EDITORIAL

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Conflicts of Interest in Medicines Safety and Regulation

How Much Conflict and How Much Interest Should We Allow?

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Conflict of interest is a well known and growing controversy in many areas of healthcare, not least in medicines safety and regulation. The direction of these concerns seems to be both narrow and conservative: narrow in the sense of being dominated by financial interests, and conservative in excluding many experts from contribution to debate and decisions. A recent publication[1] provoked my interest. It concerned the global donor agencies and, after the authors had delved into donors' background dealings and their decision making, they came to the conclusion that sometimes donor investments, board member interests and lack of alignment with real public health needs represented conflicts that should be addressed. They also quoted some conflict of interest definitions. In US law, a conflict exists when there is ''a real or seeming incompatibility between one's private interests and one's public or fiduciary duties''. Wikipedia's definition is also quoted as when ''an individual or organisation is involved in multiple interests, one of which could possibly corrupt the motivation for an act in another''.[2] Furthermore, a WHO definition includes ''… when a partner's ability in one role is impaired by his or her obligations in another role or by the existence of competing interests. Such situations create a risk of a tendency (sic) towards bias in favour of one interest over another or that the individual would not fulfil his or her duties impartially … A conflict of interest may exist even if no unethical or improper act results from it. It can create an appearance of impropriety that can undermine confidence …'' None of these definitions is confined to financial interest but the article by Stuckler et al.[1] largely is!

Money is perhaps the most tangible cause for biases, and the WHO definition captures a second – the organization that one represents. Certainly they are identifiable but I argue that they may not be the most important and will use pharmacovigilance as an example discipline.

The late Professor Sir William Trethowan, a wise psychiatrist, taught us students that when first meeting any patient we should ask ourselves 'do I like this person or not?' He explained that our treatment of the patient may well be different depending on that insight. For those who may think this is trivial, I have seen many situations where doctors treating colleagues omit routines that are unpleasant to spare their friend discomfort, but to the ultimate detriment of that patient's care. The opposite may also occur with patients one dislikes being treated perfunctorily. Such preconceptions and prejudices cannot always be discerned, but they are very powerful. They may cause us to leave out important references that oppose our work when writing a paper, or they may lead us to write a more negative review on a paper involving abortion, for example, if we are very much opposed to it. More in keeping with my introductory example, if we generally do not like an author, might not we, as reviewers or readers, be more negative to his/her work. The prejudice may only be a more general one, such as 'nothing good was ever written in that university', or indeed that 'if it is from Yale or Oxford it must be good' (that has certainly been the reasoning

proposed by one colleague for awarding a grant to a dubious project).

There are two important matters here, one is that public disclosure of reviewer conflicts of interest are not publicly available and the second is just how important are the non-financial conflicts. The latter has been considered and recently reconsidered in June 2010 by the International Committee of Medical Journal Editors.[3] This resulted in reversing a previous decision from asking for specific non-financial disclosures of interest to a general question about any other competing interests. This was because of negative feedback: ''people who commented about this issue made it clear that there is immense difficulty in defining competing interests beyond those that involve the direct exchange of money from an interested party to an individual author or the author's institution''.[3] The statement, on the other hand, seems to maintain that these conflicts are important but puts the onus on authors to answer this general question. Is it logical to maintain the importance of this issue and then reduce the rigour of questioning? What is the actual evidence concerning the importance of financial conflicts against scientific obsessions for example? To my knowledge, some of the worst examples of damage to patients come from obsessed professionals who were not challenged by their peers. See Coney ''*The Unfortunate Experiment*''[4] for an example.

Conflict of interest in pharmacovigilance goes beyond writing or reviewing papers. Many pharmacovigilance professionals make direct decisions or write reports that affect the future use and availability of drug products. They also sit on advisory committees or act as expert witnesses in trials, both of which indirectly affect the drug product's future and public health. Declaration of interest is commonly required by committees, or is subject to examination of the expert in court. In the latter case, any avenue of interest may be explored, but the evidence of the witness *is* heard. This seems fine. In advisory meetings, declarations of interest often debar people entirely from decision making or even the discussion of the topic in which they have noted an interest. Particularly in pharmacovigilance, this seems unwise since there are relatively few professionals in our discipline to fulfil such roles, and it may also result in useful opinion not being heard.

A variation of conflict of interest arises in the fairly common situation of being required to sign a confidentiality agreement before a meeting. This may occur in meetings with the pharmaceutical industry, regulatory agencies or non-governmental organizations such as the WHO. At more than one meeting I have found myself in serious conflict with the need for secrecy. On one such occasion I sought ethics advice from the UK's British Medical Association and the General Medical Council (GMC). Both agreed that I had an ethical duty to reveal content of the meeting in the public interest; the GMC held that I could be struck off the register of practitioners if I did not.

From the general media it would seem as though only involvement with the pharmaceutical industry need be declared. This seems wrong since any bias is not good for science and may also be unfair to industry if those who hold negative views about industry are always allowed to speak. It is now commonplace in the media to find that any scientific evidence produced by the pharmaceutical industry directly, or paid for by the industry, is viewed as biased. Whilst it is true that there are several occurrences that have confirmed this view, we seem to have come to a situation where evidence paid for by the industry is never trusted. This situation needs to be changed if essential public-private partnerships in research and drug development are to succeed.

So far, I have painted a limited picture of conflict situations that face pharmacovigilance professionals. Overall I see a chaotic situation where there are many potential conflicts of interest for pharmacovigilance professionals of different kinds. One really important consideration is that in order to fulfil our role adequately we must make value judgements on early signals with preliminary data. This leaves us vulnerable because of potential bias or accusations of bias.

1. The Way Forward?

I looked for help from other areas such as ethics committees' guidelines and medical journal guidance. There were general guidelines over issues

but little consistency, except perhaps that financial conflict should be declared: but how much? Can I never accept a beer from an industry colleague? I found most help in a discipline that must confront conflict of interest daily, whose deliberations are mostly before the public and whose court performance and decisions are a matter of meticulous, written record. A paper on how judges consider these conflicts makes interesting reading.[5] Judges recuse (withdraw voluntarily) from hearing cases or giving judgements according to both conscience and established precedents. Using the legal model described in the paper,[5] I shall make some suggestions about the various situations affecting pharmacovigilance.

1.1 Writing Papers and Reports

This activity does not involve a judgement; one is providing evidence for review as witnesses give evidence in court: reviewers and readers must make judgements about any scientific bias. The Hon Mr Justice David Hayton[5] holds that we all have biases. As responsible people we should monitor these and account for them in our professional work. ''It must be assumed that they (judges) can disabuse their minds of any irrelevant personal beliefs or predispositions''(c.f. Professor Trethowan). On the other hand, a judge must recuse himself or herself if ''a fair-minded and informed observer, having considered the facts, would conclude that there was a real possibility that the judge was biased.''[5] Whilst this seems to beg the question of what is fair-minded, it supports the view that one should view all possible conflicts of interest similarly. This means that financial interests can be considered sensibly; indeed, there is a statement that minor financial conflicts of interest might not even be declared if the amount of money concerned is trivial, although this involves judgement and is therefore controversial.[5] The main point is that disclosures of any interest should be made according to conscience and being aware of what the fair-minded person will think.

A consequence of this is that papers and reports should not be rejected outright because of conflict of interest, but also that the reviewer/reader should have enough information to take that into account. A suggested responsibility for the reviewer could be both to comment on and suggest corrections for bias where appropriate, as well as to determine what the degree of conflict of interest might be.

1.2 Reviewing Papers for Publication

Papers in pharmacovigilance usually deal with the probability that a drug has caused an ADR, often serious. The consequences of publication/rejection are, on the one hand, perhaps contributing to a scare and also damage to a useful drug, but, on the other, perhaps contributing to a critical delay in publishing a signal that might save lives. The reviewers' responsibilities are important in several ways; in assessing how the results are presented and, more particularly, in how the discussion deals with attributability and relevance to public or individual health. Case series are particularly challenging and the strength of causality for each case, and the series as a whole, needs to be justified. The benefit of any doubt must be apportioned with valid reasons. This *does* involve judging authors' works and consequently requires disclosure of conflicts and even more careful self-examination by reviewers. As far as I know, conflicts of interest of the reviewers are not published, although there have been some moves to have the reviews themselves published. This is a good idea since one of the advantages of the legal system is that cases are usually heard in open court and word-by-word accounts of the proceedings recorded. Ideally, science would be promoted by having reviews published with the papers. Failing that, I propose that a reviewer's conflict of interest should be made available to the authors of papers, allowing for appeal where appropriate.

The comments made in section 1.1 apply to reviewers as well – only significant interests need be declared, and only those related to the outcome of the review. For example, a reviewer who has previously worked in the same area need not declare that as a conflict (on the contrary), but a reviewer undertaking current work with a competing approach to the author's approach should.

In this instance, the review itself would need to have obvious objectivity and sufficient detail to be acceptable.

Reviewers' style and comments vary considerably. Some are very detailed, others are high-level critique, but many do not give enough information to support a decision. This needs to change, but a weakness in the current review system is its voluntary nature relative to the amount of work a thoughtful review requires. There is no easy answer here, although I know the efforts taken by editors to have a large enough range of reviewers is immense.

1.3 Acting as Experts on Committees and in Court

This is pharmacovigilance's most difficult area because, even more than in the previous sections, value judgements and experience are likely to be significant. In the courtroom, experience is questioned by barristers and the judge; similarly, I believe experience as well as conflicts of interest that are relevant to the outcome of the discussion should be *fully* declared in committees. In committees, there are those who may have a good deal of experience, but not related to the matter in hand, although they can be overly influential and conflicted. Conversely, quiet domain experts can be ignored even though they may have a relevant minority opinion. Whilst the chairperson of the committee should manage these situations, there are many who will seek to limit heated debate and may even ignore a minority opposing view on the grounds of producing consensus. This is utterly wrong and cannot be ethically maintained, particularly if the committee has signed confidentiality statements. In my view, confidentiality statements signed at the beginning of meetings should always have the rider that minority views expressed in the meeting will be in the report and in the minutes. It should be clear at the outset to whom the report will be released; also, the conditions of release of reports should be reconsidered by the committee in the meeting. If the report is not managed according to the committee's wishes, then the committee chairperson should be free to say so publicly.

1.4 Working with the Pharmaceutical Industry (or Any Other Group with a Strong Vested Interest)

In pharmacovigilance, we should be working with several stakeholders and, as the latter term implies, they each have a firm set of views around their interpretation of uncertain data. This leaves us with a challenge that easily attracts allegations of bias from one or the other group. Currently, the pharmaceutical industry seems vilified in a general way that makes any associations with them subject to allegation of conflict of interest for the third party, who can seem to become tainted by this association. This attitude is further alienating for the industry and limits their chances of demonstrating reliable partnerships.

Perhaps the most obvious way out is to invite clearly independent representatives (two or three), perhaps from patients' associations or even responsible media, to act as monitors to the joint activity, simply to ensure that no excessive pressure or other improper influence occurs. It seems preposterous to allow some misdemeanours of the past to chronically infect relationships with other stakeholders. I am aware that there are many active working relationships between industry and other partners, but it is the perception of malpractice by industry in the media that needs to be dispelled, and this is one way to do it. Moreover, the same approach should be adopted with other extremely motivated parties. Even if their particular strong biases are acceptable to society, *any* bias is not the friend of good science.

2. Conclusions

Pharmacovigilance deals in value judgement and probabilites that concern relatively rare clinical outcomes relating to individual drugs, but which, overall, have become a considerable public health epidemic; we owe it to individual patients and the public to give enough information for them to judge our work.

We have transparent conflict of interest statements for authors, but they should be enhanced to allow for the degree of conflict to be assessed and to include all potential conflicts equally.

Reviewers should be asked explicitly to comment on bias and conflict of interest matters. Their own conflict of interest statements must at least be available to the authors.

Expert advisors should give *full* descriptions of both their experience and conflicts of interest to committees, as in court. Such descriptions should be available in writing to all committee members. Meetings' confidentiality agreements must include a statement that a report of the meeting will be published and any minority views recorded.

We should all work with the pharmaceutical industry in ways that allow for rehabilitation of its reputation as a public health partner in the public's perception, perhaps by using independent 'fair-minded, informed people' as monitors to evaluate for biases.

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