

DO PHARMACEUTICAL COMPANIES SELECTIVELY REPORT CLINICAL TRIAL DATA?

Syed Ahmer¹, Imran Ijaz Haider², Duncan Anderson³, Pradeep Arya⁴

ABSTRACT: Many studies have shown that there is an association between a positive outcome of clinical trials, economic analyses and systematic reviews, and funding by the manufacturer of the drug of interest. Selective reporting of clinical trial data has been suggested as one of the possible explanations of this so-called funding bias. We conducted a review of the literature to find out if there is any evidence that this selective reporting of clinical trial data occurs. We report the several systematic reviews and cross-sectional surveys, and many case studies of this phenomenon that we found in the medical literature. We searched Medline, Embase and PsycINFO databases for this study besides hand searching BMJ from January 2003 to November 2005. We included systematic reviews, cross-sectional surveys, letters, editorials, comments or news items that referred to actual incidences of withholding, suppression, selective release or selective publication of clinical trial data by pharmaceutical companies.

KEY WORDS: Clinical Trials, Selective reporting, Funding bias, Systemic reviews.

Conflict of interest: None.

Pak J Med Sci July - September 2006 Vol. 22 No. 3 338-346

INTRODUCTION

“Underreporting Research Is Scientific Misconduct.” (Chalmers 1990).¹

Over the past quarter of a century many studies have been published that have concluded that outcomes of Randomised Controlled Trials, systematic reviews and economic analyses sponsored by pharmaceutical companies are more favourable to the sponsors’ drugs than non-sponsored studies.²⁻⁵ Multiple hypotheses have been put forward to explain this so called “funding bias” including publication bias,⁶

pharmaceutical companies selecting for study drugs that have been previously shown to be efficacious,² selective release and publication of data by pharmaceutical companies,⁷⁻¹⁰ multiple publications from the same trial,^{11,12} biased interpretation of results,^{7,13} and pharmaceutical companies influencing study designs or reporting ensuring that the results favour their drug.¹⁴⁻¹⁶ In this study we have tried to find out if there is any evidence in the literature to support the assertion that pharmaceutical companies do selectively release and publish clinical trial data.

METHODOLOGY

We searched Medline, Embase and PsycINFO using the following search terms; academic freedom, withhold(ing) data, suppress(ing) data, sponsorship and clinical trials, research ethics and publication, whistleblowing and research, scientific misconduct and clinical trials, scientific misconduct and sponsorship, academic freedom and sponsorship, conflict of interest and clinical trials, conflict of interest and publication, and research ethics. We also hand searched BMJ from January 2003 to November 2005.

1. Dr. Syed Ahmer MRCPsych
Department of Psychiatry
The Aga Khan University, Karachi-74800.
2. Dr. Imran Ijaz Haider MRCPsych
Department of Psychiatry
Fatima Memorial Hospital, Lahore.
3. Dr. Duncan Anderson MRCPsych
Specialist Registrar in Forensic Psychiatry
West London Mental Health NHS Trust
Uxbridge road, Southall, Middlesex UB1 3EU, U.K.
4. Dr. Pradeep Arya MRCPsych
Specialist Registrar in General Adult Psychiatry
St Charles Hospital, Exmoor Street, London W10 6DZ, U.K.

Correspondence:

Dr. Syed Ahmer MRCPsych*,
E-Mail: syed.ahmer@aku.edu

* Received for Publication March 11, 2006

* Revision Accepted: April 28, 2006

RESULTS

Our initial literature search retrieved 3084 potentially relevant titles with or without abstracts. After going through these titles and/or abstracts we retrieved 75 full articles. Of these 22 met our inclusion criteria. The BMJ search identified 74 potentially relevant articles which were retrieved. These yielded 20 further articles and news items which were included in the review. The rest of the studies and articles were found by searching the references, references of the references and going through our personal files. We have initially listed systematic reviews and surveys studying the phenomenon of selective reporting and then described case studies relating to individual drugs and groups of drugs.

SYSTEMATIC REVIEWS

We found two systematic reviews specifically investigating selective reporting of outcomes from clinical trials. One systematic review¹⁷ looked at outcome reporting bias in RCTs funded by the Canadian Institutes of Health Research and the other¹⁸ looked at differences in outcomes specified in trial protocols and reported in published studies of RCTs approved by Scientific-Ethical Committees in Denmark. Another pilot study¹⁹ looked at within-study selective reporting of outcome variables from clinical research. Although all of these studies demonstrated evidence of selective reporting of outcomes, none of these looked at bias in reporting in relation to pharma companies.

CROSS-SECTIONAL SURVEYS

We found two questionnaire surveys about personal knowledge or experience of data withholding amongst life science faculty members²⁰ and geneticists²¹ in the USA, and three, including a pilot study, on research fraud or misconduct.²²⁻²⁴ However, we found only one study that specifically looked at data withholding by pharmaceutical companies, along with agriculture and chemical companies. In this study Blumenthal et al²⁵ surveyed senior executives of 306 life science companies of which 69% replied. 56% of respondents said that in practice, the research they support in universities

often or sometimes results in information "that is kept confidential to protect its proprietary value beyond the time required to file a patent." A separate analysis of withholding of data by pharmaceutical companies was not reported.

CASE STUDIES

These can be covered under four broad headings i.e.

1. Unreported negative results
2. Partial disclosure of clinical trial findings
3. Concealment of adverse events
4. Pressure on investigators to stop publication of results

1. Unreported negative results:

Selective Serotonin Reuptake Inhibitors (SSRIs): Whittington et al,²⁶ conducted a meta-analysis on the use of SSRI antidepressants in children and adolescents, combining data from RCTs published in peer-reviewed journals with unpublished data from a review by the Committee on Safety of Medicines UK. They noted that in two published RCTs of fluoxetine in this patient group but that data on suicidal behaviour had not been published. For paroxetine there was one favourable published trial and two unpublished trials which showed little evidence of efficacy but evidence of an increased risk of serious adverse events. For sertraline there were two published RCTs but data on remission which provided little support for benefit was unpublished. For citalopram there were no published RCTs but two unpublished RCTs showed no evidence for efficacy and increased risk of attempting suicide. For venlafaxine there was a small published RCT. Two other RCTs which showed venlafaxine was unlikely to provide clinically important improvement in depressive symptoms, but had increased risk of discontinuation because of adverse events and raised risk of suicide related events were unpublished. Whittington et al²⁶ concluded that while published data presented a favourable risk: benefit profile, addition of unpublished data indicated that risks could outweigh benefits of these drugs (except fluoxetine) in this patient group.²⁷

Jane Garland²⁸ has reported that none of the large negative trials of paroxetine and venlafaxine (two each) for treating depression in children and adolescents were published.²⁹

Melander et al³⁰ compared studies submitted for regulatory approval to Swedish drug regulatory authority for marketing approval of five SSRIs for treating major depression, with studies published in peer-reviewed journals. Twenty one studies found experimental drug to be significantly more effective than placebo on the primary variable. Nineteen of these were published as stand alone publications. However, another 21 studies did not show significant results. Only six of these were published as stand alone publications. Four studies never reached the public domain all of which showed non-significant results on the primary variable.

The Canadian Medical Association Journal (CMAJ) published details from an internal document prepared by the Central Medical Affairs Team (CMAT) of SmithKline Beecham (which later merged with Glaxo Wellcome to form GlaxoSmithKline[GSK]) on how to manage the results from two clinical trials conducted to assess the efficacy of paroxetine.^{31,32} As the clinical trials results were, according to the document, “insufficiently robust” to support an application to regulatory authorities to get paroxetine approved for use in paediatric depression, CMAT recommended that the firm “effectively manage the dissemination of these data in order to minimize any potential negative commercial impact.” It also stated that “It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.”

In June 2004 New York State Attorney General Eliot Spitzer filed a consumer fraud lawsuit against GSK for allegedly engaging in “repeated and persistent fraud by concealing and failing to disclose to physicians certain information about Paxil (paroxetine)”.^{33,34} He said that the concealed information “impaired doctors’ ability to make the appropriate prescribing decisions for their patients and may have jeopardized public health and safety,”.

GSK finally settled the lawsuit on 25 August 2004 for £1.4m (US\$2.5m) stating in a statement that although it believed that the allegations were “unfounded” it wanted to avoid the expense of a protracted legal battle.³⁵

Alteplase: Alteplase is a fibrinolytic agent which is indicated for the treatment of acute ischaemic stroke by neurologists. In one of the trials, alteplase thrombolysis for acute noninterventional therapy in ischemic stroke (ATLANTIS), the result of the first phase (part A) of the trial was negative for alteplase. Alteplase did not improve stroke recovery and actually increased mortality. The results of part A of the study were not published until six years after the trial’s completion, even after results from the second phase of the same trial (part B) had been released.³⁶⁻³⁸

Remune: Remune was an HIV-1 immunogen which was studied in a RCT to determine if its addition conferred added clinical efficacy to that achievable by Anti Retroviral Therapies.³⁹ The RCT ran from mid 1990s to May 1999. The Data Safety Monitoring Board concluded that “the study was finding no difference in efficacy between the vaccine and placebo and that it was unlikely that by continuing the study the outcome would change”.⁴⁰

The manufacturer of Remune, Immune Response Corporation (IRC) initially wanted the researchers to include in the paper that in a certain subset of patients the viral load levels were lower and the CD4 T-cell counts were higher in patients receiving the vaccine. The authors refused saying that it would be improper to include a post-hoc analysis that had not been part of original study protocol.⁴⁰ IRC filed an unsuccessful claim with the American Arbitration Association seeking to prevent publication of the paper. In the paper the authors stated that they had to analyze an incomplete dataset and they also failed to get from the sponsor a complete list of co-investigators.³⁹ After failing to prevent the publication of the study IRC filed a claim of US\$ 7-10 million against the investigators and their universities to cover financial damages they said the paper’s publication would cause them.⁴⁰

In another letter published in JAMA it was revealed that IRC had earlier been “accused of previous attempts to improperly influence the presentation of scientific data on its HIV-1 Immunogen”.⁴¹ The FDA had warned IRC in a letter in 1995 that in a previous published report of a trial of Remune sponsored by IRC the results for two subjects had been excluded for the report even though the report stated that data for all subjects had been included, and that the statistical analysis was not the one included in the study protocol. The warning letter also accused IRC of “changing data retroactively for several reports; modifying adverse experience information; and changing data categories retrospectively, after unblinding”.⁴¹

Neuraminidase inhibitors: Symmonds et al⁴² reported in a letter to the BMJ that they had failed to find any published data on the use of oseltamivir (Tamiflu) for asthmatic children suffering from Influenza while doing a Cochrane Review⁴³ on this topic as the manufacturer of oseltamivir had failed to publish two studies W V15759 / W V15871. The unpublished data was submitted when the company made an application for European Marketing Authorisation for the drug. There was no significant difference in time to freedom from illness between children taking the drug and placebo.⁴⁴ Symmonds et al also alleged that this unpublished data seemed not to have been made available to NICE as the systematic review commissioned by NICE to inform their guidance on this topic excluded the study because there were no data.

The company responded by saying that the data from the above mentioned studies had been made available to NICE and they intended to publish the results.⁴⁵

Interferon Beta: In a report to the parliamentary health committee in 2002 National Institute of Clinical Excellence UK (NICE) accused drug companies of refusing to disclose the patient-level data needed to calculate cost-effectiveness of interferon beta for treating multiple sclerosis.⁴⁶ Dr Sheila Bird, a member of the Institute’s appraisal committee,

suggested that NICE could produce more accurate estimates of cost-effectiveness if it was partially covered by the Medicines Act to allow it access to companies’ post-license trials data. Dr Ian Chalmers, director of the Cochrane Centre, said that “Important data have been withheld from NICE by companies whose interests would not be served by that.”

2. Partial disclosure of Clinical Trial Results:

Celecoxib: Celecoxib (Celebrex) is a member of COX-2 inhibitors class of non-steroidal anti-inflammatory drugs. Celecoxib Long-term Arthritis Safety Study (CLASS)⁴⁷ was reported as a three arm trial comparing celecoxib with ibuprofen and diclofenac, for incidence of upper GI complications and symptomatic ulcers over 6 months. The study concluded that celecoxib “was associated with a lower incidence of symptomatic ulcers and ulcer complications combined”. It was later reported that according to data available to the FDA CLASS was actually selective reporting of 6 months data from two separate longer trials comparing celecoxib vs diclofenac over 12 months, and celecoxib vs ibuprofen over 16 months.⁴⁸⁻⁵¹ Most of the ulcer complications beyond six months occurred in the celecoxib groups, but this data was not reported in the paper.⁵⁰ The primary outcome in the protocol submitted to the FDA was complicated ulcers, which showed a non-significant difference between celecoxib and NSAIDs. An additional primary outcome reported in the published CLASS paper was ulcer complications plus symptomatic ulcers, which showed a significant difference in favour of celecoxib.⁴⁷

According to the study protocol the primary outcome measure (complicated ulcers) had to show a statistically significant difference before subgroup analyses were to be conducted. However, the study presented a subgroup analysis on aspirin use despite the primary outcome measure being statistically non-significant. The CLASS study claimed that the decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.⁴⁷ However, the data available to the FDA showed that in patients not taking

aspirin, diclofenac and celecoxib seemed to have similarly low GI toxicity compared with ibuprofen, and that patients taking ibuprofen had about the same GI risk regardless of whether or not they were also taking aspirin.⁴⁸

The FDA found that "For upper GI safety, and also for global safety, there does not appear to be any meaningful advantage for Celebrex,"⁵² a conclusion completely opposite to the one reached by the authors of the CLASS study. Before the publication of the CLASS study, the investigators gave the 6 months data for a review published in JAMA.⁵³ Dr Wolfe, one of the co-authors of the review later saw the full data as a member of the FDA arthritis advisory committee and was surprised to see that the results of the complete study were overall less favourable for celecoxib than the shorter 6 months data he had been given for the review.⁵⁴

Prostaglandin: In a letter to the Lancet Lauristen et al⁵⁵ reported that in December 1983, a pharmaceutical company initiated a multi-centre RCT to compare healing rates for their synthetic prostaglandin analogue with ranitidine for gastric ulcer. The trial was stopped in August 1995 when the target number of patients was recruited. When one of the trial centres in Denmark asked for a trial report in March 1986 they were told by the sponsoring drug company that ranitidine had performed better than the company drug in all centres except one centre which had decided to publish its own findings.⁵⁵ By April 1987 the Danish investigators had still not received the full report by which time the company was already making applications with several national drug licensing authorities to register their drug.

3. Concealment of adverse events:

Rofecoxib: Merck's withdrawal of Vioxx (rofecoxib) as a result of increased cardiovascular risk was international news reported in most medical journals.⁵⁶ It was suggested in a cumulative meta-analysis that Merck had been aware of the increased cardiovascular risks since at least the year 2000 but had failed to act.⁵⁷ Merck and the French Marketing

Authorization Committee responded by saying that the prior increased risk of rofecoxib had been demonstrated against naproxen, predominantly in the VIGOR trial,⁵⁸ but not against other NSAIDs or placebo, until the APPROVe trial.⁵⁹

The Wall Street Journal published multiple emails between Merck's executives which confirm that by 2000 they were aware of the cardiovascular risks of rofecoxib.^{60,61} They were discussing internally that the cardiovascular events were "clearly there," and that if in a trial Vioxx patients could not take aspirin "you will get more thrombotic events" and it would "kill the drug". This was all at the time when Merck was issuing news releases such as "Merck confirms favorable cardiovascular safety profile of Vioxx".

It was stated in an editorial in JAMA that there had been three additional myocardial infarctions during the VIGOR trial, all in the rofecoxib group, that had not been included in the VIGOR paper⁵⁸ when it was published in JAMA.^{62,63} The authors responded by saying that the three MIs had happened after the cut off date for reporting cardiovascular events and that is why these weren't reported.⁶⁴

It has also been alleged that the sponsor of the trials was apparently aware of possible myocardial toxicity before the trial as it set in place a separate adjudication procedure to study this event.⁶⁵ It came out at the FDA hearings that an internal (sponsor-based) committee had preselected cases for adjudication. Although this selection was blind, it reduced the absolute number of cases with the adverse event. Merck actually sued Juan Laporte, a Spanish pharmacologist, for repeating the above assertion in his drugs and therapeutics bulletin.^{66,67} However, the judge absolved Professor Laporte and the institute, and demanded that the company pay the court costs.⁶⁸

Amrinone: In a letter to the Lancet Wilmshurst stated that Sterling Winthrop had tried to influence the results and publication of scientific trials. The specific complaints included, amongst others, discontinuation of trials when the results appeared to show its drug amrinone

in an unfavourable light and failure to report adverse effects with amrinone.⁶⁹⁻⁷¹ The Netherlands drug authorities, when refusing a license to amrinone, stated that “our assessor drew our attention to the fact that all quantitative data on peripheral blood and bone marrow had been deleted from the registration file”; amrinone frequently causes thrombocytopenia.⁶⁹

4. Pressure on investigators to stop publication of results:

Deferiprone: Deferiprone is an oral iron chelating agent used in patients with thalassaemia to prevent iron toxicity from repeat blood transfusions. In 1989 Dr. Nancy Olivieri of the Hospital for Sick Children in Toronto started studying the efficacy and safety of deferiprone. The trials were supported initially by the Medical Research Council of Canada, and later by a Canadian pharmaceutical firm Apotex. The trials showed that Deferiprone did not adequately control hepatic iron accumulation, and the hepatic iron concentration exceeded the safety threshold for increased risk of cardiac disease and early death.^{72,73} More extended studies suggested that the drug might accelerate the development of hepatic fibrosis.⁷⁴

Dr. Olivieri communicated her findings to the company but the company threatened to take legal action against her if she revealed her findings to her patients and the scientific community citing a non-disclosure agreement under the terms of which she was not allowed to disclose the findings of her research to any third party for 3 years.⁷⁵ Within a few years two lawsuits totaling \$20 million were formally lodged against her.⁷³ Apotex dismissed her from the steering group of the trials, stopped all clinical trials involving Olivieri and tried to stop her from publishing her results.⁷³⁻⁷⁶ She was dismissed from her position at the hospital,⁷⁷ removed as director of the Toronto haemoglobinopathies program, charged with “research misconduct” and referred to the College of Physicians and Surgeons of Ontario, which later exonerated her of all charges.⁷⁸ Dr Olivieri did eventually get her findings pub-

lished in scientific journals^{74,79,80} despite being under severe pressure from the company.

Synthroid: In 1987 Dr Betty Dong of University of California at San Francisco (UCSF) signed a contract with Flint Laboratories to study whether Synthroid (a branded preparation of levothyroxine) was more effective than another branded preparation and two generic preparations.⁸¹ When the study was finished in 1990 it showed that all four preparations were bioequivalent. Over the next 4 years Boots(which had taken over Flint) leveled many criticisms at the study to discredit it and to prevent its publication including making complaints to the Chancellor, Vice Chancellors and department heads at the UCSF.⁸² In April 1994 Dr Dong submitted her paper to JAMA for publication but in January 1995, just before publication, Dr Dong withdrew her paper stating as her reason “impending legal action by Boots Pharmaceuticals, Inc against the University of California, San Francisco and the investigators.” She said that she had signed a restrictive covenant with Knoll and the UCSF attorney had told her that the University would not defend the authors if a lawsuit was brought by Knoll/Boots. Dr. Dong claimed to have been twice threatened with the possibility of lawsuit should sales of Synthroid suffer as a consequence of publication. The company denied making this threat.⁸¹

While Dr. Dong and colleagues were being prevented from getting their paper published, employees of Knoll/Boots published a reanalysis of Dr. Dong’s data,⁸³ without acknowledging the original investigators and reaching opposite conclusions to Dong et al. Finally, after the story had been published by the Wall Street Journal⁸⁴ and under pressure from the FDA, Knoll agreed to let the study be published. The study was finally published 7 years after its completion and 3 years after its original acceptance by JAMA.⁸⁵ Knoll still insisted that the conclusions of the analysis by Dr. Dong and her colleagues were not supported by data.^{86,87}

Isradipine: Several investigators of the

Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) dropped out of the investigative group when the final paper was in preparation. In a letter to JAMA they explained that they dropped out because they believed that the “sponsor of the study was attempting to wield undue influence on the nature of the final paper. This effort was so oppressive that we felt it inhibited academic freedom”.⁸⁸

DISCUSSION

It was not surprising to us that we found some evidence of selective reporting of clinical trial data, what was surprising was how much evidence we found, and we only report what has been published. At least in UK and USA this selective reporting of trial data has been recognized as a major problem and recent reports by the UK House of Commons Health Committee^{89,90} and the American Medical Association⁹¹ discuss this phenomenon in significant detail.

What difference does it make if companies do selectively report clinical trial data? As Arthur Schafer⁷⁸ has tried to explain, suppose there are 20 studies of a new drug of which 6 are positive and 14 are negative. If someone tries to perform a metaanalysis on this drug the evidence would be overwhelmingly against it. Now suppose that only 2 of the 14 negative studies are published while all 6 positive studies are published. If a metaanalysis is attempted now the evidence would most likely be in favour of the new drug. It is this ability of selective reporting of data to shift the whole balance of evidence about a drug that makes it so dangerous for evidence-based medicine, when it depends on published evidence alone.

Many remedies have been suggested to tackle this problem. The first step which most journals now require is full disclosure of any financial support of the study, financial ties between the researchers and the sponsors and any role the sponsor played in the design, conduct or reporting of the study.⁹² However, these guidelines are not always adhered to.⁹³ International Committee of Medical Journal Editors (ICMJE) has also issued guidelines on authors' access

to data, integrity of data, accuracy of data analysis, and authors' right to publish.⁹² The ICMJE has now declared that for trials starting enrolment after July 1 2005 the ICMJE member journals will require prospective registration in a public trials registry as a condition for consideration for publication.⁹⁴ Arthur Schafer⁷⁸ has proposed a more radical approach recommending that “university research and university researchers must be sequestered from the process of commercialisation...”

Great emphasis has also been placed on all data from a trial being released into the public domain after completion of the trial.^{95,96} Pharmaceutical companies have argued in the past that data collected during a trial is their property and it is their prerogative whether to release any part of it or not. This has led to many incidences of companies releasing favorable data about their drugs and not releasing unfavourable data, or even unfavourable studies, as documented above. The good news is that drug companies have now agreed to make clinical trials results public⁹⁷, but it is worth remembering that these promises have been made and broken in the past.⁹⁶

CONCLUSION

We feel that the two crucial steps that would go a long way towards ending the fundamental breach of trust that underlies the practice of selective reporting of data are, first, registration of all trials before they start, and second, release of all data after the completion of the trial. The first goal has been realized now, the second is hopefully within our sights. Until it is achieved clinicians and researchers should continue to strive towards it.

REFERENCES

1. Chalmers I. Underreporting Research Is Scientific Misconduct. *JAMA* 1990; 263(10):1405-8.
2. Davidson RA. Source of funding and outcome of clinical trials. *Journal of General Internal Medicine* 1986; 1:155-8.
3. Lexchin J, Bero LA, Djulbegovic B, Clark C. Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *BMJ* 2003; 326(7400):1167-70.
4. Bekelman JE, Li Y, Gross CP. Scope and impact of of financial conflicts of interest in biomedical research: A systematic review. *JAMA* 2003;289(4):454-65.

5. Ahmer S, Arya P, Anderson D, Faruqi R. Conflict of interest in psychiatry. *Psychiatric Bulletin* 2005;29:302-4.
6. Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the *BMJ*. *BMJ* 2002; 325: 249-53.
7. Rochon PA, Gurwitz JH, Simms R et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Internal Medicine* 1994;154:157-63.
8. Blumenthal D, Campbell E, Anderson M et al. Withholding research results in academic life science: Evidence from a national survey of faculty. *JAMA* 1997;277:1224-8.
9. Rennie D. Thyroid storm. *JAMA* 1997;277:1238-43.
10. Nathan, DG, Weatherall, DJ. Academia and industry: Lessons from the unfortunate events in Toronto. *Lancet* 1999;353: 771-2.
11. Gøtzsche PC. Multiple publication of reports of drug trials. *Eur J Clin Pharmacol* 1989;36:429-32.
12. Huston P, Moher D. Redundancy, disaggregation, and the integrity of medical research. *Lancet* 1996;347:1024-6.
13. Friedberg M, Saffran B, Stinson T, et al. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA* 1999;282:1453-57.
14. Johansen H, Gøtzsche P. Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. *JAMA* 1999;282:1752-59.
15. Bero LA, Rennie D. Influences on the quality of published drug trials. *Int J Tech Assessment in Healthcare* 1996;12:209-37.
16. Safer DJ. Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. *J Nervous Mental Dis* 2002;190:583-92.
17. Chan AW, Krczeja-Jeric K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004;171(7):735-40.
18. Chan AW, Hrobjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to Published Articles. *JAMA* 2004;291(20):2457-65.
19. Hahn S, Williamson P, Hutton J. Investigation of within study selective reporting in clinical research: follow-up of applications submitted to a local research ethics committee. *J Eval Clin Practice* 2002;8(3):353-9.
20. Blumenthal D, Campbell E, Anderson M, et al. Withholding research results in academic life science: Evidence from a national survey of faculty. *JAMA* 1997;277:1224-28.
21. Campbell EG, Clarridge BR, Gokhale M, Birenbaum L, et al. Data withholding in academic genetics: Evidence from a national survey. *JAMA* 2002; 287(4):473-80.
22. Ranstam J. Fraud in medical research: an international survey of biostatisticians. *ISCB Subcommittee on Fraud. Controlled clinical trials* 2000;21(5):415-27.
23. Martinson B, Anderson M, de Vries R. Scientists behaving badly. *Nature* 2005;435:737-8.
24. May C, Campbell S, Doyle H. Research misconduct: A pilot study of British addiction researchers. *Addiction research* 1998;6(4):371-3.
25. Blumenthal D, Causino N, Campbell E, Louis K. Relationships between academic institutions and industry: an industry survey. *New Engl J Med* 1996;334(6):368-73.
26. Whittington J, Kendall T, Fonagy P, Cottrell D. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004; 363 (9418):1341-5.
27. Anonymous. Depressing research. *Lancet* 2004; 363 (9418):1335.
28. Garland J. Facing the evidence: antidepressant treatment in children and adolescents. *CMAJ* 2004; 170 (4):489-91.
29. Anonymous. The "file drawer" phenomenon: suppressing clinical evidence. *CMAJ* 2004;170(4):437-9.
30. Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* 2003;326:1171-3.
31. Kondro W, Sibbald B. Drug company experts advised staff to withhold data about SSRI use in children. *CMAJ* 2004;170(5):783.
32. Spurgeon D. GlaxoSmithKline staff told not to publicise ineffectiveness of its drug. *BMJ* 2004;328:422.
33. Sibbald B. Legal action against GSK over SSRI data. *CMAJ* 2004; 171(1):23.
34. Dyer O. GlaxoSmithKline faces US lawsuit over concealment of trial results. *BMJ* 2004;328:139.
35. Dyer O. GlaxoSmithKline to set up comprehensive online clinical trials register. *BMJ* 2004; 329:590.
36. Lenzer J. Alteplase for stroke: money & optimistic claims buttress the "brain attack" campaign. *BMJ* 2002; 324:723-9.
37. Lenzer J. Controversial stroke trial is under review following *BMJ* report. *BMJ* 2002; 325(7373):1131.
38. Mann H. Alteplase for stroke. Uncertainty remains about efficacy. *Letters. BMJ* 2002;324:1581.
39. Kahn J, Cherng D, Mayer K, Murray H, et al. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial. *JAMA* 2000;284(17):2193-2202.
40. McCarthy M. Company sought to block paper's publication. *Lancet* 2000;356:771-2.
41. Lurie P & Wolfe S. *Letters. Outcomes of a trial of HIV-1 immunogen in patients with HIV infection. JAMA* 2001;285(17):2193-5.
42. Symmonds M, Matheson NJ, Harnden A. Guidelines on neuraminidase inhibitors in children are not supported by evidence. *BMJ* 2004; 328: 227.
43. Matheson NJ, Symmonds-Abrahams M, Sheikh A, Shepperd S, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (Cochrane Review). In: *The Cochrane Library, Issue 3, 2003. Oxford: Update Software*
44. European Agency for the Evaluation of Medicinal Products. Tamiflu. *European Public Assessment Report* 2002.
45. Panahloo Z. Data on neuraminidase inhibitors were made available. *BMJ* 2004;328:523.
46. Burke C. NICE accuses drug companies of withholding data. *BMJ* 2002; 324:320.
47. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study. JAMA* 2000; 284: 1247-55.
48. Berg HJ, Mora M. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA* 2001; 286: 2398.
49. Okie S. Missing data on Celebrex. Full study altered picture of drug. *Washington Post* 2001;5 Aug:A11.
50. Juni P, Rutjes A, Dieppe P. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? *BMJ* 2002;324(7349):1287.
51. Juni P, Rutjes A & Dieppe P. *Letters. Authors' reply. BMJ* 2002;325(7356):161-7.

52. Wright JM, Perry TL, Bassett KL, Chambers KG. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA* 2001; 286: 2398-9.
53. Lichtenstein R, Wolfe M. COX-2-Selective NSAIDs. New and Improved? *JAMA* 2000;284:1297-9.
54. Gottlieb S. Researchers deny any attempt to mislead the public over JAMA article on arthritis drug. *BMJ* 2001;323(7308):310.
55. Lauristen K, Havelund T, Laursen L, Rask-Madsen J. Withholding unfavourable results in drug company sponsored clinical trials. *Lancet* May 9 1987;p1091.
56. Singh D. Merck withdraws arthritis drug worldwide. *BMJ* 2004;329:816.
57. Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; 364:2021-9.
58. Bombardier C, Laine L, Reicin A, et al for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343:1520-28.
59. Kim P, Reicin A, Lièvre M, Abadie E, et al. Discontinuation of Vioxx / Authors' reply. *Lancet* 2005; 365(9453):23-28.
60. Horton R. Vioxx, the implosion of Merck, and aftershocks at the FDA. *Lancet* 2004; 364: 1995-6.
61. Matthew AW, Martinez B. E-mails suggest Merck knew Vioxx's dangers at early stage. *Wall Street Journal* 2004; A1 Nov. 1.
62. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N Engl J Med* 2000; 343:1520-8. *N Engl J Med* 2005;353:2813-4.
63. Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., Jeffrey M. Drazen, M.D. Expression of Concern Reaffirmed. *N Engl J Med* 2006; 354: 1193.
64. Bombardier C, Laine L, Burgos-Vargas R, et al. Response to expression of concern regarding VIGOR study. *N Engl J Med* 2006; 354:1196-8.
65. Boers M. Seminal pharmaceutical trials: Maintaining masking in analysis. *Lancet* 2002;360(9327):100-101.
66. Bosch X. Spanish editor sued over rofecoxib allegations. *Lancet* 2004;363(9405):298.
67. Gibson L. News. Drug company sues Spanish bulletin over fraud claim. *BMJ* 2004;328:188.
68. Gibson L. Spanish drug editor wins case brought by Merck, Sharp & Dohme. *BMJ* 2004;328:307
69. Wilmshurst P. An investigation by the ABPI. *Lancet* 1987; I: 104.
70. Erlichman J. Company tested heart drug without DHSS clearance. *The Guardian* Nov 3, 1986; 6.
71. Wilmshurst P. Policing the drug industry. *Lancet* 1986; II: 1280-81
72. Nathan D. & Weatherall D. Academia and industry: Lessons from the unfortunate events in Toronto. *Lancet* 1999;353:771-2.
73. Nathan DG & Weatherall DJ. Academic Freedom in Clinical Research. *N Engl J Med* 2002; 347:1368-71.
74. Olivieri NF, Brittenham GM, Matsui D, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; 339: 617-23.
75. Schuchman M. Consequences of Blowing the Whistle in Medical Research. *Annals of Inter Med* 2000; 132(12): 1013-4.
76. Thompson J, Baird P, Downie J. Report of the Committee of Inquiry on the case involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc. Toronto: Canadian Association of University Teachers, 2001.
77. Olivieri N. Patients' Health or Company Profits? The Commercialisation of Academic Research. *Sci Eng Ethics* 2003;9:29-41.
78. Schafer A. THE OLIVIERI SYMPOSIUM. Biomedical conflicts of interest: a defence of the sequestration thesis-learning from the case of Nancy Olivieri and David Healy. *J Med Ethics* 2004;30:8-24.
79. Olivieri NF, Long-term follow-up of body iron in patients with thalassemia major during therapy with the orally active iron chelator deferiprone (LI). *Blood* 1996; 88 (suppl 1): 310.
80. Olivieri NF, Brittenham GM. Final results of the randomized trial of deferiprone and deferoxamine. *Blood* 1997; 90 (suppl 1): 264.
81. Rennie D. Thyroid storm. *JAMA* 1997; 277:1238-43.
82. Wise J. Research suppressed for seven years by drug company. *BMJ* 1997;314:1145.
83. Mayor GH, Orlando T, Kurtz NM. Limitations of levothyroxine bioequivalence evaluation: analysis of an attempted study. *Am J Ther.* 1995;2:417-32.
84. King R. Bitter pill: how a drug company paid for university study, then undermined it. *Wall Street Journal*. April 25,1996:1.
85. Dong B, Hauck W, Gambertoglio J, Gee L, White J, Bulp J, Greenspan F. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997;277:1205-13.
86. Eckert C. Martin J. Bioequivalence of Levothyroxine Preparations: Industry sponsorship and Academic Freedom. [Letter] *JAMA* 1997; 277(15):1200-1
87. Spiegelman M, Dong B, Gambertoglio J, Greenspan F, Hauck W. Bioequivalence of Levothyroxine Preparations for Treatment of Hypothyroidism. [Letter] *JAMA* 1997; 277(15):1199-1200.
88. Applegate W, Furberg C, Byington R, Grimm R. The Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). [Letter]. *JAMA* 1997; 277(4):297-8.
89. House of Commons Health Committee. The Influence of the Pharmaceutical Industry. Fourth Report of Session 2004-05. The Stationery Office Limited. London. UK.
90. Ferner R. The influence of big pharma. *BMJ* 2005;330:855-6
91. <http://www.ama-assn.org/ama/pub/category/14314.html>. last accessed on 26.02.2006
92. <http://www.icmje.org/index.html#ethic> Last accessed on 27.02.2006
93. Gross C, Gupta A, Krumholz H. Disclosure of financial competing interests in randomised controlled trials: cross sectional review. *BMJ* 2003;326:526-7
94. http://www.icmje.org/clin_trial.pdf. Last accessed on 26.02.2006
95. Roehr B. Law is introduced in US Congress to give access to details of clinical trials. *BMJ* 2004;329:996
96. Herxheimer A. Open access to industry's clinically relevant data. *BMJ* 2004;329:64-5
97. Mayor S. Drug companies agree to make clinical trial results public. *BMJ* 2005;330:109.