Therapeutics Initiative

Better prescribing. Better health.

How do YOU respond to Conflicts of Interest?

prominent endocrinologist is a keynote speaker at a primary care conference that has attracted "Platinum, Gold, and Silver" sponsors. To begin her presentation on evidence about a new diabetes drug, she shows for one second a mandatory conflict of interest (COI) disclosure, indicating paid consultancies to Janssen and Novo Nordisk, and clinical research grants from Eli Lilly and Merck.

In the audience, many don't seem to notice how rapidly the issue of possible bias was dismissed. Clinical pharmacist Kirsten has a different response. Potential COI piques her interest; she feels challenged to identify possible biases in the presentation. In this setting, how do YOU respond?

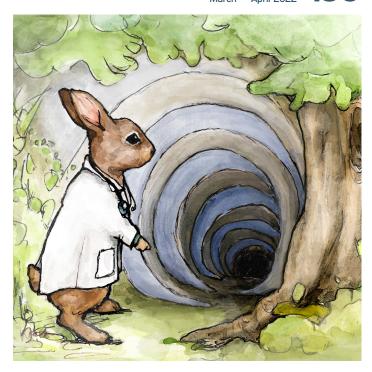
Infectious disease specialist Xavier notes that "conflicts of interest are normalized in our profession to the point that **not having a COI is unusual**." With an important role in antibiotic stewardship, he worries that conflicts worsen the quality of prescribing. Like Kirsten, Xavier tries to avoid professional education events that depend on commercial sponsorship.

Background

Soon after discovery and patent of a new potentially therapeutic molecule, a pharmaceutical company's marketing department may help design "pivotal" randomized clinical trials (RCTs), including selection of comparator treatments and outcomes to be measured.\(^12\) It is also common practice to cultivate "expert" Key Opinion Leaders (KOLs) such as the vignette's endocrinologist.\(^3.4\) Financial rewards for KOL's can be substantial.\(^5\) In the USA they have been disclosed since 2013 at Open Payments\(^6\), though little known to the public. Similar disclosure does not exist in Canada.

While intended to maximize a product's commercial success, such influences also help determine what health professionals learn about "evidence".4

THERAPEUTICS LETTER



Marketing influences on clinical trial design may not be obvious to readers of medical scientific reports, but they inevitably favour sponsors' products. Commercial influence on trial design can include the nature of the hypothesis tested, selection of comparator treatments and doses, outcome definitions, what results are ultimately reported (or not), and the packaging of "takeaway" messages to prescribers. Biased trial designs exaggerate apparent beneficial effects, underestimate harms, and even disguise results that are unfavourable to the drug. (Table)

What is the effect of Sponsorship Bias?

A 2017 Cochrane review concluded that "sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources." This influence cannot be explained by analyzing the "risk of bias" (experimental rigour). A study of 195 RCTs published in major clinical journals in 2013 identified 132 (68%) with personal financial ties between principal investigators and the drug industry. Authors with financial ties

Commercial sponsorship of RCTs influences experimental design and what is reported

Example	Experimental hypothesis	Takeaway messages to clinicians	Contrasts with evidence
Type 2 diabetes	Lower glucose \rightarrow better outcomes	Prescribe to ↓ HbA1c	HbA1c is not a reliable proxy for clinically important outcomes or long-term safety
Low impact fractures	↑ bone density prevents fractures	Prescribe drug to ↑ bone density (as measured)	Bone density and vertebral collapse fractures detected only by x-rays not reliable proxies for clinically important fractures or long-term safety
Pain	New drug "better" or safer than old; ↓ in mean pain scale = improvement	Prescribe new drug and ↑ dose if tolerated	Inappropriate comparator or dose; dose-response not proven; reported pain outcome may not correlate with improved function or long-term safety
Depression	New drug "better" than old; ↓ mean depression rating scale or ↑% "response" or ↑% "remission" defined as improvement	Prescribe new drug and ↑ dose if tolerated	Control only placebo or inappropriate comparator; dose-response not proven; "improvement" on depression scales may not correlate with function or long-term safety



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were more likely than independent researchers to publish results that are positive for a company's products.⁹ Reporting of financial ties also remains unsatisfactory for meta-analyses, although Cochrane reviews have improved more than non-Cochrane reviews.^{10,11}

Professional bodies define COI

Canadian Medical Association (CMA) Guidelines for physicians in interactions with industry state: "Conflicts of interest occur where judgments or decisions about a primary interest – in this case, patient well-being, trustworthy medical research and knowledge, and excellent medical education – are unduly influenced by a secondary interest ... Physicians have a responsibility to ensure that their participation in collaboration with industry primarily serves the interests of their patients and the public"¹² The BC College of Physicians and Surgeons¹³, College of Pharmacists¹⁴, and College of Nurses & Midwives¹⁵ all emphasize professional independence from the influence of industry. They counsel registrants to identify and avoid actual, potential or perceived COI.

Therapeutics Initiative's approach to COI

The Therapeutics Initiative requires its members to avoid financial conflicts of interest. Thanks to public funding, we do not accept commercial support for our activities, including for our educational events.

Are YOU too smart to be influenced?

Many clinicians believe they are immune to pharmaceutical company influence, even if their colleagues are not.¹⁸ Like other humans, we underestimate our susceptibility to conflicted influencers who are expert at exploiting our subconscious biases.¹⁹ The CMA agrees: "physicians may not always be aware of, or be able to accurately self-assess, how their industry affiliations can subconsciously influence their judgment, their assessment or presentation of medical evidence, their clinical decisions and their prescribing."¹² Disclosure of potential COI does little or nothing to protect us.^{20,21}

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What can YOU do to avoid conflicted education?

Kirsten's awareness of the speaker's COI stimulates her feedback to the conference organizers: "Please aim for unconflicted speakers next time." She also plans to seek high quality, unconflicted drug information for a more nuanced perspective. In his teaching about antibiotics, Xavier draws attention to the importance of understanding how COI can influence our prescribing, and he continues his work toward unconflicted treatment guidelines. Anyone can look for evidence from systematic reviews whose authors are limited to scientists without conflicts. (Box)

Guidelines We Can Trust, a 2011 report of the US Institute of Medicine, concluded that COI can affect "the integrity of scientific investigations, the objectivity of medical education, the quality of patient care, and the public's trust in medicine". Its strong recommendations about handling COI during clinical practice guideline development are yet to be applied to most Canadian guidelines.

Conclusions

- Industry sponsorship of clinical trials can lead to biased conclusions, including exaggerated claims of efficacy and underestimation of harms
- Sponsorship influences research design, conduct, publication, and use of results in systematic reviews and guidelines.
- Many Key Opinion Leaders provide promotion, not unbiased education.
- In research reports, review articles, guidelines, or continuing professional development events, look for commercial sponsorships. Ask yourself "Who paid for this and why? Is bias likely? What am I not being told?"
- Look for evidence reviews (like those from the Therapeutics Initiative) that strictly avoid conflicts of interest.
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The draft of this Therapeutics Letter was reviewed by multiple experts and primary care clinicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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