu

Consequence of reporting

- Lab director falsifies information in a grant
- Students discover problems, wonder what to do?
- Director says nothing is wrong
- Students discuss what they should do?
- Agree to report the suspected misconduct
- Director resigns
- Outcome for students:
 - 2 - move to another university, start over
 - 1 - drops out, becomes lab tech
 - 1 - goes to law school
 - 2 - shift to a new lab, start new projects

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