*Journal & Proceedings of the Royal Society of New South Wales*, vol. 151, part 1, 2018, pp. 59–68. ISSN 0035-9173/18/010059-10

# Influences on evidence: putting the cart before the horse

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## Abstract

Conflicts of interest, particularly those related to financial gain, can influence policymaking, and mechanisms exist to try to minimize their impact on decisions. There has been a great deal of investigation and concern about the role of evidence in policymaking compared to other influences. But have we been putting the cart before the horse? Should we be paying more attention to what influences the evidence? Conflicts of interest can bias the design, methods, conduct, interpretation and publication of research. These biased findings deviate from the truth and have led decision makers to underestimate harms or overestimate effectiveness of interventions. The research community has responded by increasing transparency about the research enterprise. But this is not enough. We should strive to reduce the influence of conflicts of interest on research so we can have trustworthy evidence.

## Introduction

Putting the cart before the horse is an analogy for doing things in the wrong order. In the Post-Truth world discussed in this issue of the *Journal*, concerns have been raised about the role of evidence in policymaking. But have we been putting the cart before the horse? Should we be paying more attention to what influences the evidence itself? Bias occurs when generating or interpreting evidence is not neutral: it leads to deviation from the truth.

One important cause of systemic bias lies with powerful groups who have a financial interest in a particular version of the truth. Such groups may fund employees, academic researchers or key opinion leaders to create or spread biased evidence, thus perpetuating fake news. These groups or individuals who have financial interests in a particular version of the truth are often said to have a financial conflict of interest. Conflicts of interest can lead to bias in evidence if the people carrying out or disseminating research do so in a manner that leads to deviation from the truth. Conflicts of interest that bias the design, methods, conduct, interpretation and publication of research have led decision makers to underestimate harms or overestimate effectiveness of interventions.

Conflicts of interest, particularly those related to financial gain, are also a powerful influence on policymaking, and mechanisms exist to try to minimize their impact on decisions. The research community has done less to minimize the effects of conflicts of interest. The community has responded primarily by increasing transparency about the research enterprise. But this is not enough. We should strive to reduce the influence of conflicts of interest on research so we can have trustworthy evidence.

## What is a conflict of interest?

A conflict of interest is a circumstance that creates a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest (Lo and Field, 2009). In the case of research, the primary interest is conducting

unbiased research while a secondary interest may be personal financial gain of the researcher. Conflicts of interest should not be confused with other interests that affect research. Research is not value free and is conducted in a social context (Bero and Grundy, 2016). Researchers have personal beliefs, experiences and opinions that may influence their choice of research topic or paradigm. These interests make a researcher who they are and are not conflicts of interest. Interests are ubiquitous, unlike conflicts of interest which are unevenly distributed among researchers (Bero and Grundy, 2016). In addition, conflicts of interest have a "megaphone effect" as multiple researchers can have the same conflict of interest that influences research in the same direction. For example, multiple investigators with ties to the same pharmaceutical company could bias research to favour the company's products (Bero, 2017). In sum, conflicts of interest are a *risk*: they do not necessarily produce biased judgments or actions. Conflicts of interest are not "potential" but real; whether they result in bias is the question.

Conflicts of interest are well understood in the realm of politics. For example, United States President Donald Trump's conflicts of interest have been documented. His failure to disclose his income tax statements prevented the evaluation of his conflicts of interest related to tax reform. Nepotism within his staff and the impact of US policies on his stocks, leasing of government property, and foreign holdings all present conflicts of interest. Simon Chapman's paper in this issue (Chapman, 2018) addresses misconceptions about the hazards of wind farms. Mr. Trump's response to wind farms was influenced by his conflicts of interest. Mr Trump owns two golf courses in Scotland and asked UK politicians to oppose wind farms. This was not because he believed they were bad for health, harmed animals, or contradicted US/UK energy goals, but because they would lower the value of his golf course property.

Biomedical researchers have trouble recognizing and acknowledging conflicts of interest. Disclosures of funding sources and conflicts of interests in scientific articles are now more common, but they can still be confusing (Dunn et al., 2016). Disclosure statements may refer to "actual" and "potential" conflicts of interest in the same statement, or to multiple funding sources with some listed as "dualities of interest." Some conflict of interest disclosures note that research article authors were "given an opportunity" to disclose, but it is not clear to readers what, if anything, was disclosed.

Or meaningful conflict of interest disclosures can be obfuscated if journals drown us in too much, or irrelevant, information. A growing trend among medical journals is to list pages of financial ties with companies for each article author. These long lists, however, fail to provide information on the relevance of the tie to the research being conducted, the financial amount of the tie, or the length of the relationship between the researcher and the company. Disclosures of "non-financial conflicts of interest" create confusion about what is a conflict of interest vs. a scientist with interests (Bero and Grundy, 2016). A systematic review examining the association of neonatal herpes simplex infection with Jewish ritual circumcision examined 6 published studies on this topic (Leas and Umscheid, 2015). The paper included this disclosure from the authors:

> B. F. L. is an adherent of Orthodox Judaism, and he is not affiliated with the religious sects that commonly practice direct oral suction during circumcision, nor is he affiliated with any of the organizations represented in the legal case addressing the New York City informed consent rule. B. F. L. and his sons underwent ritual Jewish circumcision, without direct oral suction. C. A. U. is a nonpracticing Roman Catholic whose wife affiliates with secular Judaism. C. A. U. and his son were circumcised by pediatricians in the hospital setting.

It is unclear how these personal characteristics would be considered conflicts of interest rather than values and preferences that could influence the research.

While conflict of interest disclosure is a necessary first step, it is not a solution for managing or reducing bias associated with conflicts of interest (Bero, 1999). In published biomedical research, disclosure is difficult to enforce or simply not required. Experiments have shown that, in the financial sector, disclosure makes those giving advice more biased (Cain et al., 2005). Finally, as shown later in this paper, disclosure does not prevent bias in research.

## Conflicts of interest and bias

Researchers are likely to deny that conflicts of interest could bias their research. Quotes from interview studies with biomedical researchers illustrate this point (Boyd et al., 2003), (Lipton et al., 2004):

- "I'm not influenced." "My colleagues are influenced, but I'm not."
- "I have ties with all the companies, so I'm not influenced by any."
- "I'm just helping out my patients."
- "I recognize that I am in conflict, but believe that I can handle it. If I couldn't handle the conflict I wouldn't have gotten involved."

These investigators fail to recognize that preventing bias is not an issue of personal responsibility. Instead, we need institutional and cultural changes to reduce bias stemming from conflicts of interest. By studying the types of bias that are associated with conflicts of interest, we can develop institutional strategies to mitigate the biases.

Meta-research studies that examine research across an entire body of evidence have demonstrated that conflicts of interest are associated with bias. Bias occurs when some study characteristic, such as the study funding source or author conflict of interest, is associated with the outcome of the study. This association is observed even when controlling for the effect of the intervention or exposure being tested or the methods of the study. For example, a 2017 meta-analysis of studies that examined the association of drug industry sponsorship with the outcomes of drug studies found that studies sponsored by the makers of the drugs being tested were about 30% more likely to find that the drug was effective compared to studies with other sponsors (Lundh et al., 2017). This association was observed even though the studies had similar methodological characteristics (eg, randomization or blinding). Similar relationships between funders and favourable outcomes have been observed for research in other fields such as nutrition or tobacco research (Chartres et al., 2016), (Barnes and Bero, 1998).

So what is going on… how does this bias happen? There are a number of ways that a study can be biased (Odierna et al., 2013). Bias can be introduced in the questions that

are asked, including whether a question is asked at all or how a question is framed. Bias can also be introduced in the methods of a study, or in how a study is conducted behind the scenes, even if the method is rigorous. Lastly, bias in a body of evidence can occur if only some studies get published or only some outcomes from a study get published.

### Conflicts of interest can affect research agendas

Funders and authors with conflicts of interest can bias entire research agendas, thus influencing the questions that are asked in a way that makes them less relevant for public health interests and more relevant for commercial interests. For example, in a sample of 213 randomized controlled trials in nutrition research, we found that 67% of the food-industry-sponsored studies focused on interventions involving manipulations of specific nutrients (Fabbri et al., 2017b). The non-food industry-funded trials addressed different levels of dietary composition, including whole foods and combinations of foods and nutrients. A similar pattern was observed among observational studies (Fabbri et al., 2017a). Thus, the food-industry-funded studies were more likely to assess formulated products that could be marketed for benefits related to a certain nutrient. Critical public health questions regarding the benefits of whole foods and interactions of foods were not addressed.

In addition, food companies have funded research that detracts attention away from the harms of certain food ingredients. For example, Coca-Cola has funded research on the benefits of exercise rather than the harms of sugar, and the sugar industry funded research on the association of fat intake, but not sugar intake, with cardiovascular disease (Kearns et al., 2016). The tactic of funding research was also used by the tobacco industry to distract attention away from the harms of second-hand smoke exposure. The tobacco-industry-supported Center for Indoor Air Research funded research on the effects of indoor air substances such as carpet fumes or oxygen from green leafy plants, rather than research on the health effects of second-hand smoke. The results of these studies were used in policy arenas to suggest that substances in indoor air other than tobacco smoke were more likely to influence health and should be regulated instead (Barnes and Bero, 1996).

### Bias in methods

Methodological risks of bias occur when components of a study design allow a systematic error in the assessment of the magnitude or direction of the results (Higgins and Green, 2008). In clinical trials testing the efficacy of drugs, studies lacking randomization or blinding falsely inflate the efficacy of the drugs compared to studies that have these design features (Page et al., 2016). They also are less likely to report statistically significant adverse effects (Nieto et al., 2007). Thus, biased methods can shift effect estimates to be larger or smaller. Inappropriate randomization and a lack of blinded outcome assessors can also bias the outcomes of animal studies (Crossley et al., 2008). Industry-sponsored studies, and those with conflicted authors, tend to use methods very similar to those in studies without financial ties. The differences in outcomes observed between industry- and non-industry-sponsored studies are more likely due to biases in how the questions are asked as discussed above, or the next source of bias in the research cycle: selective reporting bias.

### Selective reporting bias

Selective reporting bias occurs in different ways (Dwan et al., 2011). Selective analysis bias occurs when the same outcomes from a study are analysed in different ways and only some of the analyses are published. For example, different statistical tests could achieve different levels of statistical significance and only the analyses with statistically significant findings are published. Selective outcome reporting occurs when some, but not all, of the outcomes of a study are published. For example, a study with depression as an outcome may use a scale to measure depression following 3, 6, 12 and 18 months of treatment. Selective reporting bias occurs if data from only one time point is reported. Or if depression was measured using different scales, selective outcome reporting would occur if only the data from one scale was reported. Publication bias occurs when an entire study is not published.

We conducted a series of studies demonstration selective reporting bias in the publication of drug and tobacco research where bias in reporting was associated with industry funding or financial conflicts of interest of the authors (Rising et al., 2008), (Hart et al., 2012). In one of these studies, we asked the simple question, "Are all drug studies that are submitted to the US Food and Drug Administration as the basis for drug approval published?" Publication of these studies would mean that doctors and other prescribers would have access to the same information as the regulator. Prescribers could then base their treatment decisions on the best available evidence rather than information provided by pharmaceutical companies.

The simple answer to this question was no. Of 128 trials that were used as the basis for regulatory approval of 33 new drugs, 78% were published within 5 years of approval. However, all trials were published for only 52% (17) of the drugs; no trials were published for 2 of the drugs. One of the drugs with no published data was for a pediatric indication. All of the trials were sponsored by the companies who made the drugs and submitted the applications for regulatory approval to the FDA (Rising et al., 2008).

We also found evidence of selective outcome and analysis reporting. Forty-one primary outcomes reported to FDA were missing from the papers. None of these was favourable to the drug being tested (Rising et al., 2008). Interestingly, 15 outcomes that were not reported to the FDA appeared in the publications. All of these were favourable to the drug being tested. Lastly, the analysis and resulting statistical significance of 5 outcomes changed between the FDA data and published data. Four out of five of these changes favoured the test drug. The bottom line is that all of the selective reporting meant that the scientific publications about each drug made the drug look more effective than it actually was.

Things get really interesting when we look at how studies are conducted behind the scenes. Litigation has given us glimpses into how conflicts of interest can introduce bias in the way a study is conducted, even when it has a rigorous methodology. As part of settlement agreements, courts have released previously confidential documents that were used as evidence in cases investigating harm from tobacco, drugs, or chemicals. These documents, which are freely available to the public, are a goldmine of information about how corporations influence research agenda, as well as the design, conduct and publication of research (White and Bero, 2010).

Internal documents from pharmaceutical companies have given us particular insight into how industry sponsorship or conflicts of interest affect the publication of science. Drug industry documents described scientific publication as part of their marketing strategy, with the goal of disseminating favourable information about their products (Steinman et al., 2006). Pfizer and Parke-Davis sponsored trials of a drug called gabapentin to test the drug's efficacy for a variety of unapproved ("off-label") indications. Demonstrating that a drug works for an unapproved indication could expand the use of the drug and increase its sales. Internal documents describe how company executives managed the publication of every trial. Directions were given that trials with "positive" results were to be published and trials with "negative" results were not (Steinman et al., 2006).

We tracked the publication of the 20 clinical trials of gabapentin for which internal documents were available by comparing the protocols for the trials found in the internal documents to the final publications (Vedula et al., 2009). The publication outcomes of these trials showed a very similar pattern to the publication outcomes of the 164 trials where we compared what was submitted to the FDA with what was published. Of the 20 trials of gabapentin, 12 were reported in publications. For 8 of the 12 reported trials, the primary outcome defined in the published report differed from that described in the protocol. Of the 21 primary outcomes described in the protocols, 6 were not reported at all and 4 were reported as secondary outcomes. Of 28 primary outcomes described in the published reports, 12 were newly introduced. Trials that presented findings that were not statistically significant for the protocol-defined primary outcome in the internal documents were not reported in full or were reported with a changed primary outcome. The primary outcome was changed in the case of 5 of 8 published trials for which statistically significant differences favouring gabapentin were reported.

Bias can also occur in the interpretation of results, otherwise known as "spin." Spin refers to reporting practices that distort the interpretation of results and mislead readers so that results are viewed in a more favourable light. Spin is a familiar concept in the media and politics, but is also prevalent in the scientific literature. Spin was defined in many different ways, but the most common manifestations were making the results look larger than they were, claiming statistical significance when there was none, and inappropriate claims of causality. We conducted a systematic review of 35 studies of spin (Chiu et al., 2017). The occurrence of spin differed by study designs. A median of 86% of observational studies had spin, 58% of controlled trials, and 26% of meta-analyses and systematic reviews. Spun interpretations meant that efficacy was inflated and harms suppressed. Nine studies examined the association of spin with conflicts of interest or industry sponsorship. No differences in spin were detected, possibly due to the high occurrence of spin overall.

## Why conflicts of interest matter and what we can do about them

Valid evidence is the foundation for systematic reviews, public health and clinical guidelines, and health policies. Bias can be difficult to detect, but the evidence that conflicts of interest bias research cannot be ignored. If the evidence is not solid in its question, design, methods or publication, the whole foundation for health policy crumbles. In

addition, we have a problem of trust that is particularly relevant in the Post-Truth era, when people do not know what to believe. Conflicts of interest not only hurt the integrity of research, but also damage trust in science and medicine (Lo and Field, 2009). It is important to note that the effects of conflicts of interest on research are not a problem of 'bad apples' or the moral failings of individuals, but an undesirable situation that requires structural solutions.

Disclosure is an essential first step in identifying conflicts of interest, but does not reduce or eliminate bias. As noted above, financial disclosures in journal articles are often inaccurate, incomplete, or obscured with irrelevant information. Rates of non-disclosure in journal articles remain high, so journals should penalize authors who fail to disclose financial ties. Disclosure can also have adverse consequences. For example, experimental psychology studies found that disclosure by individuals in an advice-giving role benefited the advice givers, but not those receiving the advice (Loewenstein et al., 2012). Lastly, disclosure of funding source or an author financial tie may not reveal the full control of the sponsor over the question formulation, design, conduct or publication of the research (Lundh et al., 2012), (Bero et al., 2005). Additional disclosures regarding the true role of the sponsor are necessary.

A number of structural reforms in clinical research are aimed at reducing reporting and analysis biases. Study registration has become mandatory for publication of clinical trials. Study registries have evolved from including minimal information about a trial's design to now including details of the methods and the results for primary outcomes (Dickersin and Rennie, 2012). Protocols published in registries can be checked to find out if a study has been published. Comparison of published trials with registered protocols enables the detection of deviations in conduct of the study and reporting biases. Clinical research registries permit the registration of observational studies, as well, although registration of these types of studies is not common practice. Registries also exist for systematic reviews and animal studies (Chien et al., 2012), (Jansen of Lorkeers et al., 2014). Registry of all these types of studies should become the norm.

Open access publication of datasets, through journals or data repositories, is a reform aimed at combating reporting and analysis biases, as well as spin. When full datasets are available, different research teams can analyze the data to determine if the findings are reproducible. Given the well documented influence of industry funding and conflicts of interest on selective outcome reporting, open access publication of data should be a requirement for industry-supported researchers and studies. Researchers should participate in industry-funded studies only if all the data are made publicly available.

Reporting guidelines, when required by journals, achieve completeness of reporting so that biases in published articles can be assessed. Over 380 reporting guidelines, covering most types of human and animal studies, can be found at the EQUATOR website (Gould, 2016). Ironically, reporting guidelines do not include detailed templates for improving the reporting of conflicts of interest. To improve study of the impact of conflicts of interest, they should be reported in a structured fashion.

Consumers should approach research conducted by private companies or by

investigators with financial ties with scepticism. Critical appraisal skills can be taught to health professionals, consumer, and even primary school children (Odierna et al., 2015), (Semakula et al., 2017), (Nsangi et al., 2017). Or consumers could leave the evaluation of research to someone else. Rigorous evidence synthesis, conducted by independent organizations such as Cochrane include an assessment for risk of bias for all studies included in the analyses.

The best option for eliminating bias stemming from conflicts of interest is to eliminate the financial conflict of interest. This is not a utopian ideal, as other professions require that key decision makers (such as a judge) have no conflicts of interest. Dependence on industry funding could be lessened by eliminating studies that are conducted to produce alternate facts for marketing or political purposes. The money diverted from these activities could be invested in more meaningful research. Companies could be charged fees, based on the amount of money they spend on advertising, to conduct research that they would normally not fund (Italian Medicines Agency (AIFA) Research & Development Working Group, 2010). Publishers of research could just say no to the publication of industry sponsored studies and extend this to include research conducted by investigators with financial conflicts of interest (Lundh and Bero, 2017). Lastly, industry funding for research could be pooled, although there is little incentive for companies to do this as they could not be guaranteed that the money would be spent showing that their particular products are superior.

The ideas for most of these reforms are not new, but the political will to enact them has been lacking. Decision makers should give greater weight to research that is free of financial conflicts of interest. If we want to protect consumers from biased facts and restore their trust in science, real reform across the research and regulatory sectors, must be undertaken. We need to put the horse back in front of the cart and prioritize structural solutions to minimize the influence of conflicts of interest on evidence itself.

## Acknowledgements

There was no financial support for the preparation of this manuscript.

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