Industry influence in evidence production

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In light of a number of recent drug development and marketing controversies, there is increasing public focus on the role of industry in determining how drugs are used.[1-3] New methods that evaluate how funding has influenced the design, reporting, and synthesis of evidence from clinical trials have identified the breadth of industry involvement in evidence production. The downstream effects on public health remain difficult to quantify. In order to identify and mitigate the potential effects of any one type of trial sponsor, we argue that these new methods should now be used routinely and systematically, in a process we call *evidence surveillance*.

Impact of industry on medical practice

There is compelling evidence that the pharmaceutical industry can influence clinical practice. A handful of notable cases illustrate some of the tactics employed by industry to ensure market uptake and widespread use of its products. The rofecoxib (Vioxx) case demonstrates how diluting the evidence base with positive reports led to prolonged use of the drug and may have caused tens of thousands of additional heart attacks and strokes in the US alone.[2] Other examples of translation problems occurred with rosiglitazone (Avandia), where industry affiliation was associated with more favourable conclusions about cardiovascular risk,[4] and oseltamivir (Tamiflu), where unpublished and previously inaccessible trial results may hold information about serious adverse effects related to its use.[3]

These examples suggest that our system of evidence production and translation remains susceptible to the agendas of drug-makers, which may not always be in line with those of clinicians. New data sources and methods are becoming available to assess the influence of clinical trial sponsors on the design, conduct, dissemination and synthesis of clinical evidence. Despite an increasing focus on transparency around financial conflicts by investigators, industry sponsors remain closely involved in the production of clinical

evidence. Among high-impact journals, published trials with stated industry funding increased from 26% in the early 1980s to 62% in the late 1990s.[5] Of the 83,482 clinical trials registered with ClinicalTrials.gov in 2007-2011, 42% were at least partially funded by industry sources.

Impact of funding source on trial design and conduct

Industry-sponsored trials appear to be designed differently than other trials. Limited evidence in the area suggests that the differences include the types of comparators against which experimental agents are assessed, the outcomes measured, and the length of subject follow up.

Network analysis enables us to examine patterns of interventions and comparators studied in trials and reveal which agents are preferentially selected or avoided. While we cannot glean information of the underlying causes of these patterns, there are strong differences based on funding source. Evidence from specific domains,[6-7] and more generally,[8] show that pharmaceutical companies appear to preferentially examine the drugs they manufacture, and may choose comparators that are more likely to produce positive results.

Industry practices in result reporting and dissemination

Even if clinical trials were systematically designed to address the decision-making needs of clinicians, we know that a substantial proportion of them are not published in a timely fashion. Among a subset of clinical trials registered with ClinicalTrials.gov, only 32% of industry-funded and 56% of otherwise funded trials had their results published within two years of completion.[9] Over half of the trials supporting FDA-approved drugs remained unpublished more than 5 years after approval.[10]

Clinical trials that produce negative or inconclusive results are more likely to remain unpublished, resulting in publication bias. This problem is more often seen amongst industry-funded trials.[11] The implication is that the available evidence supporting certain drugs and drug classes may appear more favourable than if all trial results—both published and non-published—could be assessed.

Industry and result synthesis and translation

Trial evidence may be further compromised by factors that restrict the flow of some published findings while promoting and pushing other evidence into clinical settings and policy changes. Analysis of a group of papers on Alzheimer's disease showed how unfounded claims quickly become widely assumed as fact through a combination of selective citation cascades and the conversion of hypothesis into fact via citation.[12] In an analysis of co-authorship networks,[13] authors with direct industry affiliations were found to be more central in networks of co-authorship, and to receive a greater number of citations for publications about the drugs their companies produce. Other investigators have found that among the most highly-cited clinical trials, a majority had industry funding (despite most trials having authors with university and hospital affiliations) and this proportion increased during the period of study.[14]

The factors that result in industry-sponsored trials more often reporting positive outcomes are not detected using current reviewer methods for risk of bias assessment.[15] Given that only 30% of systematic reviews report the funding of included trials,[16] it appears that industry influences are often able to permeate through the process of evidence synthesis without being detected.

The effects of industry in the design, reporting, and synthesis of clinical evidence suggest that industry can have a profound influence on the perceived safety and efficacy of their own products.

Recommendations and potential solutions

The monitoring of trial registrations and protocols,[6] clinical study reports,[17] and publications,[18] serves to identify evidence gaps and inconsistencies. Releasing data from completed clinical trials more quickly and improving the collaborative use of these data may help to prevent critical failures in evidence translation. An important first step has been the development of clinical trial registries, which have been greatly strengthened by legislative efforts mandating registration for nearly all types of clinical trials. These registries provide the basis from which the surveillance of emerging evidence has become possible. We have previously argued that the corpus of clinical trials should be treated more like a repository – greatly expanding the potential synthesis of patient-level data from clinical trials.[19]

We believe that with improved access to large datasets of registrations, protocols, clinical study reports and publications, we will improve our ability to detect the risk of inappropriate evidence translation. The methods cited above have already been used with some of these large datasets to retrospectively identify system-wide differences in the way industry trials are designed, reported, and amplified during evidence translation.

We propose that these methods could be extended as forms of surveillance – to monitor evidence as it is produced and translated into clinical practice using automated approaches. The goals of evidence surveillance should be, firstly, to examine the breadth of trial registrations and subsequent publications for evidence gaps relative to the burden of disease. The second goal will be to examine the clinical utility of trials – specifically how trial designs (in registrations and protocols) and reporting (in publications or missing publications)

directly address questions of clinical relevance. Finally, the synthesis of evidence should be examined to reveal where trials are ignored or amplified in reviews and guidelines. The examples cited above are amongst a group of exemplars for the methods used to achieve these three goals – but they are currently relatively time-consuming to undertake. If they are extended to be more easily implemented, these methods have the potential to improve clinical evidence translation, as well as to measure the important contributions of all groups invested in the provision of healthcare.

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