Sponsorship bias in clinical trials

Joel Lexchin, the author of the translated article, indicates that the pharmaceutical industry is in a situation of conflict. The economic fate of pharmaceutical companies depends on the favourable outcomes of the trials they sponsor, which may make it tempting for them to try and influence studies they are involved in. This situation exists not only in the pharmaceutical industry, but also in the tobacco industry, the banking community, the food and drinks industry and even, as has recently emerged, in the automotive industry.

Lexchin mentions several interventions that the pharmaceutical industry can use to influence the results of the scientific research they sponsor. When these positively biased results are published in journals as research papers, readers who are unaware of this bias can be misled. Below we discuss a number of points that could help readers evaluate papers that present overly optimistic messages. In fact, most of these aspects have already been discussed in previous issues of Geneesmiddelenbulletin. In Gebu 2012; 46: 138-145, Lexchin discussed several aspects of the way the pharmaceutical industry is influencing the results of clinical drug trials. The present article can be regarded as a further clarification of these matters.

Information about new drugs should not be provided by persons who might stand to gain financially from the information provided, even more so when gifts or presents are involved. When doctors of pharmacists read or discuss articles, it might be useful if they do so together with an expert on evidence-based medicine (EBM). They should always check who sponsored the trial.

In selecting articles, readers should limit themselves to the scientific literature, and take several key points into account. For instance, the conclusions presented by authors in the abstracts of their articles often do not follow logically from the research findings. They tend to be too optimistic, and there is usually little reason to attach great value to them. The titles of articles are intended to draw the readers’ attention, but lack subtlety and rarely represent the content correctly. When Geneesmiddelenbulletin discusses articles in the section on New Research, it first presents the conclusions drawn by the authors, and then evaluates this conclusion using criteria to assess the internal and external validity of the study.

Occasionally, the authors’ conclusion is judged to be fairly correct; in most cases, however, the validity proves to be highly doubtful. Nor should one attach great value to interviews with the authors presented on the journal’s website, especially if they are in the employment of the industry and depend on external sponsors. Similarly, the press releases published by the manufacturers will not offer a critical assessment of the internal and external validity of the research, as they are intended to convince people of the value of the new drug or the new treatment. Newspaper and magazine journalists are often insufficiently or not at all able to evaluate the problems of the validity of study findings, and tend to take the authors’ conclusions for granted. The value of newspaper headlines has frequently been discussed.

Supplements of medical journals are usually paid for by the manufacturers, and the articles published in them are not subject to the usual process of peer review. Geneesmiddelenbulletin does not regard articles published in such supplements as evidence and does not include them in reference lists. Proceedings of symposia and articles from journals not included in the electronic PubMed database are not regarded as scientific evidence either. Nor does Geneesmiddelenbulletin waste any time on video conferences or abstract services.

Reading and evaluating ‘Papers to change practice’ takes a lot of time and effort, and readers would do better to wait for the new version of the guidelines published by their professional associations. Readers who nevertheless want to evaluate article themselves, can find recommendations for this in sources like Geneesmiddelenbulletin. A recent issue of the Nederlands Tijdschrift voor Geneeskunde (Ned Tijdschr Geneeskd 2015; 159: 1044-1052) elegantly presented advice on the way in which articles should be read.

In addition to the abovementioned criteria for the evaluation of articles and other publications, which can be relatively easily applied, some more general? criteria could be added. The larger the number of patients included in a trial, the higher the
chances that a statistically significant effect will be found, and the lower the clinical relevance of the effect for individual patients. If an effect can only be found using various highly complicated statistical procedures, such as non-protocol subgroup analyses, the scientific significance of the evidence is doubtful. In evaluating an articles, one should take the sponsoring and the conflicts of interest reported by the authors into account. Weaknesses in an article or study are often revealed in letters to the editor, but such letters usually only appear in the journal several months after the original article was published. In addition, the European registration authorities have to authorise a new drug if it has been proven not be inferior to the drugs that are already on the market.

Geneesmiddelenbulletin has previously discussed some other methodological aspects of evaluating drug research. Gebu 2015; 49: 27-34 explained the pitfalls of interpreting non-inferiority studies. This type of study is usually not the best option to assess the efficacy of a new drug; the best option for this purpose are superiority trials. Furthermore, there are major problems with the use of compound outcome measures (Gebu 2009; 43: 33-34), and with the use of the types of analysis that offer the greatest chance of a positive outcome (per-protocol analysis, last-observation-carried-forward (LOCF) analysis (Gebu 2000; 34: 17-22)). And readers should also consider the relevance of the outcome measures used.

Lexchin recommends erecting ‘a firewall between the money and the people doing the research.’ This would indeed eliminate a large part of the problem, viz. the influence of financial conflicts of interests on the results of research, and hence deserves recommendation.

The abovementioned aspects should be part of the curriculum of medical and pharmaceutical students, and be included in their exams. This will however become ever more difficult to realise, as the researchers are often affiliated to universities and are subject to these undesirable conflicts of interest. University-based researchers who cooperate with the industry should sign a contract stating that they will have to carry out their research completely independently, and obliging them to disclose all their study protocols, including all rough data and findings.

Finally, the editorial boards of journals should evaluate articles submitted to them more critically, and apply stricter requirements for the statistical analyses, the interpretation of findings and the conclusions drawn from them. Comparisons with the original study protocol ought to be standard practice for editorial boards. Generally speaking, journals should also publish articles with negative results.

Readers who take the above key recommendations into account when evaluating articles will often be disappointed about the scientific merits of most of the articles. This is unfortunate, but nevertheless a reality.

References*

47. Krzyzanowska MK, Pintilie M, Tannock IF. Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA 2003; 290: 495-501.


*The literature refers to the Dutch text*