CONFLICT OF INTEREST & WHISTLEBLOWING
What is a Conflict of Interest?

- COI exists when unacceptable risk that a primary interest unduly influenced by secondary interest (D.F. Thompson)
- Primary interest is in well-being of clients, patients, integrity of research
- Secondary interest is personal gain ($$, professional advancement, fame, etc)
- COI does not mean proven bias – means risk of influence
Types of Conflicts
(Usually defined by secondary interests)

- Intellectual bias
  - pet theories, personal preference
- Conflict of commitment
  - Affects ability to perform primary duties (to employer/program)
- Conflict of Financial Interest*
  - You (or a spouse or relative) benefit financially from a relationship that might lead to bias in research
- Institutional Conflict of Interest
What is Conflict of Interest?

- In research, a \textit{conflict of interest} is present when an actual or potential personal or institutional financial benefit threatens the \textit{objectivity} of the design, conduct, analysis, or reporting of research or program results.
- Can mean \textit{appearance} of such a conflict.
- Expectation of unbiased results reporting.
Why Do We Care?

- Individual conflict leads to credibility concerns
- Institutional conflict can lead to degradation of institutional reputation, loss of public trust
- Can lead to physical/monetary/psychological harm to research subjects/employees/students or trainees
- Can lead to additional regulatory oversight resulting in greater scrutiny, expanded programmatic requirements, and greater institutional investment.
How Widespread is COI?

- Survey of medical school/teaching hospital faculty (1663 at 50 schools, 2007)
  - 52% had “any relationship” with industry
  - 41% had relationship that contributed to most important research
  - 20% had industrial funding (48% clinical trials)
  - Average industry funding per year: $33,417
  - Average industry funding of clinical trial PI’s: $110,869

DE Zinner, EG Campbell, JAMA 302:969-76 (Sept. 2, 2009)
What Do You Think?

• Scenario:
  ◦ Faculty member develops a technology that is subsequently licensed to a start up exclusively formed for this technology.
  ◦ The technology won’t be used directly in humans (i.e. it’s for tissue transport)
  ◦ The faculty member will receive equity instead of $ for his services
  ◦ The start up would like to fund continued research in the faculty’s laboratory in order to advance the technology
  ◦ Is this a conflict of interest?
Does COI Exist in the Scenario?

- **YES!**
- The COI is NOT in the faculty invention being licensed to a company and the faculty having equity in the company – although the faculty member would have to disclose his equity interest to the University.
- The COI occurs when the company in which the faculty member owns equity want to sponsor research in the faculty member’s lab.
- Opportunities for faculty member to act on his bias abound in this scenario.
Things to Consider:

- **Risk of bias**
  - Value of equity
  - Value of research contract
  - Possibility of continued funding relationship
  - Consulting arrangement?
  - Other involvement of PI with company?
  - Institutional conflict?

- **Ability to manage bias**
  - Full disclosure
  - Oversight
Financial Conflict of Interest

- Basic threshold values defined by NIH
- Any monetary value including, but not limited to:
  - Salary or other payments (e.g. fees or honoraria); NIH threshold > $10K/year in aggregate
  - Equity; NIH threshold > $10K in aggregate or 5% equity
  - Intellectual property rights (patents, copyrights, or royalties from such)
  - Other institutions may use different thresholds
  - PHS 42CFR Part50
State Law

- NJ Law – NJSA 52:13D-19.1
- Absolute ban on state employee (or family member) conducting business with state entity
- *Except* in the case when IP rights are in question then is allowable but must be disclosed if ≥1% equity interest and undergo COI review and management.
Back to Scenario: how would others manage this COI?

- Utah State University
  - Review technology to see if research work could be done by others but probably allow
  - Provide rigorous research and financial oversight if allowed to proceed
  - Set milestones for research and require company to pay for outside benchmark testing of technology to confirm results of PI
Back to Scenario: how would others manage this COI?

- **UTMB**
  - Impose Management Plan
    - PI Re-submit updated COI disclosure form
    - PI Notify COI Committee of future proposed research prior to contract execution
    - Appoint independent reviewer – semi-annual reports (PI can suggest reviewer)
    - PI Inform Committee of any trainees working on the sponsored research
    - Disclose relationship with sponsor in publications and presentation
    - Notify Committee of publications and presentations (provide annotated CV to Committee) – update regularly
Back to Scenario: how would others manage this COI?

- Duke
  - Disallowed
    - Use of non-profit facilities for personal gain of PI
    - Pressure on students and post-docs to develop favorable results
    - Possible that another faculty member at Duke could perform research but not PI

- Does this de-incentivize the PI?
- Case where PI donated all royalties to foundation as per COI management plan
- Affect Bayh Dole?
What if the sponsored research were a clinical trial?

Would human subject involvement change the management plan?
Issues Unique to Clinical Research

- What to test
- Placebo vs. active control
- Endpoint selection
- Inclusion/exclusion criteria
- Design of informed consent document
- Rules for stopping trial for proven efficacy or adverse events
- Which eligible patients will be enrolled
- Enrolling ineligible patients for compassionate reasons
COI Effect on Clinical Research

- Potential of harm to subjects
- Study defects may harm future patients as well as future research
- Exposure reduces public trust, reducing willingness of public to serve as subjects
- Risk of lack of faith by funding sources
- BASIC research has rules, but not as strict as CLINICAL research
Concerns About Industry-Sponsored Clinical Trials

- Academic investigators lack
  - Access to all data
  - Independent statistical analysis
- Drafting of papers by medical writers
- Not report negative findings
- Associations between funding and conclusions
Example of Failure to Report

- Forest Labs accused of hiding negative data regarding efficacy and AE’s of antidepressant, Celexa, in children (off label prescription in peds)
- Accusations that Forest paid kickbacks to physicians that prescribed the drugs (sporting events tickets, paid vacations)
- Accusations that marketing efforts were disguised as trials
- *WSJ, Feb 26, 2009/NYT Feb 26, 2009*
Reporting on ClinicalTrials.gov

- **Required**
  - For FDA consideration
  - By leading medical journals
  - By federal funding agencies

- **Before trial begins**
  - Protocol

- **After completion**
  - Basic results
  - Serious Adverse Events (SAEs)
  - Important exceptions
Selective Outcome Reporting Remains a Problem

- 323 trials in cardiology, rheumatology, GI in 10 top journals in 2008
  - 45.5% registered before end with outcomes
  - 27.6% not registered
  - 13.9% registered after completion
  - 10.8% without clear outcomes
  - 31% discrepancy between outcomes registered and outcomes published (reported new outcome or did not report original outcome)

S. Mathieu et al., JAMA 302:977-84 (Sept. 2, 2009)
Association Between Funding and Conclusion

- Investigator Ties to Manufacturer
  - 3.6 times more likely to find drug effective
- Sponsored by Manufacturer
  - 4.0 times more likely to find drug effective

JAMA 2003; 289:454
BMJ 2003; 327:1167
Explanations for Association

- Publication bias
  - Investigators
  - Journals

- Less rigorously designed trials
  - No real evidence to support this

- Manufacturers “stack the deck” – only sponsor trials that are likely to succeed
Other Issues in Clinical Research

- Fees for patient recruitment. General covering costs OK, but large sums are seen as coercion.
- Finder’s fees (payment for referral of patients) considered unethical (illegal in clinical practice).
Remedies for COI

- Disclosure
  - Annual
  - Upon submission of grant (NIH requirement)
  - Some Universities publicly report relationships
  - Public databases from industry (Merck, Lilly, GSK)

- Management of Relationship

- Prohibition

- Goal: Reduce Undue Influence and Bias

- Note: goal of COI policies is to prevent bias and loss of trust, not respond to misbehavior
Disclosure

- “Sunshine is best disinfectant”
- Required, although not always sufficient
- Disclose to: study participants, co-PIs, trainees, sponsors, University, IRB, journal editors
- Include all payments (received or planned), equity interest, fiduciary responsibility, personal financial interest including relatives (spouse, parent, child, siblings, domestic partner, including “step,” “half,” “in-law,” etc.)
Who Needs to Disclose?

- Investigator = principal investigator and any other person who is responsible for the design, conduct, analysis or reporting of research.
- Not just PI, it can be anyone (key personnel, even tech) who is involved in design, conduct, or reporting of sponsored research.
- Term also includes investigator’s spouse and family.
Federal COI Reporting Requirements

- At time of application, all investigators must submit information to institution.
- Prior to expenditure, institution reports COI to NIH & assures management, reduction or elimination of COI.
- Financial COI identified after initial report must be reported within 60 days of discovery and managed, reduced or eliminated.
Concerns About Disclosure

- Not specific or standardized
  - Categories like “consultant” ambiguous
- May be misinterpreted
  - Discrepancies due to different requirements
  - Can deter desirable behaviors
- Not prevent undue influence or bias
  - Necessary but limited first step
Management of COI

- COI Management Aims to Protect:
  - Integrity of research
  - Students/post-docs
  - Research participants
  - Institution

- Goal = remove conflicted person from decision making process which would allow him to act on his bias.
Management of COI (continued)

- Public Disclosure
- Monitoring by Independent Reviewers
- Consenting done by someone with no conflict
- Remove cause of conflict
  - Sell ownership interest/place in escrow
  - Resign office or board position
  - Reduce or eliminate compensation/fees/proceeds to charity
  - Modification of research plan
Patient Views on Financial COI

- **Method:** Interviewed 253 patients in cancer-research trials (93% response rate) at 5 US Medical Centers

- **Results:**
  - >90% expressed little or no worry about financial ties researchers or institutions might have with drug companies
  - Patients would have enrolled in the trial even if drug company paid researcher for:
    - Speaking engagement (82%)
    - Consulting (75%)
    - Royalty Payments (70%)
    - Owned stock in company (76%)

  - *Hampson, L et.al., NEJM 2006, 355;22*
Patient Views (continued)

• Patients would have enrolled in trial if:
  ◦ Cancer Center owned stock in co. (77%)
  ◦ CC received royalties (79%)

• Patients believed it ethical if researcher:
  ◦ Received speaking fees from co (81%)
  ◦ Received consulting fees from co (82%)

• Some wanted disclosure:
  ◦ Of oversight system for researcher (40%)
  ◦ Of researcher’s financial interests (31%)
  ◦ 17% thought no disclosure to patients was necessary
University
Investigator develops IP
Investigator owns IP

Investigator starts
Company
Investigator’s lab
animal trials
IP +
$2-8M/yr for research

Outside Company
invests research
$37M

Human Trials

Investigator’s lab
animal trials
improved IP
development

Investigator’s lab
animal trials
IP +
$2-8M/yr for research

Shareholders
- Investigator
- University
- Chancellor takes out personal investment

• FDA approved informed consent changed to delete SAEs and deaths reported in animal trials and SAEs in the human trial
• Patients enrolled did not meet inclusion/exclusion criteria
• Changed protocol without IRB/FDA approval
• Failed to report SAEs or deaths. Lead to Death of subject
COI Resources

- UMDNJ Policies
  [http://www.umdnj.edu/oppmweb/university_policies/Academic_affairs/PDF/00-01-20-89_00.pdf](http://www.umdnj.edu/oppmweb/university_policies/Academic_affairs/PDF/00-01-20-89_00.pdf)

- 42 CFR Part 50, Subpart F

- AAMC site
  [http://www.aamc.org/research/coi/start.htm](http://www.aamc.org/research/coi/start.htm)

- FOCI Academe (Forum on Conflict of Interest)
  [http://www.aamc.org/members/foci/start.htm](http://www.aamc.org/members/foci/start.htm)
WHISTLEBLOWING

How to Report Research Misconduct

Adapted from Presentation by Celine Gelinas, Ph.D.
Associate Dean of Research, RWJMS
Grantee institutions have the responsibility for preventing and dealing with research misconduct

UMDNJ Policy on Research Misconduct 00-01-20-60:00
http://www.umdnj.edu/research/index.htm

• Intended to implement the Federal Law 42 U.S.C. Section 289b and the regulations promulgated pursuant thereto, 42 CFR Parts 50 and 93.

Policy and Procedures to:

• Ensure the prompt and appropriate investigation of alleged or apparent misconduct

• Protect the rights of those who report misconduct and those about whom allegations are made

Who does this apply to?

• Applies to faculty members, housestaff, trainees, students (including postdoctoral fellows), volunteers, attending physicians and staff members
What If You Suspect Misconduct?

- Talk to School’s Research Ombudsperson
- Role of Ombudsperson
  - Hear problems, concerns, complaints concerning research activities
  - Act in a neutral and confidential role to help achieve equitable and acceptable solutions
  - Impartial representation -- does NOT represent either individual or School or University
  - Can collect information/interview others
  - Makes recommendations to the party or parties to achieve solutions (advice, persuasion, referral etc)
  - Ombudsperson is key resource in addition to dept chair, research mentors, research dean and deans
RWJMS Research Ombudsman

Dr. Paul Manowitz
Professor of Psychiatry
675 Hoes Lane, UBHC D-447
Piscataway, NJ 08854
Phone: (732) 235-4347
Email: manowitz@umdnj.edu
Report Suspected Research Misconduct to....

- Campus Committee on Research Integrity
- Individuals who become aware of, or suspect, research misconduct should report the details of the alleged misconduct (preferably in writing) to any member of their Campus Committee on Research Integrity
UMDNJ - PISCATAWAY/NEW BRUNSWICK CAMPUS COMMITTEE ON RESEARCH INTEGRITY

To whom allegations of Research misconduct should be made:

Jerome A. Langer Ph.D. (Chair)
Mol. Genetics, Microbiology & Immunology
RWJMS Rm729
RWJMS, Piscataway
Ext: 5-5224

Cande V. Ananth, PhD, MPH
Obstetrics, Gynecology & Reproductive Sciences
CAB 2152
RWJMS/New Brunswick
Ext: 5-7940

Kenneth J. Gill, PhD
Psychiatric Rehabilitation & Counseling Professions
1776 Raritan Rd, Rm 517
SHRP/Scotch Plains
Tel: 908-889-2438

Weichung Joe Shih, PhD
Biostatistics
CINJ 2008
SPH/New Brunswick
Ext: 5-6791

Victor Stollar, MD
Mol. Genetics, Microbiology & Immunology
RWJMS 731
GSBS/Piscataway,
Ext: 5-4596

Nancy C. Walworth, PhD
Pharmacology
RWJRT 536
RWJMS, Piscataway
Ext: 5-5661
Relationship between Ombudsman and Committee on Research Integrity

- If an issue brought first to Ombudsman is potential research misconduct, the Ombudsman may investigate and bring information to Committee while maintaining anonymity of the complainant (if desired & possible)
- If an issue brought first to the Campus Committee on Research Integrity does NOT fall under the definition of Misconduct, the Committee can refer matter back to Ombudsman.
How Are Allegations Handled?

- Multistage process
- Stage 1: Preliminary Assessment by Committee Chair
- Stage 2: Inquiry by the Campus Research Integrity Committee -- decide if further investigation required
- Stage 3: Formal Investigation by Special Panel (appointed by Executive VP for Academic and Clinical Affairs)
- Complainant notified of outcome
A Recommendation of Research Misconduct Requires:

- That there was fabrication, falsification or plagiarism in proposing, conducting, or reviewing research or reporting results.
- Was committed intentionally, knowingly or recklessly; and
- Was proven by the preponderance of the evidence.
- Ultimately, the EVP for Academic and Clinical Affairs makes the final decision and takes appropriate action.
Protection and Responsibilities of “Whistleblowers”

- Initially, identity of complainant is kept confidential
- If allegation leads to inquiry or investigation, testimony by complainant may be required
- The University will protect all “good-faith” whistleblowers
- HOWEVER, “whistleblowers” whose allegations are made in bad faith are subject to appropriate disciplinary actions