IF I’M INTERESTED, WHY IS IT A CONFLICT?
Overview

- Define Conflicts of Interest
- Consider the effects of COI on research
- Propose that bias and non-reproducibility are larger problems than financial COI
- Show a few cases of egregious financial COI and the effect it does have on research
- Propose some ideas to improve the quality of contemporary medical research
Conflict of Interest Notices

- I am a member of Data Monitoring Committees for Gilead Sciences
- I consult for Janssen Pharmaceuticals (J&J)
- I consult for the National Football League Players Association
- I have funding from the NIH through several mechanisms
- I am chair of the Duke School of Medicine Conflict of Interest Committee
Definition

- A conflict of interest exists when a primary interest or responsibility is (unduly) affected by a secondary interest or responsibility.
Illustrations of COI - #1

- Dental chair
Is this a COI? (Illustration #2)

- I am a photographer
  - I am debating a new telephoto lens
- I go to a local camera store
- I ask the salesperson for advice
I ask the salesperson for advice
- She recommends an expensive model
- How should I frame her recommendation?

I then asked a parent of a patient who happens to be a professional photographer
Is this a COI? (Illustration #2)

- Same advice: invest in your glass

- In the first case, I attributed the advice to a desire for increased profit

- In the second case, I considered the advice valid

- Same advice, different interpretation – perceptions matter
COI is part of every day life

- Human beings are very aware of COIs
- Every sales encounter
- All fee-for-service medical encounters
- Our problems come when someone has an ulterior motive and we can’t uncover it
  - The hired gun speaker where you weren’t told they were working as an academic prostitute
  - The researcher funded by a corporation through a neutrally named foundation
The real “enemy”

- The real enemy of good science is bias, not financial conflict of interest *per se*
  - Maybe we should emphasize overlapping interests more than financial *conflict* of interest
Validating Science

- Some degree of bias is almost inevitable in all science
  - We have hypotheses & beliefs
  - Scientists are rewarded for establishing new ideas
    - Publications
    - Grants
    - Higher pay
    - Personal satisfaction

- In short, in science we have strong incentives to prefer positive outcomes
Validating Science

- In basic science, the means to limit the effects of bias:
  - Controls – often blinded
  - Consistency with a logical hypothesis
    - Mixed blessing: confirmation bias
  - Reproduction
    - Often done by others
    - Requires publication of methods, provision of reagents
    - Note – may be a challenge in proprietary research
  - Peer review
Validation: In Clinical Research

- Reproducibility is the key test for validation, but...
- In clinical research, trials are often too expensive to reproduce
- Don’t want to put people at risk unnecessarily
  - Clinical Equipoise in therapeutic trials
  - If one therapy is already established as better, how do we randomize? Would you volunteer?
Concerns in Clinical Research

- Primary means of validation is audit (specifically, monitoring)
- Audit is not generally effective as a means to identify bias
  - Problems occur in study design
  - Subjectivity in endpoint and AE assessments
  - Statistical criteria may be biased
- Articles as written may not reflect the initial study design (rarely checked against the protocol)
Bias happens in science
There are historically tested methods to improve the quality of science
Many of those tools are less effective in clinical research than basic science
Most of the biases are NOT the result of financial interests, but they are one of the few types of potential sources of bias we can quantify
The Streetlight effect

The Nighthawks – Edward Hopper, 1942
What is the currency in our realm?

- Funded grant applications
  - And corporate grants & contracts
- Publications in high impact journals
- Promotion
- Identification with a hot idea
What is the currency in our realm?

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- Identification with a hot idea

- BUT: Corporate studies may be spun
- Start-ups may hold the promise of $ but rest on a very fragile research foundation
- Royalty amounts may be very substantial
Why do we collectively care?

- Biased research is a serious problem
- Bad research may be used as the basis for future experiments or clinical decision making
- Biased research wastes resources and time
- In some cases, it may lead to harm or even death
The Reproducibility Project - 2015

- The Open Science Collaboration tried to reproduce 100 published experiments in psychology
- 97% of studies had statistically significant results in the original article
- 36% of the studies had statistically significant results on replication
- 47% of the results were within the 95% confidence interval of the original study

Published: Science – August 2015
The Reproducibility Project

- **39%** of the second studies were subjectively judged to have replicated the initial study.
- Studies with stronger initial relationships (lower P-values) were more frequently reproducible.
- The mean effect size was 50% of the expected.
- Some of this outcome might be luck, or subtle changes in experimental conditions, but it generally bodes poorly for the quality of the work.
In 2011, Bayer reported that 75% of preclinical studies could not be replicated (multiple fields).

In 2012, Amgen announced they were able to replicate only 6 of 53 research studies in hematology-oncology, despite working with the authors (Begley, Nature, 2012).

- All published “landmark” studies
- Pre-clinical research – list of actual studies not published since Amgen worked with the authors
The meaning?

- These studies confirm a general suspicion that current research methods are not doing an adequate job of evaluating science
  - Peer review
  - Detecting the ever present bias toward selection of positive results
- The results raise a key question – how do we make our science better?
So, Bias...

- In basic science, more reliance on standard methods and reproduction
- In clinical research, wariness that warrants some oversight
- Returning to the streetlight problem, at times financial incentives are given attribution when an outcome is bad, even if the attribution is tenuous or even wrong
Financial COI

An Interlude
What are the COI ground rules?

- Most COI Policies are based on the PHS rules issued in August 2011 that went into effect August 24, 2012

- The PHS regulations specifically exclude institutional COI
  - Interest of the institution itself or of an individual who can independently act for the institution (president, dean, chancellor, department chairs, etc.)
Financial conflict of interest (FCOI) means a significant financial interest that could directly and significantly affect the design, conduct, or reporting of PHS-funded research.

Key elements
- D&S – direct and significant
- DCR – design, conduct, and reporting
Significant Financial Interest - SFI

- ≥$5,000/year in payment
- ≥$5,000 in equity value (publically traded)
- Any privately held equity or options

Royalty rules
- Apply on a case-by-case basis to non-institutional payments (≥$5,000)
- Allowed to exempt payments through the institution
- Duke treats royalties as income regardless of whether it comes through the institution
What does a COI office do?

1) Guards the integrity of research – primarily by evaluating & managing sources of bias
2) Protects human subjects (by limiting the roles of conflicted investigators)
3) Evaluates whether the research might lead to personal inurement (use of institutional resources for personal gain)
4) Evaluates whether the proposed research is c/w the institution’s non-profit mission
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The Effects of fCOI

Despite the theme so far, financial COI biases are real and demonstrable
Merck’s ADVANTAGE study - 2003

- ADVANTAGE study: Assessment of Differences between Vioxx and Naproxyn to Ascertain Gastrointestinal Tolerance and Efficacy
- After 3 months, 27% more people stopped taking Naproxyn than Vioxx

![Bar chart showing % Discontinued for Vioxx and Naprosyn]
After 3 months, 27% more people stopped taking Naproxyn.

Of course, that was 5.9% vs 8.1%.
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Brief Illustration

- or better, 94% vs 92% tolerance

% Remaining on original Rx

- Vioxx: 94.1%
- Naprosyn: 91.9%
Seeding Study

- ADVANTAGE was designed by the marketing department at Merck
- Real subjects were the MDs
  - Did use of study increase prescription rate?
  - Complimented enrolling doctors
  - Used many primary care sites, rather than a few high enrolling centers
A small addendum

- While Advantage was only a 12 week study, the FDA reported that 8 patients on rofecoxib (Vioxx) died of myocardial infarctions or sudden cardiac deaths, vs 1 on naproxen.
- Not included in the published report.
370 randomized trials

Considered: 1) Outcome of trial; 2) Sponsor

- Non-profit Sponsor - 16% recommended experimental drug as treatment of choice
- Funding not reported: 30%
- Mixed funding: 35%
- For-profit organization: 51%

Difference significant (p < 0.001) OR: 5.3; 95% CI 2.0-14.4
Turner NEJM Study - 2008

- Studies of 12 anti-depressants; 12,564 patients
- 38 studies with positive FDA results, of which 37 were published, 1 not published
- 36 with negative FDA results
  - 3 published, 22 not published
  - 11 published with data selection to appear positive
- In literature, 94% of publications were positive
- Turner: NEJM 2008;258:252-260
Merck and VIGOR

- Compared rofecoxib (Vioxx) to naproxen for rheumatoid arthritis
- 8076 patients
- Similar symptomatic efficacy
- Confirmed GI events: rofecoxib 2.1/100 pt-years
  - Naproxen 4.5/100 pt-years (i.e. ~2x worse)
- Noted MI’s were less common in naproxen group (0.1% vs 0.4%)
Vioxx and VIGOR

- A study was published in the NEJM in 2000
- Data was provided supporting Merck’s claim that rofecoxib (Vioxx) only increased cardiovascular risk in high risk individuals
- NEJM found a deleted figure on the submitted floppy disk that included data on heart attacks for three low risk patients (the deletion 2 days before submission to NEJM), making Merck’s claim suspect.
- Vioxx removed from the market in September 2004
Supplemental information

Data not included in the VIGOR report

Serious CV events:
- Rofecoxib 47
- Naproxen 20

Net: prevented 65

Upper GI events at

Cost of 27 additional thromboembolic events
The point should be clear

- When financial incentives are sufficient, pharmaceutical companies may hide information that leads to patients’ death.
- When corporate profits are considered more important than patient lives, know that COI is a serious issue.
- Most cases of COI are, however, far more subtle – shades of gray, not black and white.
Where should we go?
To this point

- COI is ubiquitous – we all deal with it every day without batting an eye
- Scientific COI is expected, but in some cases it can lead to significant distortions in the Science and can put human beings at risk
- Financial COI is one important, and quantifiable, source of bias
General strategies to manage fCOI

- Low level – disclosure
  - Publications, presentations, grant applications, and IRB documents
  - Doesn’t change the conflict
  - Allows the reader/hearer/reviewer/potential research volunteer to understand that someone who could affect the outcome of the research has an interest beyond the scientific
  - Unfortunately, disclosure may “free” the discloser of guilt
The Rebuttable presumption

- Mostly ICOI, but principles may hold for personal
- Decide whether to live under the “rebuttable presumption” (or when to...)
  - The RP states that the research should be done elsewhere, or by some other investigator, if a significant conflict exists and it could affect human subjects
  - If there is some unique skill or resource (patient population, tool, etc) can override the RP
Options – HSR & ICOI

- When the rebuttable presumption is to be overridden and the research involves human subjects
  - Use a non-institutional IRB
  - Consider a DSMB-Plus (DSMB with COI oversight)
    - Evaluate DCR of the research
  - Decide what limitations on the PI
  - Consider external monitoring

- Take risks into consideration

- Consider an ICOI committee with external members
Summary & Suggestions
Science is fast approaching a crisis
Our credibility is diminished by failures in reproducibility of key papers and experiments
We need to emphasize the scientific method
  - Controls
  - Masking
  - Internal reproduction by others
The short term cost will go up, but long term we will avoid useless research pathways
Longer term

- Local peer review of study design – not an IRB task
- More single IRB reviews, rather than the diffusion of responsibility that comes with multiple IRBs, on multi-center studies
- Make research data available for others to review, particularly in clinical research
Institutionally

- Institutions need to provide tools for data provenance and funding for scientific audits
  - Independent statisticians should be required
  - Data dredging is too easy with statistical packages
- Grant reviews should emphasize planned controls and validity checks, not just preliminary data
- Increased emphasis on subsequent validation by others rather than self-reference, in grant applications as well as the promotion process
Promotions

- Promotions should be based on quality, more than quantity, of papers
  - Allow only 5-10 papers to be considered, with no incorporation of the total number of papers in the promotion review process
- If grants emphasize replicability, they will better serve as gauges in the promotions process
- In calculating impact, don’t allow self-citation
Financial conflict of interest in research is a problem

- Big, like the Vioxx fiasco
- Smaller, like the everyday desire to make our work look good for funding purposes

We’re looking at financial COI incorrectly – it’s time to move the spotlight and look at the larger, more important systematic sources of bias
Summary

- As its very foundation, Science is built on trust
- Let’s do the type of work that shows we deserve the trust the public has put in us
- Our patients, and our peers, deserve good, honest, meaningful research