



Tomorrow's Doctors, Tomorrow's Cures

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Learn

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Lead

# If I'm interested, why is it a conflict?

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# Overview

- Define Conflicts of Interest
- Consider the effects of COI on research
- Propose that bias and non-reproducibility are larger problems than financial COI
- 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 (now unpaid)
- I consult for the National Football League Players Association (now unpaid)
- I spent almost a decade as the Chair of the COI Committee at Duke University School of Medicine

## 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 was debating a new telephoto lens

I went to a local camera store

I asked the salesperson for advice

## Is this a COI? (Illustration #2)

I asked the salesperson for advice

- She recommended 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
- This is an illustration of the “attribution effect”

# The meaning of COI

- There is a subtle dance between our perceptions and reality
  - We are aware that financial interests can influence someone's behavior
  - We are also aware that personal loyalties can influence behaviors, even interpretations
- We also believe in a concept of “professionalism”, where an individual can put their personal responsibilities above self-interest

# Trust

- When you are aware of someone's multiple interests, you increase your level of skepticism
- You may still trust the individual
  - History
  - Relationship
  - Reasonableness of the explanation
  - Solid nature of any evidence
- Harder when it's an impersonal interaction
  - Lecture, paper, grant application to review

# 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
- We should consider all potential sources of bias, not just money

# Bias toward the positive

Some degree of bias is inevitable in all science

- We have hypotheses & beliefs
- Scientists are rewarded for establishing new ideas and positive results
  - Publications
  - Grants
  - Higher pay
  - Personal satisfaction

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

# Validating Basic Science

In basic science, we have means to limit the effects of bias:

- Controls – often blinded
- Randomization
- Statistical tests
- Consistency with a logical hypothesis
  - Mixed blessing: confirmation bias

# Validating Basic Science

- Reproduction
  - Often done by others
  - Requires publication of methods, provision of reagents
  - Note – may be a challenge in proprietary research
- Peer review

# Validating 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 evidenced through:

- Problems in study design
- Subjectivity in endpoint and AE assessments
- Inappropriate statistical criteria

Articles as written may not reflect the initial study design (rarely checked against the protocol)

# Point of emphasis

- 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

# 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

# What is the evidence?

This being science, is there evidence that COI actually disturbs science, that bias is introduced?

# JAMA – 2003 – Als-Nielsen, et al

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:

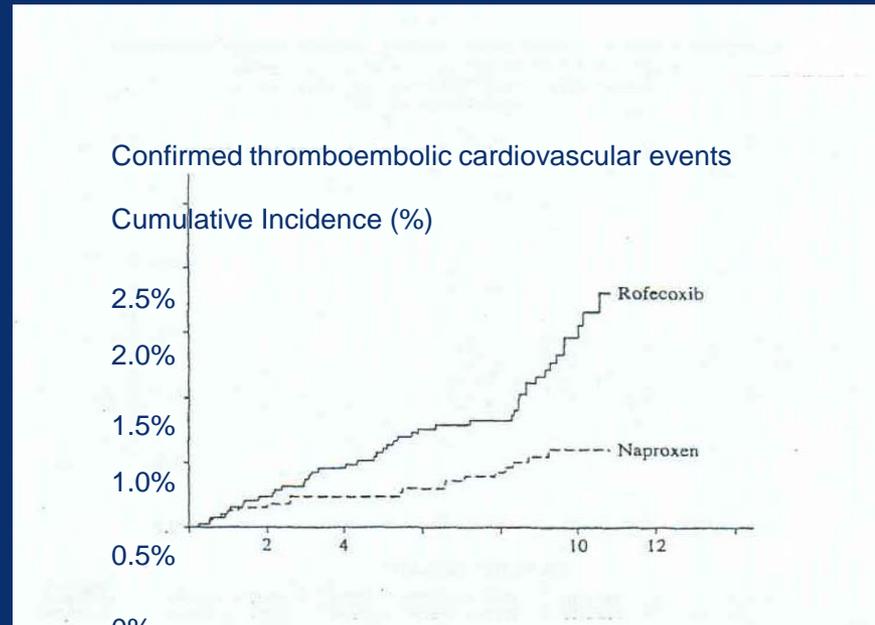
Rofecoxib 47

Naproxen 20

Net: prevented 65

Upper GI events at

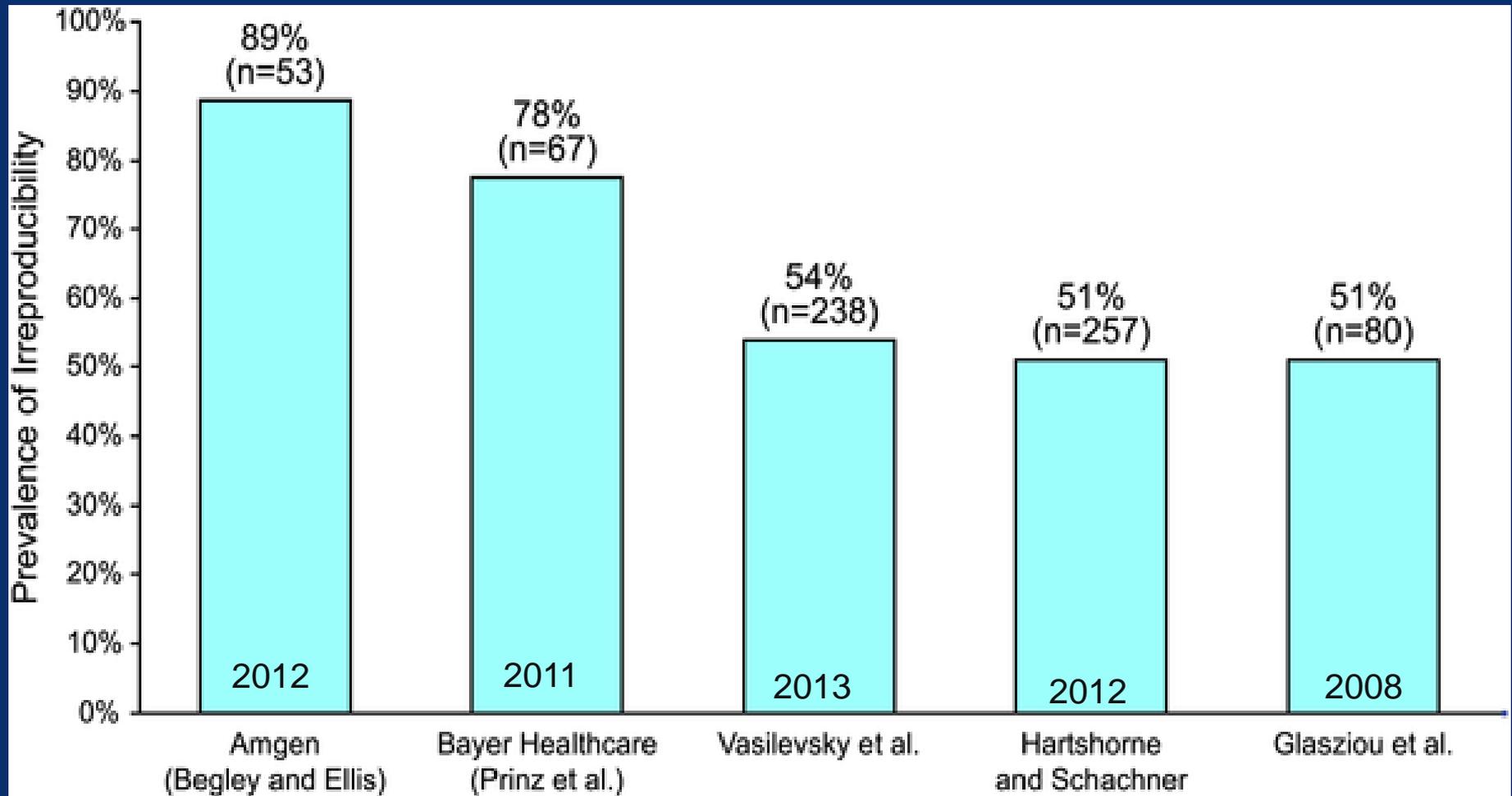
Cost of 27 additional thromboembolic events



# The problem is larger than fCOI

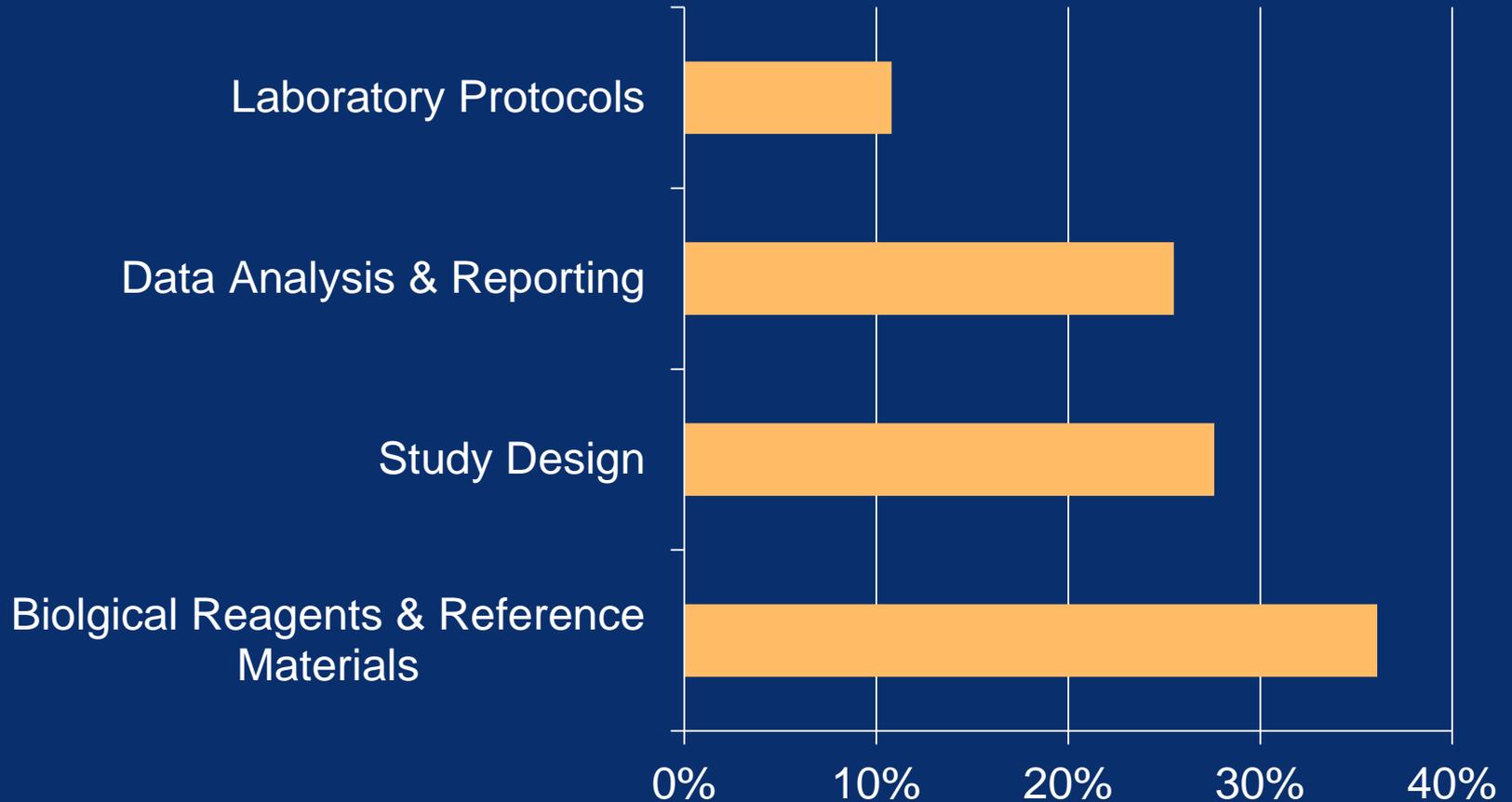
- While we can demonstrate the reality of fCOI, our problems are much larger
- Increasingly there is evidence that a high proportion of academic science is not reproducible

# Studies reporting the prevalence of pre-clinical irreproducibility.



# Estimated US preclinical research categories of errors that contribute to irreproducibility.

## Preclinical categories



Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. *PLoS Biol*3(6): e1002165.  
doi:10.1371/journal.pbio.100216

# The meaning?

These studies confirm a general suspicion that current research methods are not doing an adequate job of evaluating science

- Peer review isn't enough
- Detecting the ever present bias toward selection of positive results

The results raise a key question – how do we make our science better?

# Where should we go?

\* Ideas for Discussion

## 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
  - Probably particularly important in clinical research

# 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

# Managing fCOI

Require the use of independent biostatistical review of study design and data as it accrues

Require participation, perhaps at a PI level, by non-conflicted investigators

Use departmental resources to review papers and presentations for evidence of bias

# 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

# Suggestions

We need to emphasize the scientific method

- Controls, masking, randomization
- Sound statistical methods
- Internal reproduction by others of key experiments

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 expected
- Pre-specified design for statistical analysis

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

# Academic 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

# Summary

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

But, 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, particularly the personal beliefs that motivate us

# 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