COI FOR DUKE FACULTY

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Overview

- Define Conflicts of Interest
- Personal and Institutional COI
  - Physician Sunshine Act
- Bayh-Dole, start-ups, and Small Business grants

This is intended to be a pragmatic, not philosophical, discussion of COI and Duke’s approach
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
Don’t get the wrong message

- In health care, almost no good idea will affect significant number of patients if it isn’t commercialized
- Pharmaceutical & device companies don’t take care of patients – they need advice from people who do
- Conflict of interest isn’t intrinsically bad – it’s a normal part of life
- As academics, we should encourage working with industry (as distinct from for industry)
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
A faculty member at your institution invented a means to decontaminate chickens of salmonella.

She created a company to develop and eventually market the process, which involves multiple sprays.

There are issues like efficacy, taste, safety.

All of the experiments have been done by the faculty member and her students.
What issues does this case raise?

- There are questions regarding personal conflict of interest
  - Investigator stands to benefit financially more from one outcome than the alternative in most studies
  - How dispassionate will the study design be?
  - Will the data interpretation be balanced?
  - What about subjective issues (like taste)?
COI is part of every day life

- Human beings are very aware of COIs
- Every sales encounter
- All fee-for-service medical encounters
Two broad categories

- **Personal fCOI**: when an individual has a financial relationship that might (or could be perceived to) lead to bias in research.

- **Institutional fCOI**: when an institution, or someone who can act for the institution (e.g. dean, department chair), has a financial relationship that might lead to bias in research, or (more frequently) inadequate supervision of human subjects research.
Why does fCOI matter?
Validating Science

- Some degree of bias is almost inevitable
  - We have hypotheses
  - We 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 control the effects of bias:
  - Controls – often blinded
  - Consistency with a logical hypothesis
  - 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

- In science, reproducibility is the key test for validation.
- In clinical research, trials are often too expensive to reproduce.
- Don’t want to put people at risk unnecessarily.
  - Clinical Equipoise
  - If one therapy is already established as better, how do we randomize?
- Use the IRB and FDA as judges.
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)
The fCOI Rules
What are the ground rules?

- Most Duke 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
  - Duke, however, has its own Institutional COI Policy
Institutional responsibilities

- COI relates to those activities that could affect any of an individual’s institutional responsibilities.

- At Duke:
  - Research
  - Clinical Care
  - Teaching
  - Administrative responsibilities
Annual Disclosure Form

- In the Spring, we require filing an annual disclosure form
- 100% of faculty must complete the form (as well as any non-faculty on a grant, funded to do research, who has a DEA number, and/or with significant administrative responsibilities)
Significant Financial Interest - SFI

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

Royalty rules
- Apply on a case-by-case basis to non-institutional payments ($\geq 5,000$)
- Allowed to exempt payments through the institution
- Duke treats royalties as income regardless of whether it comes through the institution
General Duke approach

- Payments <$5K – don’t tell us (other than Boards of Directors – need to know those, even if non-profit)
- $5K-<$25K – Management will be mostly disclosure (in publications, presentations, and grant applications). The IRB will be notified. Rarely considered “Direct and Significant”, so in most cases not reported to the NIH
General Duke approach

- For $\geq 25K$ (or any options or private equity)
  - Continue to require disclosure
  - Not allowed to be PI
    - Both because of bias concerns and inurement issues
  - Not allowed to obtain informed consent for research related to the fCOI
  - May need to inform students of the fCOI
  - NIH reporting nearly always required (on PHS grants)
Travel

- Individuals must report to their institution (Duke) all sponsored travel unless the sponsor is:
  - A university
  - A medical center
  - A research institute
  - A government

- This means travel paid by foundations, professional societies, and companies, MUST be reported
Travel

- Institution must evaluate the travel to see whether it might produce bias, either as a single event or collectively (for example, multiple trips for one sponsor).
- Do NOT report trips where the travel is run through Duke (a clinical trial start-up meeting, for example).
Duke’s Travel App

- You can report sponsored travel at:
  - radapps.duke.edu/phs_travel

- The app will require
  - Sponsor
  - Destination
  - Purpose of the travel
  - Dates (departure, return)
  - Check box on whether the travel is international
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
Process

- PHS regulations require that institutions must manage the COI for all personnel who meet the fCOI criteria (D&S, DCR)
- The NIH must be notified of the fCOI & Plan
- Should the institution NOT manage someone, and discover it in retrospect, they will required to inform the NIH and create a remediation plan
- If the NIH does not accept the remediation plan, the grant money may need to be returned
Primes and subs

- The prime grant recipient is required to manage reporting of conflicts to the NIH
  - Allowed to defer COI management to the sub, which must attest that it has managed its participants. Reporting still done by the prime.

- If an individual has a personal contract with Duke, not through their home institution, they must complete the Duke form and be managed by our COI program
So what happens?

- At Duke, when a grant is awarded (actually JIT notification) the COI program reviews:
  - The abstract of the grant
  - The list of key personnel
  - The list of SFI (significant financial interests) of those personnel
- The grant is released (or further information is requested)
- No money can be spent until grant cleared
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 institutions non-profit mission
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Physician Sunshine Act

- External to Duke!
- Companies must report to the Federal Government all payments >$10 to physicians and health systems.
- These payments will be categorized and posted on a searchable, federally maintained web site accessible to the public.
- Applies to all pharmaceutical companies, medical device manufacturers, and medical service delivery companies.
Physician Sunshine Act

- Data will be posted for 2013 in late 2014, then annually
- Expect the press (and the NIH) to use the data to look for examples of fCOI
  - Large numbers (larger honoraria)
  - High profile researchers
  - Start-up links
- Will malpractice attorneys also use the database?
What can I do?
Duke

- Encourages its faculty to consult
  - Research focus
  - Watch the contract
- In general, avoid marketing efforts
Duke

- Does not review personal contracts
- Limits faculty to 44 days per year in consulting
  - 1 day per week (default University policy)
  - Department may limit to a greater degree, primarily because of PDC/clinical obligations
- Issues are labelled “Conflicts of Commitment”
Regarding speaking

- Faculty can lecture for companies
  - True CME is allowed
    - Independent content
  - If non-CME, requirements
    - Slides and content must be faculty prepared
    - Must be independent
    - Faculty member must be a recognized expert
  - Companies are increasingly moving to disease state talks, which are less FDA regulated
Gifts

- Not allowed to accept gifts from industry
- Dinners with non-CME talks are considered a gift
  - May purchase the dinner and attend
- Gifts of educational materials generally allowed
- Open dinners at national meetings are generally allowed
The Precedent Setting Case

- Jesse Gelsinger
  - 18 years old
  - Ornithine transcarbamylase deficiency – stable in him, fatal for some infants
  - Treated with adenovirus vector containing the deficient gene – 9/99
  - Died 4 days later of adenovirus hepatitis
1992 – Genovo founded by James Wilson
1995 – Penn and Genovo linked – Genovo invests ~$25M, in trade gets all commercialization rights
Wilson owns equity in Genovo
Liver was not functioning at an eligible level (ammonia too high)

Previous side effects had not been reported to the FDA

Informed consent signed was not the same as that approved (several side effect issues omitted)
Penn I-COI outcome

- Settlement by all parties
- Amount not known: millions of dollars assumed
- Wilson banned from human investigation. Later discovered some animal studies done in faulty manner
What should we learn?

- Gelsinger case treated as a model of ICOI
  - Some conclude Penn’s failure to regulate was at fault
  - Next level assumption is that doing the research somewhere other than Penn might have added a level of protection

- Others would argue that precedent was exaggerated – that it established unnecessary precautions as a norm. There are risks on every frontier of human research
Duke example

- Anil Potti’s research on a genomic predictor of sensitivity to specific chemotherapies
- Patients enrolled
- Predictor determined to be invalid
- Did Duke allow enrollment prematurely because it was going to make money? (plaintiffs’ position)
  - License agreement did appear to predict a large revenue flow
Back to our chicken case

- Let us assume (this is a thought experiment)
  - The method works as advertised
  - Consumers in focus groups agree there is no impact on taste
  - Cannot detect residual spray materials after use

- Hence, clears the short term bar
How had this been translated?

- IDF internally, review, then patent application filed
- License arranged (probably exclusive) to a faculty start-up created basically to be able to receive small business set-aside grants
  - Means faculty and institution are bonded by shared desire for company to succeed
- SBIR, STTR, state grants to support small businesses
ICOI concern

- FDA approves the chicken processing on the basis of company & university data generated during STTR
- Some bad outcome
  - Salmonella in an immunocompromised host
  - Anaphylaxis
  - Gastrointestinal cancer in a few chicken consumers
- Company and university sued
  - What oversight did the university provide?
  - What should have been the expectation?
Should the institution have imposed some limits on what could be done by the researcher?
The Rebuttable presumption

- 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
    - Some institutions might also apply it to basic science research – I wouldn’t
  - If there is some unique skill or resource (patient population, tool, etc) can override the RP
General strategies to manage COI

- 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
Potential boundaries

- Don’t allow someone to be PI
  - Esp. for grants from their company or SBIR/STTRs
- Limitations on whether investigators can request informed consent
- Limitations on what role in the research process
  - Investigator?
  - Writing Committee?
  - Analysis of data?
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
- Might take risk into consideration
- Consider an ICOI committee with external members
What are the SBIR/STTR rules?

- Filing done by the company, may or may not involve the institution (if there’s no subcontract)
- SBIR, STTR grants require a significant portion of the work be done at the company site
  - SBIR – Phase I $\geq 67\%$ at SB; Phase II $\geq 50\%$ at SB
  - STTR - $\geq 40\%$ at SB, $\geq 30\%$ at research institution
- By law, the university lab cannot be the company site – need an independent facility that is actually used…
What’s an institution to do?

- The institution 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
Institutional COI and personal COI both involve decisions about risks and benefits – incentives and oversight.

The answers aren’t black and white, and there will almost certainly be inconsistencies.

The issues regarding COI and bias are real.

The solution, however, is not to divorce academics from industry…