

CONFLICT OF INTEREST IN BIOMEDICAL RESEARCH: How it happens, why it matters, what can be done about it



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OBJECTIVES

- ✚ To raise awareness of Conflicts of Interest (COI) in research situations
- ✚ To understand how COIs develop and unduly influence professional judgment
- ✚ To consider approaches to managing conflicts of interest without hindering fruitful scientific collaboration



BENEFICIAL COLLABORATION WITH INDUSTRY

BENEFICIAL COLLABORATION

- Patients and the public benefit when medical researchers collaborate with commercial funders (IOM, 2009)

COLLABORATION AND CONFLICT

- “wide-ranging financial ties to industry may **unduly influence professional judgments** ...” (IOM, 2009)

CONFLICT OF INTEREST: A DEFINITION

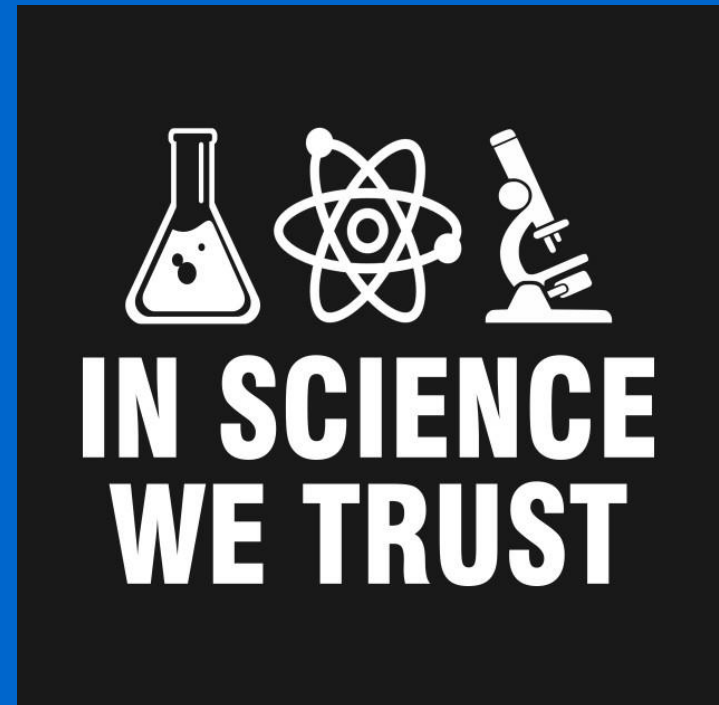
✚ A set of conditions in which **professional judgment** concerning a primary interest tends to be **unduly influenced by a secondary interest**

- Thompson, 1993



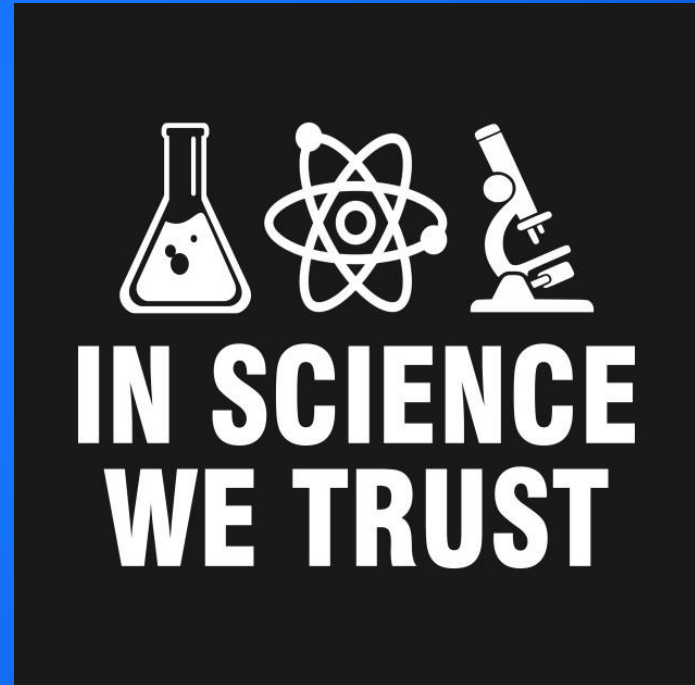
OBJECTIVITY IN SCIENCE

- ✚ Essential for scientific research
- ✚ Basis of **public trust**.



IF NOT PROPERLY ADDRESSED, CONFLICTS OF INTEREST

- ✚ Undermine trust of public in scientists
- ✚ Threaten scientific integrity and fidelity



FIDUCIARY RELATIONSHIP

✚ Between unequals

✚ More powerful party (e.g.,
researcher) is entrusted to protect

well-being of less powerful party
(e.g., the research participants and
the public)



FIDUCIARY RELATIONSHIP

✚ Researchers should act conscientiously to avoid conflict between their own interests and those of the dependent party”

Dickens, 1995





CONFLICTS OF INTEREST DYNAMICS

Empirical studies have shown:

HOW CONFLICT OF INTEREST WORKS

- ✚ Physicians who attended grand rounds by a pharmaceutical company speaker – more likely to prescribe company's drug
- ✚ For conditions for which it was not appropriate
- ✚ Even if many attendees could not recall what company sponsored the grand rounds
- ✚ (Interviews done 90 days after grand rounds)



COMPANY SPONSORED GRAND ROUNDS: UNDUE INFLUENCE

- ✚ Grand rounds effectively change residents' beliefs, in favor of sponsoring company's drug
- ✚ Resulting in poor, or more expensive treatment



WHAT PHYSICIANS THINK

‘I am not affected by conflicts of interest but other physicians are affected by conflicts of interest in their decisions’

McKinney, et al, 1990



WHAT PATIENTS THINK:

✚ Other physicians are affected by conflicts of interest but my physician is not

Palmisano & Edelsteinm 1980



BIASES ABOUND

✚ “Self-interest distorts the way that people weigh arguments”

Dana & Loewenstein, 2003

Babcock, Loewenstein, & Issacharoff, 1997



UNDERESTIMATING ONE' S BIAS



✚ Even when people accept that they are biased, they underestimate how strong their bias is

✚ Informing disputants of the bias had no impact on the magnitude of the bias

Babcock, Loewenstein, & Issacharoff, 1997

Babcock and Loewenstein, 1997

ALL PRESENTS BIG AND SMALL

Bias arising from conflicts of interest is strong, even in studies with small stakes

Dana & Lowenstein, 2003



EVEN SMALL GIFTS CREATE BIAS

- ✚ Limiting gift size not likely to eliminate bias



BIAS IS UNCONSCIOUS

- ✚ Individuals are not aware of their bias even when told about it



Residents' perceptions of pharmaceutical industry interactions and gifts over time

✚ "Appropriate" gifts of minimal value were generally perceived as increasingly appropriate

✚ "Inappropriate" gifts were perceived as increasingly inappropriate over time.

PSYCH RESIDENTS: INTERACTIONS WITH PHARMA INDUSTRY

Scope

- ✚ 7 teaching hospitals affiliated with the University of Toronto
- Department of Psychiatry

Participants

- ✚ 105 Residents, Interns and Clerks

PSYCH RESIDENTS: INTERACTIONS WITH PHARMA INDUSTRY

- ✚ 34% (25/73) felt that discussions with representatives would have no impact on their prescribing practices
- ✚ 56% (41/73) felt that receiving gifts would have no impact on prescribing
- ✚ The more money and promotional items a physician-in-training had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing



PSYCHIATRY INTERACTIONS WITH PHARMA INDUSTRY

- ✚ Faculty and psychiatric residents and fellows
 - Belittle pharmaceutical representatives' teaching role
 - Mistrust the information they offer BUT
 - Do not want to lose industry's financial support

Misra, 2010



PHYSICIAN INTERACTIONS WITH PHARMA INDUSTRY

- ✚ The physicians-in-training perceive little educational value in these contacts
- ✚ Clerks, interns and junior residents disavow the potential of these interactions to influence prescribing.

Hodges, 1995



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Review of cross-sectional studies and cohort studies, but also (non-)randomised trials and survey designs comparing at least one facet
- ✚ PubMed, Embase, Cochrane Library and Google Scholar electronic databases (January 1992 to August 2016)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Most common gifts received were medical samples, promotional materials, invitations for dinners, invitations for CMEs, scientific journals and free lunches
- ✚ Physicians do not believe that PSR interactions impact their prescribing behavior (most studies)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Physicians considered their colleagues more susceptible than themselves to med rep marketing strategies (5 studies)
- ✚ Strong correlation between the amount of gifts and the belief that med rep interactions did not influence their prescribing behaviour.



PHYSICIAN-INDUSTRY INTERACTION

- ✚ better scores on knowledge and attitudes were significantly associated with fewer interactions with representatives and their gifts



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Physicians considered themselves immune to the influence of gifts (8 studies), BUT
- ✚ Accepting samples lead to higher branded drug prescription rather than generic prescribing (2 studies)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Company-sponsored lectures/symposia led attendees to prescribe more drugs from the sponsors
- ✚ Without sufficient evidence supporting superiority of those drugs. (56, 57)
- ✚ Majority of attending physicians failed to identify inaccurate information about the company drug (18)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Physicians who received money ... to perform research requested addition of the company's drug to the formulary more often than other physicians
- ✚ Brief encounters with sales reps and receipt of honoraria/ support were predictors of faculty requested change in hospital formulary. (68)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Significant increase (3X) in the prescribing rate of two company drugs was observed after the physicians attended a company-sponsored symposium with all their expenses covered.
- ✚ Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour. (57)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Physicians who refused CME sponsorship prescribed more generics and lower price meds compared with sponsored physicians (22)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Majority of physicians do not believe that they are affected by med rep interactions. (1 10 32 33 35 37 43 59)
- ✚ However, they thought that their peers are vulnerable to med reps. (1 20 21 37 43)



PHYSICIAN-INDUSTRY INTERACTION

- ✚ Physician-pharmaceutical industry's interactions and acceptance of gifts from the company's med reps:
 - contribute to irrational prescribing of the company's drug
 - put the trust of patients in physicians at risk
- ✚ Policy implementation and education about the implications of these interactions is needed.



RCT OUTCOMES: INDUSTRY VS NON-PROFIT FUNDING

- ✚ Randomized controlled trials (RCTs) financed by industry are associated with more favorable outcomes compared with other types of funding sources

Ridker & Torres, 2006



SELF-DECLARED STOCK OWNERSHIP AND POSITIVE TRIAL OUTCOME

- ✚ All parallel-group RCTs (509) published in *JAMA*, *The Lancet*, and *NEJM* between 2013 and 2015
- ✚ **Conclusion: Stock ownership in the funding company among any of the authors was associated with a favorable outcome** (odds ratio = 3.53; 95% confidence interval = 1.59–7.86; $p < 0.01$)

Delgado & Delgado, 2017



SELF-DECLARED STOCK OWNERSHIP AND POSITIVE TRIAL OUTCOME

- ✚ For-profit-funded RCTs have a higher OR for a favorable outcome than nonprofit- and mixed source-funded RCTs.
- ✚ This difference is associated mainly with the use of surrogate endpoints in for-profit-financed drug trials.

Delgado & Delgado, 2017



SELF-DECLARED STOCK OWNERSHIP AND POSITIVE TRIAL OUTCOME

- ✚ COI in for-profit funded RCTs is extensive with several COI domains associated with favorable outcomes

Delgado & Delgado, 2017



Study on trials having industry funding

- ✚ 219 articles from 10 high-impact journals describing the results of drug and device trials

Roper, et al., 2014



Trials having industry funding

■ More likely to

- Report a positive primary outcome (69.8% vs 52.2%; RR, 1.34; 95% CI, 1.03-1.75 [$P = .03$])
- Use a surrogate primary end point (51.2% vs 16.4%; RR, 3.11; 95% CI, 1.75-5.56 [$P < .001$])

■ Less likely to discuss limitations (40.7% vs 58.2%; RR, 0.70; 95% CI, 0.50-0.97 [$P = .04$])



Trials having industry funding

- ▣ Collaborative trials' more common **use of a surrogate primary end point** may, in part, explain why these trials were more likely to have a positive primary outcome



INDUSTRY SPONSORSHIP AND RESEARCH OUTCOME

- ✚ Sponsorship of drug/ device studies by manufacturing companies leads to **more favorable results and conclusions.**
- ✚ Such bias cannot be explained by standard 'Risk of bias' assessments.
- ✚ **Less agreement between the results and the conclusions** than in non-industry sponsored studies, RR: 0.84 (95% CI: 0.70 to 1.01)



RESEARCH OUTCOMES AND STUDY SPONSORSHIP

- ✚ Systematic review of reviews of the effects of artificially sweetened beverages on weight



RESEARCH OUTCOMES AND STUDY SPONSORSHIP

- ✚ Sponsorship of reviews and authors' financial conflicts of interest introduced bias
- ✚ affecting the outcomes of reviews of artificially sweetened beverage effects on weight
- ✚ could not be explained by other sources of bias



RESEARCH OUTCOMES AND STUDY SPONSORSHIP

- ✚ Reviews sponsored by artificial sweetener industry – more likely to have favorable results
- ✚ Reviews performed by authors with financial COI (disclosed or not) – more likely to have favorable conclusions



The Rosuvastatin-JUPITER Controversy: Bias introduced by Early Termination

- ✚ JUPITER (Justification for the Use of Statins in Primary Prevention) trial
- ✚ Reported a substantial decrease in the risk of cardiovascular diseases among patients without coronary heart disease and with normal or low cholesterol levels



Terminated early, citing benefits



The Rosuvastatin-JUPITER Controversy: Bias introduced by Early Termination

- ✚ Prespecified **rules for stopping were not detailed** in the study protocol:
 - What **endpoints** to use
 - What **level of benefits** to justify early termination
- ✚ Conclusion: Trial was terminated **prematurely**
- ✚ Review of both results and methods showed trial was flawed



INDUSTRY INFLUENCE ON GUIDELINES

- 60 — 90 % of clinical practice guideline developers have a financial relationship with a company that makes a product addressed by those guidelines



INDUSTRY INFLUENCE ON GUIDELINES

- ✚ National Kidney Foundation issued guidelines for anaemia management in 2006
- ✚ Using consultants connected with companies manufacturing erythropoietin
- ✚ Recommended erythropoietin use at levels significantly increasing the risk of death, myocardial infarction, congestive heart failure, and stroke (13,14)



Ghostwriters

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"IT'S OKAY DEAR. HE'S MY GHOSTWRITER."

JOSEPH
FERRAS



Medical Papers by Ghostwriters Pushed Therapy

By NATASHA SINGER

Published: August 4, 2009

Newly unveiled court documents show that ghostwriters paid by a pharmaceutical company played a major role in producing 26 scientific papers backing the use of hormone replacement therapy in women, suggesting that the level of hidden industry influence on medical literature is broader than previously known.



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Special Communication

Guest Authorship and Ghostwriting in Publications Related to Rofecoxib

A Case Study of Industry Documents From Rofecoxib Litigation



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Ghost Authorship

- Kung ang sumulat ng protocol, gumawa ng statistical analysis, o sumulat ng manuscript ay **hindi nakalista bilang author**.
 - **75% ng mga publications may ghost authors**
 - Marami sa multo ay statisticians



Academic mercenaries?

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"I can prove it or disprove it! What do you want me to do?"



Honorary/ Gift Authors

✚ Hindi sapat ang kaalaman sa inilalathala



STUDY OF PUBLICATION AGREEMENTS

- ✚ 647 randomized trial protocols approved in 2000–2003 by RECs in Switzerland, Canada, and Germany, and in 388 corresponding journal publications
- ✚ 70% of protocols mentioned an agreement on publication rights between industry and academic investigators
- ✚ in 86% of those agreements, industry retained right to disapprove or review manuscripts before publication.



STUDY OF PUBLICATION AGREEMENTS

- ✚ Funding statements in the 171 funded trials indicated the source in 100%, amount in 1% and **roles of funders in 50%**.



STUDY OF PUBLICATION AGREEMENTS

- ✚ Of 54 funding statements in which the **source was a not-for-profit** organisation, [BUT]
- ✚ we found evidence of undisclosed support from private-for-profit organisation(s) in 26 (48%).



STUDY OF PUBLICATION AGREEMENTS: Roles of Funders

- ✚ The most frequently reported roles of funders in the 171 funded trials:
 - Study design (42%) and
 - Data analysis, interpretation or management (41%)



Pinakamalalaking Aregluhang Pharamaceutical

(Pakikipag-areglo sa
US Department of Justice)



Abilify

- ✚ 2007: Squibb, **\$515 million**
- ✚ Ilegal na promosyon ng antipsychotic sa mga bata at seniors
- ✚ (kahit may warning tungkol sa nakamamatay na side effects sa mga nakatatanda).



Seroquel

- ✚ 2010: AstraZeneca, \$520 million
- ✚ Panunuhol sa mga doktor upang ireseta sa di-aprubadong gamit
- ✚ maaaring makamatay



Oxycontin

- 2007: Purdue Pharma,
\$634.5 million
- Mapanlinlang na pagbebenta
ng Oxycontin
- Pagtatakip sa laganap na
adiksiyong dulot nito



Epogen

- ✚ 2015: Amgen, **\$495 million**
- ✚ Pagbibigay ng paraan sa mga doktor na makakuha ng di makatarungang masmalaking kita.



Vioxx

- ✚ 2011: Merck, **\$950 million**
- ✚ Mapanlinlang na promosyon
- ✚ Napatunayang nakadagdag sa panganib ng heart attack at stroke ito;
- ✚ higit sa 70,000 katao ang namatay.
- ✚ Daan-daang milyon pa ang ibinayad sa mga pasyente



Zyprexa

- ✚ 2009: Eli Lilly, **\$1.4 billion**
- ✚ Promosyon ng Zyprexa para sa off-label uses
- ✚ Ibinenta bilang sleeping pill para sa seniors
- ✚ kahit na maaari silang makatulog nang forever dahil dito



Depakote

- ✚ 2012: Abbott Laboratories, \$1.5 billion
- ✚ Promosyon para sa off-label use sa dementia patients
- ✚ Walang ebidensiya na ito ay ligtas
- ✚ (sa kabila ng side effect tulad ng anorexia, sa nakatatanda).



Risperdal

J&J Ordered to Pay Millions in Risperdal Jury Verdicts

AA

Posted February 27th, 2015 by [Michelle Llamas](#) & filed under [Current Litigation & Lawsuit News](#).

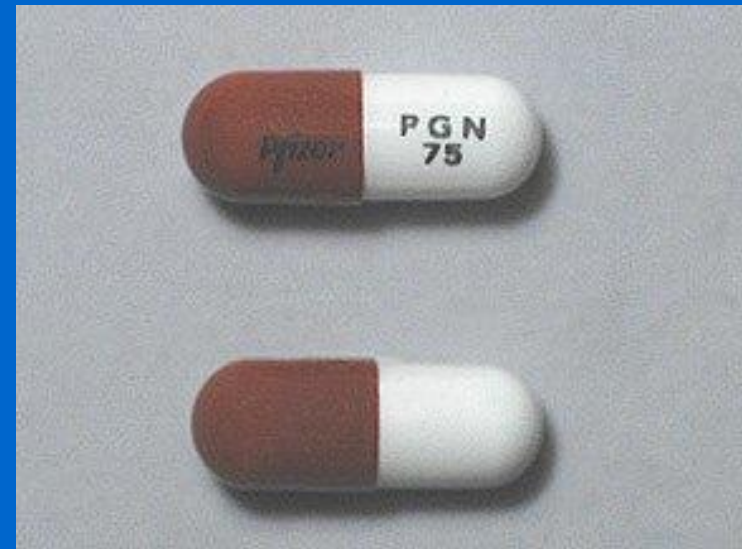
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Johnson & Johnson and subsidiary Janssen Pharmaceuticals face ongoing legal troubles with Risperdal after the drug giant was slapped with two multimillion dollar verdicts this week – one



Bextra, Lyrica

- 2009: Pfizer, \$2.3 billion
- Mapanlinlang na promosyon
- Off-label uses, kickback sa mga doktor



Paxil, Welbutrin at Avandia

- ✚ 2012: GlaxoSmithKline (GSK), **\$3 billion**
- ✚ Ilegal na marketing ng Paxil at Welbutrin at pagtatago sa panganib dala ng Avandia
- ✚ Panunuhol sa mga doktor



Paliwanag para sa pag-aareglo

✚ “Although we believe strongly in the merits of our case, we decided it was in our stakeholders’ best interests to resolve it,”

✚ “The potential mandatory penalties for being found in the wrong in even a small percentage of instances were simply too large.”



LEKSIYON:

ANG BUHAY, KALUSUGAN AT KAPAKANAN NG
TAO AY MADALING MAISUGAL AT MABAYARAN
SA LARANGAN NG KOMERSIYO



Self-Deception about Bias

- ✚ Social psychology research provides abundant evidence:
 - Human beings respond strongly to self-interest incentives, but
 - Firmly believe that they do not

Kjaergard, 2002 & Dana 2003



MITIGATING BIAS

- ✚ For experience to mitigate bias ..., two conditions must be met:
 - become aware of the bias, and
 - such awareness must have the effect of reducing the bias

Babcock, Loewenstein, & Issacharoff, 1997



Ano ang iyong COI?



Ano ang puwede / dapat gawin?



Residents' perceptions of pharmaceutical industry interactions: Recommendations



- ✚ Intensive education programs to train physicians about gifts from and interactions with industry.

- ✚ These programs must be coupled with broader institutional policy to be effective

(Schneider, 2006)

Dealing with Declared COI: Options for Guideline Formulators

- ✚ Not to take part in the portion of the discussion or work affecting that interest,
- ✚ Not to take part in the meeting or work altogether, or
- ✚ Public disclosure of interest



WHO: Conflicts of Interest Declaration

- ✚ **Financial interest**, e.g. shares or bonds, in a commercial entity with an interest in the subject-matter



WHO: Conflicts of Interest Declaration

- ✚ Employment, consultancy, directorship, or other position during the past 4 years, paid or not, in any commercial entity which has an interest in the subject-matter



WHO: Conflicts of Interest Declaration

- ✚ Paid work or research during the past 4 years commissioned by a commercial entity with interests in the subject-matter



WHO: Conflicts of Interest Declaration

- ✚ Payment or other support covering a period within the past 4 years, or an **expectation of support for the future**, from a commercial entity with an interest in the subject-matter



RECOMMENDATIONS

- ✚ A standardised approach to reporting of funding information

Hakoum, 2017



- Research phases for which funding was received: planning, conduct and/or reporting of the research study under consideration. When funding relates to provision of supplies, the appropriate answer is 'conduct'.
- Type of funding received including monetary support, provision of supplies, and so on.
- Value of monetary support and value of other supports.
- Whether the funding provided by any of the funding sources is supported by an entity other than/external to the funding source.



WHAT COI TO REPORT

Involvement (role) of funding sources

- Involvement (role) of each funder in the process of the research study, including:
 - Study planning and conduct: design and protocol drafting, study management, participant recruitment, data collection, data management, data analysis, quality control.
 - Study reporting (manuscript): preparation, review, approval, decision to submit.
 - Authorship: authors employed by the funder.



RECOMMENDATIONS

- ✚ Diligent assessment of adherence to reporting guidelines (CONSORT) by authors, reviewers and editors to promote transparency and unbiased reporting of abstracts.

Hays, et al., 2016



RECOMMENDATIONS

- ✚ Require investigators submitting proposals to ERCs to disclose all financial ties to companies that could financially benefit from the results
- ✚ Disclosure to comply with guidance stated above



Ano ang iyong COI?

