SAFE SEX WITH STRANGERS: THE COMPLEX ETHICS OF ACADEMIC-INDUSTRY RELATIONSHIPS

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Overview

- What is COI, really?
- What the COI Office does
  - How the PHS rules changed in 8/12
  - Travel
- The rules for faculty
- Sensible approaches

RIO = Research Integrity Office / COI Program
Duke Philosophy

- Working with industry is very important
  - Most innovations that matter will pass through a commercialization process
  - Clinical research should be done well by people who understand the process
  - Pharmaceutical companies and device manufacturers don’t take care of patients – we do
- Hence, a scientific relationship is in the best interest of the Public, Duke, Industry, and our faculty
Advantages of Industry Relationships

- Access to cutting edge research
  - Clinical studies
  - Information at scientific advisory boards
  - Direct consultation
- Can be reputation building
Industry and Education

- For decades, industry has funded a large proportion of post-training medical education
  - Sponsorship of National & regional meetings
  - After-dinner and lunchtime talks
- Often not CME (Certified medical education) because it is spun with an industry perspective
- Increasingly feeling the effect of FDA regulations
Speaking for Industry

- A mixed blessing
  - Opportunity to meet regional physicians, often in their environment
  - Provide education
  - Market yourself & Duke
  - Lucrative

- Reputational enhancement – and degradation
What are the Problems?
A conflict of interest exists when a primary interest or responsibility is (unduly) affected by a secondary interest or responsibility.
Illustrations of COI - #1

- Picture yourself in dentist’s chair…
You walk in to Best Buy to purchase a new interchangeable lens camera.

You know a lot about your needs, but not about the available resources.

You turn to the store’s sales clerk for domain knowledge – how do you treat the source?
Illustration of COI - #3

- What Blue are You????
Take Home Points

- COI is ubiquitous
- We humans understand it and adapt to it
- We are limited when there are situations where we do not recognize the interests affecting the person from whom we are receiving information
Is COI really a problem in research?
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
Merck Again

- NY Times Friday February 15
  - “Merck Settles Suits Over Cholesterol Drug”
  - “Merck has agreed to pay $688 million to settle lawsuits claiming it had harmed investors by delaying the release of unfavorable study results for its cholesterol drug Vytorin, the company announced Thursday”
  - What about the harm to patients?
The back story

- The ENHANCE study compared a combination drug Vytorin (ezetimibe plus simvastatin) against Zocor (simvastatin) alone
- Vytorin was a Schering-Plough drug, Zocor a Merck drug that was going off patent
The back story

- Trial found the combination was no better at preventing atherosclerosis than simvastatin alone, although it was better at lowering cholesterol
- In short, the biomarker was not adequately linked to the desired outcome
- Companies delayed releasing the information (and publications) more than 2 years (2006 to 2008)
- During that time sold billions of dollars of Vytorin
The point should be clear

- When financial incentives are sufficient, pharmaceutical companies have hidden information, even to the point that concealment led to patients’ death (I did not go over the Avandia case, the novel antipsychotics, nor Hemametrics)

- 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
The rules
What are the 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.)
Duke vs. PHS rules

- Duke rules match the PHS rules with two notable exceptions
  - We do have an institutional COI policy that may require management of human subjects research on ideas developed at Duke, even if the investigators have no personal COI
  - We consider royalties paid through the institution to be possible source of COI
Significant Financial Interest - SFI

- $\geq 5,000 / \text{year in payment}
- $\geq 5,000 \text{ in equity value (publically traded)}
- Any privately held equity or options
- Royalty rules
  - Apply on a case-by-case basis to non-institutional payments ($\geq 5,000$)
  - Allowed to exempt payments through the institution
  - Duke treats royalties as income regardless of whether it comes through the institution
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
- What to make of “could”?
What’s an institution to do?

- Duke wants investigators to do research that “makes a difference”
  - Often that means the research has commercial potential
  - With commercial potential also comes financial ramifications for the research – COI
- Those financial incentives are a force for good – they encourage pursuing important research ideas.
- And then there’s the effect on judgment
What RIO tries to do re: FCOI

FCOI:
1) Protect the integrity of research from bias
2) Protect human subjects from apparent bias
   - Future patients could be affected by biased interpretation (see Merck/Vioxx, GSK/Avandia, etc)
   - Future research could be wasteful because of mis-interpretation of results
What RIO does because of reports

- **Non-FCOI**
  1) Evaluate whether there are potential violations of Duke’s tax-exempt status
  2) Evaluate whether the research is consistent with Duke’s tax-exempt mission
Tasks of convenience

- In addition to research FCOI, RIO identifies and evaluates
  - Clinical FCOI
    - Threshold is $25K, equity, or IP
  - Purchasing FCOI
    - Threshold is $25K, equity, or IP
  - Potential conflict of commitment
    - >$100K
    - >1 day per week
    - Patterns of behavior
The Problematic Rule Changes

- Institutions must attest to the PHS that all significant FCOIs have been managed prior to expenditure of the first federal dollar
  - Software tools developed at Duke
- Prime grant recipients are responsible for all sub-recipients
  - Can accept assurance that all COI is managed from a PHS compliant institution
  - Must manage all direct contractees & employees of non-PHS compliant entities (companies, for example)
Risk check

- When to allow expenditures of NIH dollars?
  - Currently as soon as a sub-recipient is cleared, we allow funding of that subcontract.
  - Individuals who are directly contracting with Duke or at non-compliant entities must be managed, but we do not currently consider them “Duke”, so that we can locally begin to spend before all management plans are in.
    - Big deal internationally
  - Need assurances from other institutions before we’ll release funds.
Travel reporting is required by the PHS for all PHS funded investigators.

Institution must evaluate for potential biasing effect of travel.

Any sponsored travel with 4 exceptions:
- Universities/governments/hospitals/research institutes

Includes spouse and dependent children.
Travel App

- Designed to be simple
- Must complete within 30 days of the travel

- https://adgapps.duhs.duke.edu/sb
Guidance and suggestions
Some common issues

- Duke generally endorses interaction with industry, albeit on our terms – esp. scientific consulting
- Don’t sign a CDA (Confidential Disclosure Agreement) – the institution should sign
- Contracts that run through the university are fine – but by law must be consistent with our non-profit mission
  - We don’t count income that comes through a Duke contract as an SFI
Common problems

- Beware of providing confidential information
  - Generally not a good idea to meet with investment advisers like Gerson Lehrman – risk of disclosing confidential information is too high

- Speaking arrangements
  - You can speak at a non-CME event IF (and only if) you control the content – your slides (you can use a few company slides, but mostly because of their graphics), and clear independence (if their lawyer’s are suggesting changes – it’s not allowed)
DUHS Limits

- Faculty are allowed to go to business meetings paid for by companies, but not educational events unless they are part of a larger meeting and generally open.
- If you are the speaker at a Non-CME event, it’s okay for the company to buy the meal (we assume the content was independent).
- Corporate gifts to employees are not allowed...
Please

- Fill out your annual COI disclosure form
- If you receive PHS funding (NIH, CDC, AHRQ, etc) Notify of Duke of travel events that are paid by sponsors other than universities, governments, hospitals, or research institutes (those 4 are exempt)
- Contact RIO or Dr. McKinney early if you have any questions. Our goal is to help keep the faculty safe, productive, and to help faculty improve health through innovation