

# Independent medical research?

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Concerns about undue influence of sponsors on research have already been heard for decades. Efforts to change this situation have had insufficient impact. Here we draw attention to an innovative proposal by the Royal Netherlands Academy of Sciences on how to prevent sponsor-induced bias.

Is the problem still urgent? Several studies suggest that it is. In a recent survey of the 289 most-cited clinical trials published between 1994 and 2003, Ioannidis' group analysed the origin of authors (academic or nonacademic) and the source of finance of these trials.<sup>1</sup> This study was done within the context of the International Campaign to Revitalise Academic Medicine (ICRAM).<sup>2</sup> During the period of observation, the proportion of investigations financed by pharmaceutical industries increased significantly: no less than 65 of the 77 most-cited clinical trials were (co-)financed with money from industry.

Obviously the increasing influence of industry is a reason for concern, especially when the boundaries of influence are unclear. Industrial involvement, particularly in drug trials, usually starts with the design of the study, the choice of the comparator drugs, and the selection of the clinical investigators. Often industry has a major involvement in the collection and control of the data, as well as in data analysis. Even the (ghost)writing of the article may be done by the sponsor.

It is of quite some concern, as Kjaergard and Als-Nielsen have pointed out, that authors of trials with competing interests, i.e., those funded by for-profit organisations, are significantly more positive towards the results of their investigation than those without.<sup>3</sup> This observation fits in with the results of the systematic review by Lexchin *et al.*,<sup>4</sup> which demonstrates that studies sponsored by pharmaceutical companies are more likely to have outcomes favourable to these sponsors than investigations that received other funding. A recent survey of major clinical trials in the cardiovascular field showed similar

results: trials funded by for-profit organisations were more likely to report positive findings than those supported by not-for-profit organisations.<sup>5</sup> Similar bias was seen in nutrition studies supported by dairy and beverage companies.<sup>6</sup>

But there are more reasons for concern: after publication, the study results may serve as promotional material and be selectively used to inform prescribers and potential consumers. In this process the investigators may be used as a vehicle.<sup>7,8</sup>

In addition, industrial influence may sneak into the process of development of professional protocols and guidelines. A recent, rather scary example is the Surviving Sepsis Campaign, a basically marvellous initiative aiming at standardising and improving the basic care for patients with sepsis. In this campaign, however, one particular industry, with a major interest, seems to have gained a pivotal position.

In a recently published perspective in the *New England Journal of Medicine*, this story has been described in detail.<sup>9</sup> The attempts of industry to influence the development and – more seriously – the contents of practice guidelines are not new. It has been found that 87% of authors of guidelines have ties with industry and these are often not revealed.<sup>10</sup>

Of concern are also the relationships between industry and members of institutional review boards (IRB). In a recent survey, Campbell *et al.*<sup>11</sup> investigated the financial relationships between IRB members and industry and found that some 36% of these members had some kind of financial relationship with industry. Formal disclosure of relationships with industry is not required by 33% of IRB. Of the respondents, 15.6% reported that in their experience at least once a protocol had been presented in a biased way by an IRB member with industrial ties.<sup>11</sup>

Also in daily practice, there is a strong influence of industry. In fact, it is a rather sad finding that

representatives of pharmaceutical industries often have a greater influence on prescribing habits than prevailing hospital protocols and objective appraisals in the literature. The persuasion of these pharmaceutical representatives is often reached with the help of 'beads and mirrors', rather than through solid information. These practices still persist despite initiatives to regulate the interaction between pharmaceutical industry and prescribing physicians. The Dutch Ministry of Health has issued a series of regulations in this respect, starting in 1999, and initially these measures met with quite some effect, but it is our impression that the effect has waned in recent years. It is interesting to note that industry is not the only party that tries to influence outcome and reporting of science. For instance, governmental bodies may assign investigations and selectively use the outcome of the research and may require that the results of the investigations are kept secret.<sup>12</sup>

If we return to the core of the problem, it is clear that the influence of industry on clinical research is too strong and difficult to disentangle. In 2001, the International Committee of Medical Journal Editors (ICMJE) took the important initiative to ask for a disclosure of conflicts of interests of all authors (and to publish those as part of the article that reports the investigation). A further definite step forward – aimed at preventing selective reporting – is the registration of clinical trials in a public repository at their inception.<sup>13</sup> See also [www.clinicaltrials.gov](http://www.clinicaltrials.gov). In this repository, the role of the sponsor is also revealed. Still, there is a need for better regulation of the relationship between sponsor or client and researcher. In a recent advice to the Dutch Minister of Science and Education, The Royal Netherlands Academy of Arts and Sciences (KNAW) voiced its concern about the independence of the investigator, and proposes a code of conduct (*figure 1*) to be signed by the university or other research institute that performs the investigation.<sup>12</sup> The declaration proposes that research institutes that wish to be certified as adherent to this code must maintain a list of all the research contracts concluded by them. Contracts would be open to inspection by the National Council on Research Integrity (LOWI) which resides within the Academy (*figure 1*, Clause 9). The Council could demand a copy of a specific contract, and could therefore perform random or directed inspections. If the text of a contract were found to violate the code, the Council could revoke the certification of the research institute. As yet, the Dutch government has not declared whether it will implement this code. We feel that acceptance and implementation of this code is an essential next step to create clarity in the relationship between research institutes and sponsors, and in the field of medicine it may help to control the unwanted influence of pharmaceutical industry.

**Figure 1 Declaration of scientific independence\***

1. The structure of the research shall not be geared towards producing the desired outcome for the client.
2. The assignment and its objective shall preferably be formulated jointly by the client and the researcher.
3. Remuneration and other tokens of appreciation shall never depend on the outcome or interpretation of the research.
4. The results of the scientific research shall be published irrespective of whether they are favourable to the client.
5. The scientist shall always be free to publish the findings of the research within a specified reasonable period of time. In this context two months can be regarded as a reasonable period, with six months generally the maximum (this period being calculated from the moment that the final results are submitted to the client). An exception should be made where there are issues of intellectual property in which case a period of no longer than 12 months would be acceptable.
6. The method of publication shall be stipulated in the contract. Publication in a scientific journal shall take place in consultation with the client, but the researcher shall have the final say on the contents, the authors, the form of publication and where the research will be published.
7. External financiers of research assignments and/or other sponsors shall be mentioned by name in publications and other forms of disclosure.
8. Relevant interests and/or advisory relations of the researcher(s) shall be cited in publications and other forms of disclosure.
9. The text of the contract shall be available for inspection in confidence by the National Council on Research Integrity (LOWI).

\* This Declaration forms the heart of the code of conduct proposed by the Royal Netherlands Academy of Sciences.<sup>12</sup>

**CONFLICTS OF INTEREST**

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