The Ethics of Incentives

Subjects and Investigators

Nicholas W. Markin, MD, FASE
Associate Professor
Department of Anesthesiology
University of Nebraska Medical Center

UNMC

Disclosures

- I have no financially relevant third party relationships

Objectives

- Describe the ethical and moral role of the IRB in Human Subject Research
- Explore the ethics of various forms of incentives to subjects participating in Human Subject Research
- Discuss ethical issues associated with providing investigators with compensation for performing research

Introduction

- Protocol reviews that generate controversy
- Generally an issue of perceived ethical concern
- Why did some of the situations result in controversy and not others?

Medical Ethics

- 4 Principles for medical ethics:
  - Autonomy - individuals in action, thought and intention
  - Justice - fair distribution of resources, risks and benefits
  - Beneficence - intention of doing good
  - Non-maleficence - avoidance of doing harm

https://web.stanford.edu/class/siw198q/websites/reprotech/New%20Ways%20of%20Making%20Babies/EthicVoc.htm

Intentions

- Intentions are the key (foresight, cause, desire, moral responsibility, motive)
- What are the intentions of the various agents involved in the research process?
- Actions should mirror intentions but intentions are first
  - Consent is a good example

Role of the IRB

- What is the IRB asked to do?
- The IRB is tasked with the protection and welfare of human subjects for biomedical research
- Review: Scientific, Ethical and Regulatory
- The IRB is the Ethical Review Board for human subject research and they apply the criteria for approval when reviewing research protocols and applications

History of Human Subject Research

- Prior to the Pure Food and Drug Act of 1906, no regulations about human subject research
    - Atrocities throughout history
- In 1948 the Nuremburg Code was established secondary to Nazi doctors experimenting on prisoners
- FDA Control in 1962 after the widespread use of Thalidomide in Europe
- US Public Health Service Syphilis Study - intentionally not treating subjects and following longitudinally

http://ors.umkc.edu/research-compliance/institutional-review-board-(irb)/history-of-research-ethics

History of Human Subject Research

- Declaration of Helsinki, first in 1964, provides ethical guidance on human subjects research
    - Lab and animals first, IRBs, informed consent, conducted by people who know what they are doing and benefits outweigh the risks
- National Research Act (1974) put forth rules that govern human subject research in the US
- The Belmont Report is published in 1979

http://ors.umkc.edu/research-compliance/institutional-review-board-(irb)/history-of-research-ethics

Belmont Report

- Summary of the Basic Ethics Principles that should dictate the conduct of Human Subjects Research

- Basic ethical principles that should assist in finding solutions to ethical problems with human research:

  - Respect for Persons - autonomy and consent

  - Beneficence - benefits outweighs the risks

  - Justice - fair selection of subjects (risks and benefits)

https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

What is the role of IRB?

- The role of the IRB is to protect human subjects
- This is accomplished by applying standards and principles to the reviews conducted and prevent situations in which subjects may be treated in a unethical manner

Ethics of Incentives

- Why do we need incentives?
  - Shouldn’t the moral imperative for research be sufficient to drive ethical behavior?
- How do these incentives influence individuals to make decisions that they would otherwise not make?
  - Specifically, decisions that go against their own principles such as honesty or integrity?
- Society expectation? “Time is money”

Definitions

- Incentive - A thing that **motivates** or encourages one to **do something**.

- Compensation - Something, typically money, awarded to someone as a recompense for loss, injury, or **suffering**.

- Rewards - A thing given in recognition of one's **service, effort**, or achievement.

-

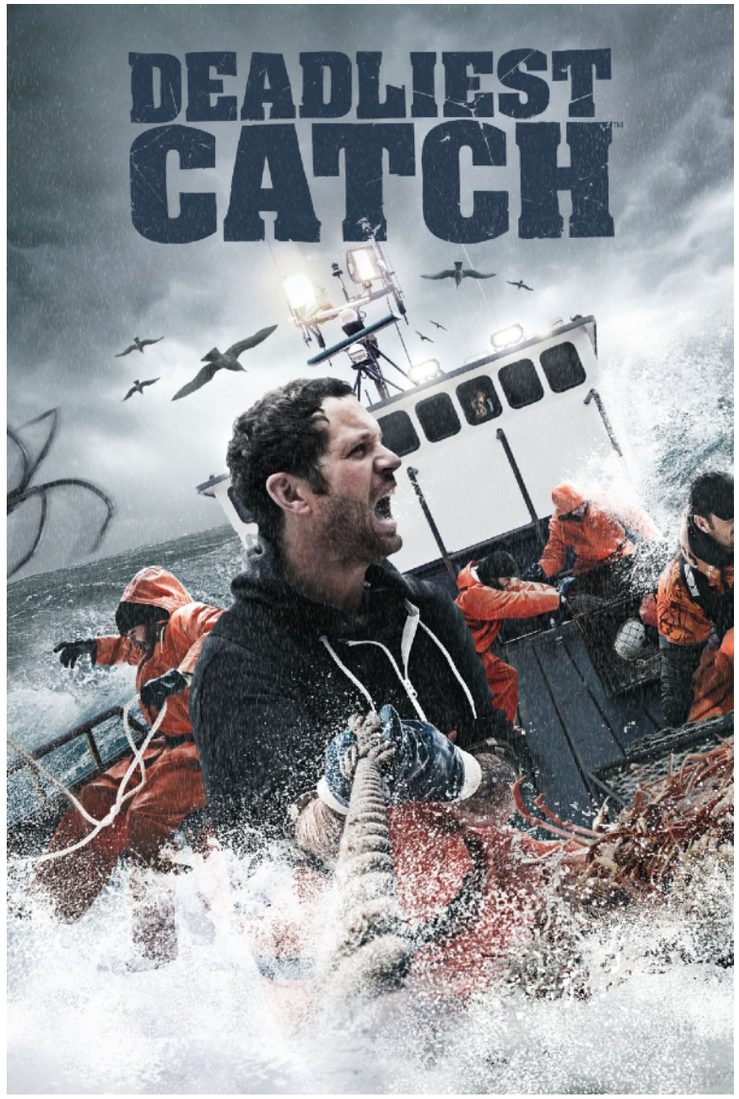
Definitions (cont.)

- Coercion - the practice of **persuading** someone to do something by using **force or threats**.

- Undue Influence (Dickert and Grady) - occurs when an incentive is so attractive that it causes people to ignore their personal values or preferences in order to participate in the research.

Undue Influence?

$$$



Why Worry?

- IRB members surveyed for their opinion about the use of incentives
- 87% of IRB members were concerned about “substantial” payments
- Concerns focused on whether it would lead to enrollment in a study that the subject would otherwise not participate

Largent et. al. IRB 2012

Incentives vs. Coercion

- Alderson & Morrow (2004): The standards of the 1947 Nuremberg Code state that no persuasion or pressure of any kind should be put on participants.

- Incentive payments can be seen as coercive – or as exerting undue influence on potential participants' decisions about whether to take part in research.

- **Financially disadvantaged groups** may be more vulnerable to this kind of coercion – because they need the money, and so their consent is not truly 'freely given' if payment is involved.

The Ethics of Incentivizing the Uninformed. A Vignette Study

By Sandro Ambuehl and Axel Ockenfels*

PAPERS AND PROCEEDINGS *MAY 2017*

- "When acquisition and processing of information about the transaction is costly, individuals with higher marginal costs of information often respond more to a given increase in incentive"

- My Translation:

  - The harder it is to understand what is going on, the more likely those subjects will participate if the incentives are considered "good" for them

At risk subjects?

- Those subjects that are financially disadvantaged
  - Incentives can become influential
- Those subjects that do not fully understand what is happening with research
  - Cost of information is high

So what is the problem?

- Lively discussion at the IRB meeting is usually a sign that there is an ethical issue getting worked out
    - Risk benefit ratio is a big thing
- Incentives can affect the risk-benefit relationships and there are concerns it could lead to undue influence or coercion
- There are concerns that the research presented could lead to misunderstanding or therapeutic misconception

Incentives that cause Discussion

- Monetary vs. Non-monetary
- Universal vs. Individualized
- Positive Subjective Impact vs. Negative Subjective Impact

Monetary Incentives

- These incentives seem easier for individuals to understand
- Most people make some form of a wage
- Non-Monetary incentives are more challenging
  - They can provide significant influence in the business world
  - They can be difficult to put a price of them

Conditional Incentives

- Universal conditional incentives are things that are benefits to “anyone” in the study

- A trip, a device, an opportunity

- Individual condition-based incentives require the subject to have a specific state

  - free immunotherapy or a free left ventricular assist device

  - These cause less issues because the subject has an undesired condition associated with the research

Subjective Impact

- Studies have different perceived participation costs, both positive and negative
- These could be time in a lab, time away from job/ family/home (potentially negative)
- Altruism (actual positive)
- Or, these could be a subject-based perception that research will be the best form of medicine (positive to subject, not real i.e. therapeutic misconception)

Examples

- Free LVAD - non-transferrable non-monetary
- Free iPhone - transferrable non-monetary
- $100 prepaid card - transferrable monetary

Vignette 1

- Cancer patient getting experimental chemotherapy as part of the BEaT-CanCER Trial.
    - What is the cost to the patient and the overall cost?
    - What are the outcomes? Phase of research?
    - What is the subject's expectation? What is standard of care vs. research?

Vignette 2

- Healthy volunteer getting an invasive procedure performed for a physiology/drug study (femoral arterial line and peripheral IV)
  - How much money should they get? $20/hr
  - Risk vs reward? Why are they doing it? $$$?
  - How much risk for how much reward? Personal risk vs. society reward?

Vignette 3

- Healthy volunteer going to a Costa Rica to climb a mountain for 4 days for minimal-risk research physiology testing
  - No money is changing hands but the location is highly desirable
  - Food is paid for, travel was paid for, no other reimbursement
  - Experience is “transferrable”

Vignette Summary

Cancer Study	Drug Physiology	Exercise Physiology
Non-monetary	Monetary	Non-monetary
Individual Condition	Universal	Universal

Vignette Summary

Cancer Study	Drug Physiology	Exercise Physiology
Non-monetary	Monetary	Non-monetary
Individual Condition	Universal	Universal
+ (-) Subjective Impact	+/- Subjective Impact	- Subjective Impact

Ethical Controversy

- Why is it ok to give someone with a disease free investigational treatment? Is it the non-transferrable aspect?
- How do we avoid the societal perception that research therapies are the “best” and therefore risk of therapeutic misconception is high?
- Why is it ok to pay someone to participate in a study without any benefit to the subject? How would we get this information otherwise?
- Why do no/low risk studies in which non-monetary benefits that are transferrable cause ethical concerns?

Ethical Questions

- The combination of undesirable subject state of health and potentially expensive treatment interventions allows society to feel that the use of resources demonstrates **justice** (if resources), **respect for persons** and **beneficence** in risk-benefit (TM?)

- The combination of healthy subject state and monetary incentive for the time and discomfort with certain studies shows **respect for persons** and **justice** (as long as incentives aren't coercive) and the individual can decide on risk-benefit showing **beneficence.**

- The combination of healthy subjects receiving a desirable non-monetary incentive and little to no issue with participation cost should be perceived as **autonomy** and **justice** (incentive is required for the research) and **beneficence** is preserved as subjects self select for the participation cost regarding risk-benefit

Research Purpose

- the sole purpose of a clinical study is to produce generalizable knowledge, with no possible benefit to the subjects

- the sole purpose of a clinical study is to produce generalizable knowledge, regardless of any possible benefit to the subjects

- the primary purpose of a clinical study is to produce generalizable knowledge, with only the possibility of benefit to the subjects.

Therapeutic Misconception

- Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge

- This is regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial.

Henderson PLoS Med 2007

PERGAMON

Social Science & Medicine 58 (2004) 1689–1697

SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

Therapeutic misconception and the appreciation of risks in clinical trials

Charles W. Lidz[a,*], Paul S. Appelbaum[a], Thomas Grisso[a], Michelle Renaud[b]

[a] *Department of Psychiatry, University of Massachusetts Medical School, 55 Lake Ave North, Worcester, MA 01655, USA*
[b] *Salem State College, Graduate School of Social Work, 352 Lafayette St., Salem, MA 01970-5353, USA*

- 23.9% of subjects could not identify any disadvantages to participating in the study, despite being explicitly told of the risks
- Only 13.5% could report disadvantage related to research design such as randomization and placebo control

Subject Belief of Risk	None	Incidental	Same as standard Treatment	Risk of Exp. Treatment	Risks related to Research Design
% identifying risk	23.9	2.6	14.2	45.8	13.5

Lidz Soc Sci & Med 2004

Therapeutic Misconception Checklist

- Check that the following steps are taken:
  - Informed consent must be given (if not waived).
  - Informed consent and recruitment materials should not promise therapeutic benefit.
  - An IRB must review and approve the informed consent document and protocol, along with any announcements or recruitment materials.
  - The informed consent process should provide enough information for a potential participant to make an informed decision about participation.

Therapeutic Misconception Checklist

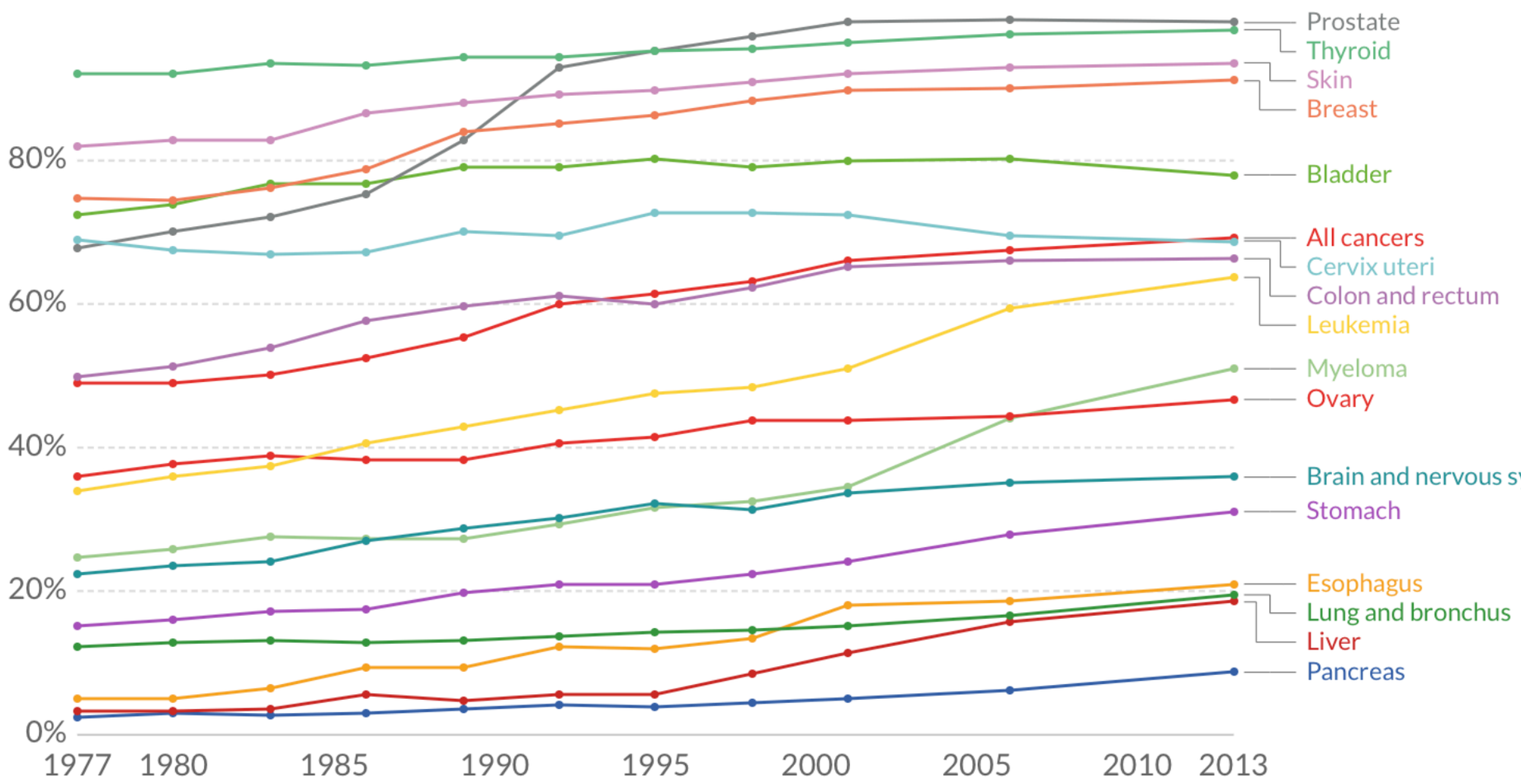
- Check that the following steps are taken:
  - Informed consent must be given (if not waived).
  - Inform[illegible] d not prom[illegible]
  - An IR[illegible] nsent docu[illegible] ments or recruitment materials.
  - The informed consent process should provide enough information for a potential participant to make an informed decision about participation.

Avoid titles, naming conventions or abbreviations that imply a benefit where one may not exist

Five-year cancer survival rates in the USA, All races, total

Percentage of cancer patients surviving at least five years since diagnosis, by cancer type. This data is available to view by sex and race.

Our World in Data



Source: National Cancer Institute

CC BY

1977 2013

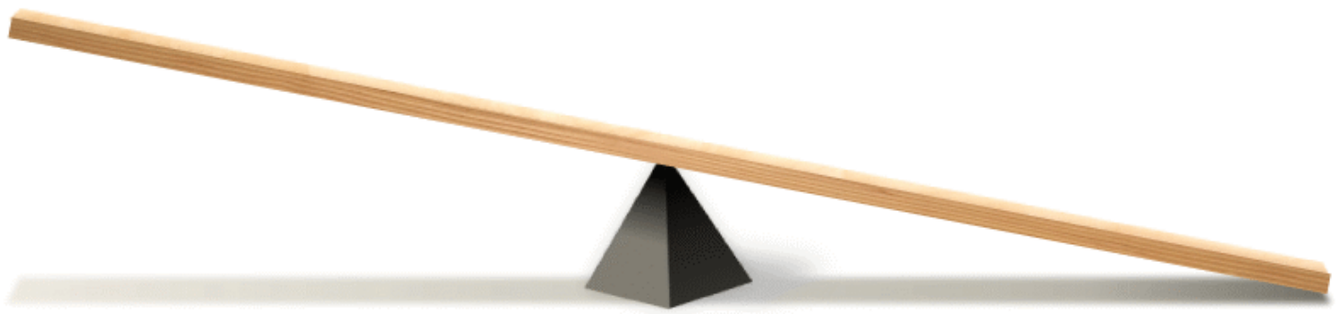
Change sex or race demographic | CHART | DATA | SOURCES

https://ourworldindata.org/cancer

Ethics Evaluation

- Respect for Persons
- Beneficence
- Justice

- Inherent state of the subject
- Types of incentives
- Subjective participation costs



What about investigators?

https://www.pinterest.com/pin/245375879669483509/

Incentives for Investigators?

- Financial market forces at work
- All things considered equal, opportunities to have improved income or improved quality of life drives decisions
- Drives individuals to do something they might otherwise not do
    - Physician-researchers often respond well to incentives

Ethical questions

- What should an investigator reveal to the subjects?
- What if they are also the treating physician?
- What if the investigator has much to gain from the research?
    - Compare this to how we treat investigators who are consultants for third parties involved in research?

Incentives for Investigators

- What are workplace motivators:
  - Challenging Work
  - Recognition
  - Employee Involvement
  - Job Security
  - Compensation

Incentives for Investigators

- What are workplace motivators:
  - Recognition **(Promotion/Fame)**
  - Job Security **(Stability)**
  - Compensation **(Money/Financial Bonuses)**

Promotion & Fame

- Research and publication leads to promotion
- Research and publication can prevent contract renewal problems
- Research and publication can lead to notoriety
- Promotion can lead to tenure and contract stability
- Promotion can lead to increases in salary

Stability

- Grants can lead to stability; funding and location
- Allows research to continue without an undue amount of time placed on seeking additional funding sources
- Focuses the attention of the lab upon the task at hand

Financial Bonuses

- Institutions can provide up to 20-25% of salary as a bonus if sufficient Facility and Administration (overhead) is brought in through federal grants
- Others provide 5% of F&A produced and faculty can receive an additional 10% of salary savings billed to external grant sources
- Can mean a significant increase in salary and a significant incentive for obtaining grant funding
- Academic productivity can result in separate financial bonuses

External Pressures

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https://transformativelearning.nl/2018/12/04/publish-and-perish-how-the-commodification-of-scientific-publishing-is-undermining-both-science-and-the-public-good/

External Pressures

External Pressures

- People write for free
- People review for free
- People want to publish to do well
- Journals need articles to fill their pages
- No shortage of opportunities

The long read

Is the staggeringly profitable business of scientific publishing bad for science?

It is an industry like no other, with profit margins to rival Google – and it was created by one of Britain's most notorious tycoons: Robert Maxwell. By Stephen Buranyi

The core of Elsevier's operation is in scientific journals, the weekly or monthly publications in which scientists share their results. Despite the narrow audience, scientific publishing is a remarkably big business. With total global revenues of more than £19bn, it weighs in somewhere between the recording and the film industries in size, but it is far more profitable. In 2010, Elsevier's scientific publishing arm reported profits of £724m on just over £2bn in revenue. It was a 36% margin – higher than Apple, Google, or Amazon posted that year.

https://www.theguardian.com/science/2017/jun/27/profitable-business-scientific-publishing-bad-for-science

Unintended Consequences

- Incentivizing performance can lead to negative outcomes

- Neff et al. demonstrated that publishing incentives can undermine progress in science by driving publishing practices that have less than ideal outcomes

- changes in methods

- changing target Journals, etc.

Neff Sci & Pub Policy 2018

External Pressures

S **submission@spinesurgeryreposi...**

To: You nmarkin@unmc.edu

Monday, August 19, 13:13

Non-UNMC email

Dear Dr. Nicholas W Markin

We are inviting you to submit your research work it can be "Full Length or Short Length" in our journal Spine and Surgery (SSG)

Please note that **"No Publication Fee"** will be charged if the manuscript is submitted on or before **26th August**.

Submit your manuscript at
submissions@sciencerepository.org

We are waiting for your positive reply. Do contact us for further information.

Thanks & Regards,

Oliver Kukk

AJ **American Journal of Biomedical...**
drugdesigning@biomedgrid.org

To: You nmarkin@unmc.edu

Monday, August 19, 07:49

Non-UNMC email

Dear Professor,

Hope you are doing well.

We are in **shortfall of articles** for successful release of **Volume 4 Issue 5.** Is it possible for you to support us with your **2-page opinion or mini review** for this issue?

We are confident that you are always will be there **to support us**.

Await your positive response.

Best Regards,
Catherine Nichols
American Journal of Biomedical Science & Research | ISSN: 2642-1747

Note: If you are interested to join as an editorial board member in our journal, please send your updated CV to our mail id. We accept eBooks, Video articles & provide reprints also.

Perception is subjective

- HBS reviewed lending practices that lead to financial crisis

- Not only did the financial bonuses lead to bad lending

- The agents actually believed that the loans would work!

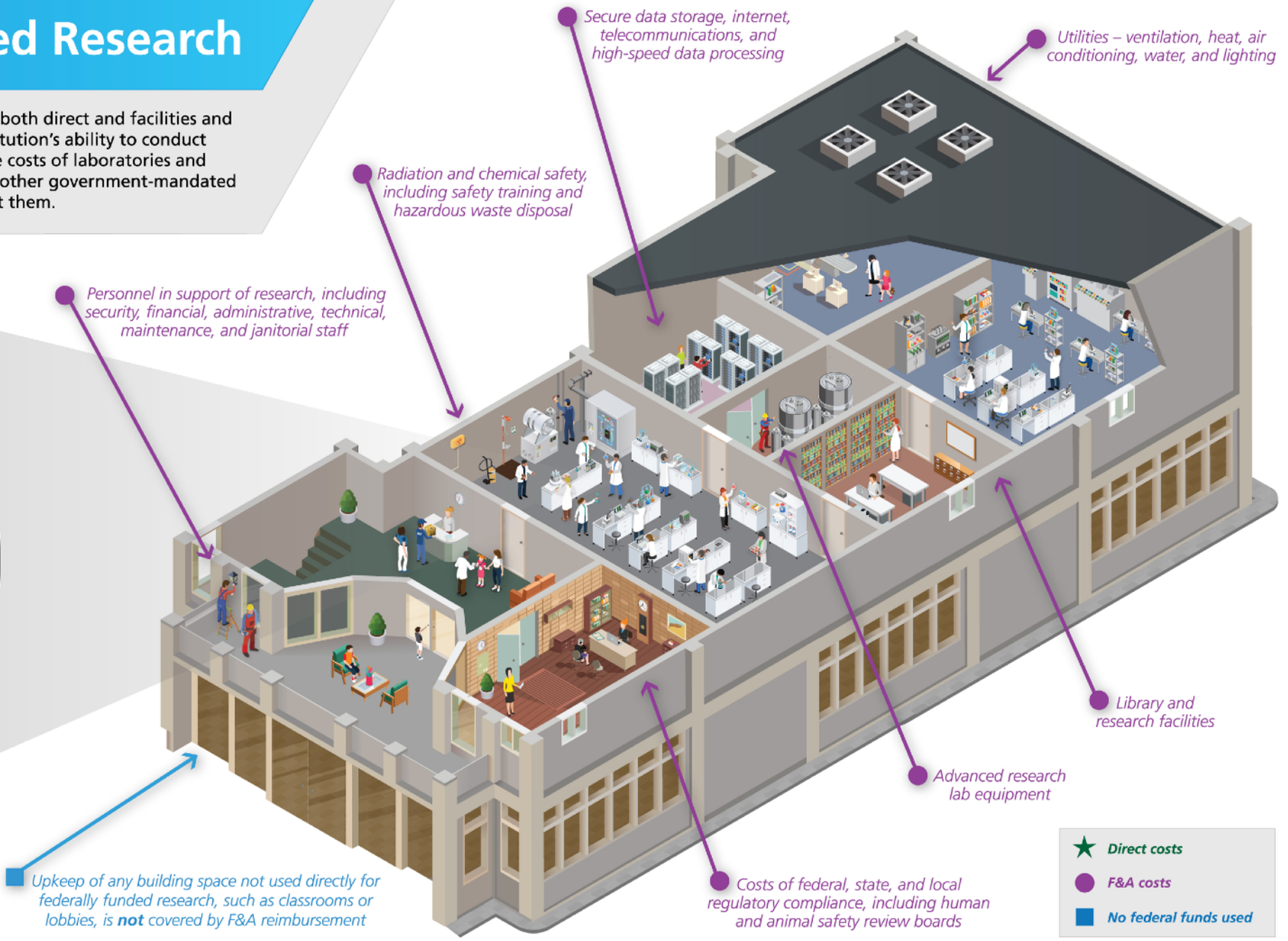
https://www.pinterest.com/pin/253979165054517709/

Research Is NOT Free!

- All this talk about money, grants and compensation but you cannot separate money from research
- For every $1 brought in to NU it cost $1.25-1.45 to do research, despite indirect costs at 52.5%
- Not isolated to Nebraska
- Stanford $1B in grants between 6000 awards, they still pay millions a year in addition to provide support
- Pressure to bring in grant funding to reduce the research cost, this drives the market and successful investigators are rewarded

Costs of Federally Sponsored Research

The total cost of federally sponsored research includes a combination of both direct and facilities and administrative (F&A) costs. Both types of expenditures are key to an institution's ability to conduct cutting-edge research. F&A consists of the construction and maintenance costs of laboratories and high-tech facilities; energy and utility expenses; and safety, security, and other government-mandated expenses. These costs are real and research cannot be conducted without them.



AAMC · Association of American Universities · AIRI Association of Independent Research Institutes · Association of Public & Land-grant Universities · COGR Council On Governmental Relations

How are subjects protected from this?

- IRB also looks at scientific merit and the biological hypothesis that drives the research

- Should help prevent the conduct of questionable research and research that has no scientific merit

    - And therefore has no benefit and cannot have a benefit-favoring risk-benefit relationship

- The IRB makes efforts to avoid ethical conflicts with investigators and subjects

    - Faculty-student relationships or Physician/Investigator- Patient relationships where the investigator has a high-stakes relationship to the research

Bad Apples?

http://www.momentum-assessor.com/?p=12893

Misconduct

EDITORIAL

Scientific Misconduct and Medical Journals

Howard Bauchner, MD; Phil B. Fontanarosa, MD, MBA; Annette Flanagin, RN, MA; Joe Thornton, JD

Although not much is known about the prevalence of scientific misconduct, several studies with limited methods have estimated that the prevalence of scientists who have been involved in scientific misconduct ranges from 1% to 2%.[4-6] Dur-

Bauchner JAMA 2018

Business

Doubts about Johns Hopkins research have gone unanswered, scientist says

By **Peter Whoriskey**
March 11, 2013

The numbers didn't add up.

Over and over, Daniel Yuan, a medical doctor and statistician, couldn't understand the results coming out of the lab, a prestigious facility at Johns Hopkins Medical School funded by millions from the National Institutes of Health.

He raised questions with the lab's director. He reran the calculations on his own. He looked askance at the articles arising from the research, which were published in distinguished journals. He told his colleagues: This doesn't make sense.

"At first, it was like, 'Okay — but I don't really see it,' " Yuan recalled. "Then it started to smell bad."

His suspicions arose as reports of scientific misconduct have become more frequent and critics have questioned the willingness of universities, academic journals and the federal government, which pays for much of the work, to

Washington Post

List of scientific misconduct incidents

From Wikipedia, the free encyclopedia

Scientific misconduct is the violation of the standard codes of scholarly conduct and ethical behavior

- 60 Entries of serious misconduct
- Numerous retractions
- In some cases, an entire area of study was anchored on research from one of these individuals

Biomedical sciences [edit]

- Anna Ahimastos-Lamberti (Australia), a former medical researcher, admitted to fabricating scientific re journal articles about a three-year clinical trial involving a medication used to treat hypertension were
- Bharat Aggarwal (US), a former Ransom Horne, Jr. Distinguished Professor of Cancer Research at th fraud was discovered in 65 papers published by him in the area of curcumin as a treatment for cancer.
- Elias Alsabti (Iraq, US), was a medical practitioner who posed as a biomedical researcher. He plagiari co-authors.[10][11][12]
- Piero Anversa (US, Italy) and Annarosa Leri (US, Italy), collaborators and former researchers at Harva data in their research on endogenous cardiac stem cells, and to have included "false scientific informa Brigham and Women's Hospital paying a $10 million settlement to the US government, and pausing a many failed replications of their work, Harvard University and Brigham and Women's Hospital called fo December 2018, 14 of Anversa and Leri's publications have been retracted.[17] Anversa and Leri lost a damaged their reputations.[18]
- Edward Awh and graduate student David Anderson (US), formerly of the University of Oregon, retract identified by The Scientist (magazine) as a Top 10 Retraction of 2015.[21]
- Werner Bezwoda (South Africa), formerly of the University of Witwatersrand, admitted to scientific mis "committed a serious breach of scientific honesty and integrity."[22][23][24]
- Philippe Bois (US), chief science officer at Algafeed and former postdoctoral fellow in biochemistry at image to conceal unwanted results in a retracted[25] 2005 paper published in *Journal of Cell Biology*, a *Cellular Biology*.[26][27]
- Joachim Boldt (Germany), an anesthesiologist formerly based at the Justus Liebig University Giessen research studies.[28] Boldt has had 96 of his publications retracted.[29]
- C. David Bridges (US), a researcher at Purdue University and formerly at Baylor College of Medicine, manuscript that Bridges had been asked to review, and used that information to produce and publish egregious misconduct of science that undermines the entire concept and practice of scientific experim funding.[33]
- Silvia Bulfone-Paus (Germany, UK), an immunologist at the Research Center Borstel and the Universi alleged scientific misconduct involving image manipulation.[34][35]

https://en.wikipedia.org/wiki/List_of_scientific_misconduct_incidents

OPEN ACCESS Freely available online

PLoS one

How Many Scientists Fabricate and Falsify Research? A Systematic Review and Meta-Analysis of Survey Data

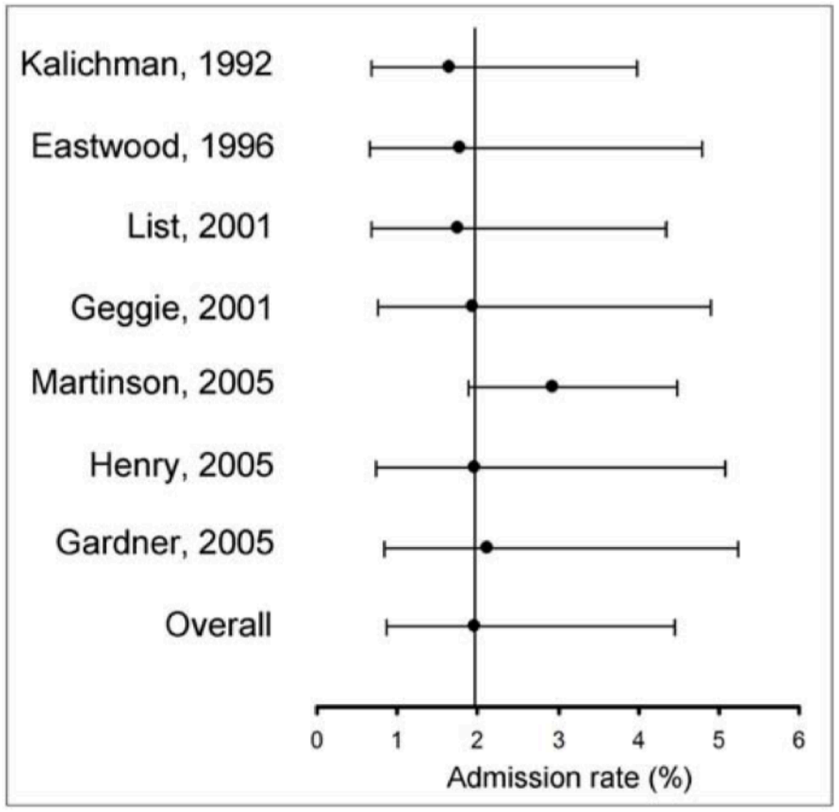
Daniele Fanelli*

INNOGEN and ISSTI-Institute for the Study of Science, Technology & Innovation, The University of Edinburgh, Edinburgh, United Kingdom

- 2% of researchers falsify data

- 3.4% Post-docs admitted to falsifying data

- Up to 81% were “willing to select, omit or fabricate data to win a grant or publish a paper”



Fanelli PLoS One 2009

Why misconduct?

- When you see people do unscrupulous things, such as falsifying research data, it must be done for one of the underlying workplace motivators:
  - Challenging Work
  - Recognition
  - Employee Involvement
  - Job Security
  - Compensation

Why misconduct?

- When you see people do unscrupulous things, such as falsifying research data, it must be done for one of the underlying workplace motivators:
  - ~~Challenging Work~~
  - Recognition **(Promotion/Fame)**
  - ~~Employee Involvement~~
  - Job Security **(Stability)**
  - Compensation **(Money)**

Ethics in Disclosures?

- Should researchers have to disclose to subjects what happens when they do research?
- Is there not a potential for conflicts of interest if there are potential financial results?
- Monetary vs. non-monetary?
- What about job security and promotion?

Intentions

- Intentions from the investigator towards the subjects
- Intentions of the subjects for the research
- Intention of the investigator towards the research
- Intention of the institution towards the research

Summary

- Compensation and incentives should promote and reward virtuous behavior
- Our job to identify issues in Autonomy, Beneficence and Justice.
- Intention is the key to determining the motive for participation in research; both subjects and investigators
- Moral imperatives to participate in research that benefits society may be insufficient to drive fair and adequate enrollment
- Society operatives with substantial financial drivers that place pressure on individuals to make decisions that make “financial” sense over morals at times. (both subjects and investigators)
- It is likely that the participation in research may result in some degree of moral injury, to both parties, when compensation is involved but it is unlikely that any significant and impactful biomedical research will be performed without any forms of compensation

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