Research Conflict of Interest
PERCSS – RCR Event 2012

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Positive Aspects of Industry-Investigator Interactions

• Medical school investigators are frequently involved in the design and testing of new drugs and devices
• In some medical specialties, collaboration between industry and physicians is essential to improved patient care
• Industry supports clinical research that the federal government is less likely to support
• Industry supports fellowships and other training programs
What is a Financial Conflict of Interest?

• Situations in which financial or other personal considerations may compromise (real), or may have the appearance of compromising (perception), an investigator’s professional judgment in conducting or reporting research.

• Includes financial interests that would reasonably appear to be affected by the outcomes of the research.
Examples of Financial Interests

- Consulting
- Serving on a Scientific Advisory Board or Board of Directors
- Position/Employment with a Company
- Speaking Fees/Honoraria for lectures (non-CME sponsored lectures)
- Product Evaluation Payments
- Personal Gifts
- Royalties for books
- Equity interests: Stock, Stock Options, Partnership or Ownership interest in the company
- Royalties for inventions and intellectual property
Conflicts of Interest

• Threaten the integrity of our research, teaching, and patient care missions

• **Reality:** Physicians, scientists, academic institutions and professional organizations have privileged positions in society and thus are subject to high expectations from the public
<table>
<thead>
<tr>
<th>Gift</th>
<th>Inappropriate (%)</th>
<th>Influential (%)</th>
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<tr>
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<tr>
<td>Small textbook</td>
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</table>

*Based on data in the study by Gibbons et al.\(^{54}\).
External Forces That Care About COI

- Journals
- NIH and other government funding agencies
- Congress
- State governments
- The courts
- The press
Cases of Non-Compliance Are Newsworthy and Threaten to Destroy Careers

• 2008: Dr. Charles Nemeroff at Emory University
• 2011: Psychiatrists at Harvard Medical School
A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors

Eugene J. Carragee, MD\textsuperscript{a,}\*, Alexander J. Ghanayem, MD\textsuperscript{b}, Bradley K. Weiner, MD\textsuperscript{c}, David J. Rothman, PhD\textsuperscript{d}, Christopher M. Bono, MD\textsuperscript{e}

- “There were no unanticipated adverse events related to the use of INFUSE Bone Graft.” (n=24) Burkus et al. [1] (industry-sponsored study, 2002).
- “[T]here were no complications attributable to the rhBMP-2/biphasic calcium phosphate [in posterolateral fusion].” (n=20) Boden et al. [2] (industry-sponsored study, 2002).
- “There were no unanticipated device-related adverse events [using rhBMP-2 with an anterior cervical fusion].” (n=18) Baskin et al. [3] (industry-sponsored study, 2003).
- “I have reported the clinical and radiographic results of three different interbody constructs in a single-level, stand-alone ALIF derived from several prospective multicenter studies... There were no adverse events due to rhBMP-2.” (n=326) Burkus [4] (industry-sponsored studies, 2004).
- “No unanticipated device-related adverse events occurred [with PLIF using rhBMP-2]... This study seems to confirm the safety results ...[of] using rhBMP-2.” (n=34) Haid et al. [5] (industry-sponsored study 2004).
- “Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy [rhBMP-2]... a 100% fusion rate and no significant morbidity.” (n=24) Boakye et al. [6] (industry-associated author).
- “No adverse event that was specifically attributed to the use of rhBMP-2 matrix [Amplify] in the study group was identified.” (n=239) Dimar et al. (industry-sponsored study, 2009) [7].
- “Yes, isn’t it pretty to think so.” Ernest Hemingway, The Sun Also Rises.

The risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry sponsored peer reviewed publications!
Different Types of Conflict of Interest

• Clinical COI - A physician takes money (e.g. as a consultant, or serving on an advisory board, or for giving lectures) from a company whose products he uses on or prescribes to his patients.

• CME COI – A faculty member who receives income from a company (e.g. as a consultant) or receives research support from a company and then gives CME talks that discuss the products of that company.

• Vendor COI - A University employee receives income from a company and controls University purchasing from that company

• Research COI
Research Conflict of Interest

• A COI exists when the investigator has a financial interest whose value could be influenced by the outcome of the research or whose financial interests could appear to influence the objectivity of the research.

• The COI problem is greater when human subjects are involved.
Risk Assessment

- Risk of a COI increases with the magnitude of the personal compensation received or expected (e.g. >$50K)
- Risk of COI is inherently greater when an investigator holds equity rather than receiving personal cash compensation from a company.
  - Research outcome $\rightarrow$ equity value
Risk Assessment

- Involvement of trainees in research supported by a company creates the risk that training will be compromised.
- Use of human subjects in work by an investigator who has a FI with a company creates for the human subjects the additional risk for adverse consequences.
- Investigators in positions of leadership in the institution have a greater risk of COI. Adverse consequences are magnified when decisions are made by those with a high level of responsibility.
Federal Conflict of Interest Regulations

• The University is responsible for developing and enforcing COI regulations
• Investigators must report any “significant financial interest” to the University
• The University must report any COI to the federal funding agencies
WUSM COI Policy

• Adopted by the Executive Faculty June 1993 and amended February 1994

• Applicable to all faculty and staff

• COI defined as: if employee’s “judgment and discretion in research or in other matters affecting the University is or may be influenced by considerations either of personal gain or financial benefit”
COI in Clinical Research Policy

• Adopted December 2001 and revised in May 2003
• Created to address increasing concerns related to the protection of human subjects
• Precludes individuals from conducting human subject research when > $10,000 financial interest in:
  – Company sponsoring the research
  – Company that owns or licenses technology being studied
  – Special consideration given to stock options
COI in Clinical Research Policy

• Permits exceptions under compelling circumstances

• Exceptions require approval by the DRC, the Dean, and the VCR. If the DRC does not approve an exception, then it is not sent to the Dean or VCR.
Disclosure Review Committee (DRC)

• The DRC assures compliance with Federal regulations and University and sponsoring agency policies regarding financial COIs

• DRC Responsibilities:
  – Implementation of COI policies
  – Identifying financial COI related to research
  – Ensuring COI are managed, reduced, or eliminated according to institutional and federal policies
  – Provide communication, education, and awareness for researchers and staff
WUSM DRC

- Faculty committee appointed by the Dean
- Membership includes 23 faculty members representing every department plus HRPO
- Ex-officio, non-voting members include reps from OVCR
- Staffed by the OVCR Research Ethics Compliance Office (RECO)
- Full committee meets 2-3 times per year
- Subcommittees meet as needed
Individual Disclosure Process to the DRC

• **Who:** Faculty and anyone involved in the design, conduct, or reporting of research

• **What:** All financial interests in non-WU entities that could possibly relate to research, patent, or licensing activities

• **When:** Annually plus HRPO protocols and clinical trial contracts, or if there is a significant change in the financial interest. Also must certify compliance with policies at time of grant submission

• **How:** On-line financial disclosure statement
WU Annual Financial Disclosure Data

Disclosures Submitted 3638 4082 4098 4828
Individuals Reporting 3147 3298 3346 3816
Disclosure Data
No FI 3128 3544 3555 4217
Reported ≥ $10K or equity/royalties 332 346 335 375
Reported < $10K and no equity/royalties 178 192 208 236
Positive Disclosures

• Staff at the RECO reviews disclosures to determine if review is needed by the DRC Chair. For WUSM, this occurs after the Department Chair has reviewed the disclosures

• Threshold:
  – Financial relationships are > $10,000 in value
  – Represents > 5% ownership interest in a publicly traded company
  – Any other ownership interest (e.g. stock/equity) or licensing revenue/royalty income, regardless of value
Positive Disclosures

• If disclosure meets the review threshold, then it is sent to DRC Chair for review

• Information is gathered regarding the financial interests and research projects in which the individual is involved
  – Research abstracts, descriptions, and protocols
  – Licensing agreements
  – Invention disclosures
  – Consulting agreements
DRC Chair Role

• Evaluate each FDS to determine if there is a real or potential financial COI
• Assess the COI and its potential impact on the objectivity of the research project, student academic programs, and safety of human subjects
• Determines if management plan and/or further review by the committee is needed
Options for Investigators

• Request an exception, or
• Reduce financial interest to < $10,000 per 12 months, or
• Discontinue involvement in design, conducting, or reporting of the research
Requesting An Exception to the COI Policy

• Are there compelling circumstances?
  – Examples:
    • Sufficient mechanisms in the study design to ensure objectivity of the research
    • Research is in its early stages of discovery and the potential for bias is negligible
    • Individual is uniquely qualified by virtue of his/her expertise and experience
    • Research presents little or no risk to the human participants
    • Research is not designed to support a new indication or application of the technology

• Can an appropriate management plan be made?
## DRC Review of Compelling Circumstances for the COI and Clinical Research Policy

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<tr>
<th>FY</th>
<th>2007</th>
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<td>8</td>
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Approved Exception - Example

• Investigator identifies a new treatment for patients with a specific disease after extensive bench and animal research. This discovery is licensed to a drug company. The expertise of the investigator is needed to design research studies to assess the efficacy of the treatment. Later clinical trials will be conducted at other sites under the direction of other, non-conflicted PIs

• Factors: research is in its early stage of discovery and the conflicted PI is uniquely qualified to do the research
Non-Approved Exception - Example

• Investigator is receiving royalties of $75,000 per year for a device he invented. He is proposing to study the efficacy of the device. The company is sponsoring the research.

• Factors: The research is too closely related to the financial interest
Management Plans

• Could include one or more of the following:
  – Disclosure of the financial interest
    • Publications, talks, students/trainees, research team, human subject participants
  – Minimize an individual’s role in the research (e.g. design, conduct, reporting)
  – Provide oversight of the research by a non-conflicted faculty member or oversight committee
  – Divestiture of the financial relationship
  – Require non-tradable equity is not-exercised without prior approval from the DRC
Management Plan Communication

• Management strategies are determined and communicated to the individual, and copied to the Department Chair

• Notifications are sent to the applicable research administrative offices regarding the management of an individual COI (HRPO, OTM, Grants/Contracts)

• When applicable, the funding sponsor is also notified (NIH, etc.)
Monitoring Compliance with COI Policies

• Internal monitoring (routine and targeted)
  – OVCR RECO
  – University Compliance Office (UCO)

• External monitoring
  – NIH reviews of policy, COI management plans, and journal “trolling”
  – Congressional reviews
  – Other agencies, including OIG, NSF, DOJ
Goals of the Process

• Clear, consistent, and transparent
• Establish a tone of being advisory rather than accusatory or prosecutorial
• Be proactive rather than reactive in order to prevent downstream adverse consequences of conflicts not being managed early on
Model Steps Recommended by The Institute of Medicine for Identifying and Responding to a Conflict of Interest

**Obtain Disclosure**

- Obtain disclosure about financial and other relationships

**Manage Conflict**

- Compare disclosure to individual’s responsibilities or activities.

- **Likelihood of Undue Influence**
  - What is the value of the secondary interest?
  - What is the scope of the relationship?
  - What is the extent of discretion?

- **Is there a conflict of interest?**
  - No
  - Yes

- **Is relationship prohibited by institutional or other policies?**
  - No
  - Yes

- **Are risks so serious that the individual should forego activity or eliminate conflict?**
  - No
  - Yes

- Devise and implement management plan

**Monitor Adherence**

- Eliminate conflict

- Assess adherence to conflict elimination or management plan

- Devise and implement response if plan not followed

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**No Relationships**

- Research grants and contracts
- Consulting agreements
- Participation in speakers bureaus
- Honoraria
- Intellectual property (patents, royalties, licensing fees)
- Stocks, options, warrants, and other ownership excepting general mutual funds
- Position with company (governing board, technical advisory committee, scientific advisory board, marketing panel, full or part time employee or officer)
- Authorship of publications
- Expert witness for a plaintiff or defendant
- Other payments or financial relationships

**STOP**
Upcoming Changes to Financial COI in Research Regulations

• DHHS issued new rules in August 2011 to amend the PHS regulations of 1995
• Any institutions applying for or receiving NIH funding must be in compliance with all revised regulatory requirements by August 24, 2012
Summary of Major Changes

• **All** financial interests must be disclosed related to **any** institutional responsibilities

• *De minimis* threshold for review **decreased** from $10,000 to $5,000

• **New** requirements for reporting:
  – Financial interests with non-profits
  – **Travel** reimbursed by or paid for by any entity other than academic institution or government agency

• **Mandatory COI education** every 4 years

• **Monitoring** of all managed COIs
Summary of Major Changes

• Investigators must disclose all new financial interests within 30 days

• Institution must complete retrospective review for non-compliance when:
  – Investigator fails to report within 30 day timeframe
  – Institution fails to identify or manage conflict

• Information about an individual’s COI must be made available to the public
  – Website or
  – Written response to requests within 5 days
Implications of Noncompliance -- for Investigators --

- Failure to comply with the Institution’s COI policies or if Investigator’s COI appeared to bias the research
  - WU must take corrective actions and report to NIH
  - NIH may impose additional corrective actions that could apply to all of the individual's NIH awards
Implications for Noncompliance
-- for Institution --

• If NIH determines WU did not adequately manage a COI or address non-compliance, NIH could impose
  – special award conditions
  – suspension of funding
  – or other enforcement actions
Contact Information

Jeneane Braden
Manager, Research Ethics and Compliance Office
E-Mail: bradenj@wustl.edu
Phone #: 747-4152

Policy, Forms, and Committee information can be found at: http://medcoi.wustl.edu