

ORIGINAL ARTICLE

The Financing of Drug Trials by Pharmaceutical Companies and Its Consequences

Part 1: A Qualitative, Systematic Review of the Literature on Possible Influences on the Findings, Protocols, and Quality of Drug Trials

Gisela Schott, Henry Pachi, Ulrich Limbach, Ursula Gundert-Remy, Wolf-Dieter Ludwig*, Klaus Lieb*

Arzneimittelkommission der deutschen Ärzteschaft, Berlin:
Dr. med. Schott,
Dipl.-Biol. Pachi,
Prof. Dr. med. Gundert-Remy,
Prof. Dr. med. Ludwig

Klinik für Hämatologie, Onkologie und Tumorerimmunologie, HELIOS Klinikum Berlin-Buch:
Prof. Dr. med. Ludwig

Klinik für Psychiatrie und Psychotherapie, Universitätsmedizin Mainz:

Cand. med. Limbach,
Prof. Dr. med. Lieb

* The authors Ludwig and Lieb have equally contributed to the manuscript.

SUMMARY

Background: In recent years, a number of studies have shown that clinical drug trials financed by pharmaceutical companies yield favorable results for company products more often than independent trials do. Moreover, pharmaceutical companies have been found to influence drug trials in various ways. This paper provides an overview of the findings of current, systematic studies on this topic.

Methods: Publications retrieved from a systematic Medline search on this topic from 1 November 2002 to 16 December 2009 were independently evaluated and selected by two of the authors. These publications were supplemented by further ones found in their references sections.

Results: 57 publications were included for evaluation in Parts 1 and 2 of this article. Published drug trials that were financed by pharmaceutical companies, or whose authors declared a financial conflict of interest, were found to yield favorable results for the drug manufacturer more frequently than independently financed trials whose authors had no such conflicts. The results were also interpreted favorably more often than in independently financed trials. Furthermore, there was evidence that pharmaceutical companies influenced study protocols in a way that was favorable to themselves.

The methodological quality of trials financed by pharmaceutical companies was not found to be any worse than that of trials financed in other ways.

Conclusion: Published drug trials that are financed by pharmaceutical companies may present a distorted picture. This cannot be explained by any difference in methodological quality between such trials and trials financed in other ways.

Clinical drug trials funded by pharmaceutical companies yield favorable results for the sponsor's products more often than independent trials do. This has been demonstrated by a number of studies in recent years (1–4). Various ways have been described in which pharmaceutical concerns exert influence on the protocol and conduct of drug trials, as well as on the interpretation and publication of their results (1, 3, 5, 6).

Two important reviews on this topic were published in 2003 (7, 8):

Bekelman et al. carried out a quantitative analysis of 37 studies to investigate the extent and the relevance of financial links between biomedical companies on one hand and academic institutions and scientists on the other (7). This systematic review showed widespread conflicts of interest in the shape of financial connections between scientists, academic institutions, and the pharmaceutical industry. Around one quarter of academic staff and two thirds of academic institutions had financial relationships with industry. Analysis of 8 review articles embracing a total of 1140 original articles (including randomized controlled trials [RCT], economic analyses, and retrospective cohort studies) revealed a statistically significant association between funding by biomedical companies and conclusions favorable to the pharmaceutical industry (summarized odds ratio [OR] 3.6, 95% confidence interval [CI] 2.6–4.9). Industry financing was also connected with limitations of publication rights and constraints on access to trial data.

In the second review, a systematic analysis of 30 publications, Lexchin et al. showed that drug trials financed by pharmaceutical companies are less likely to be published, but that those published more frequently yield positive results for the sponsors' products than do independently funded studies (8). The quality of the methods employed (analyzed in 13 publications) in trials financed by pharmaceutical companies was not inferior to that in studies with other sources of funding.

Cite this as: *Dtsch Arztebl Int* 2010; 107(16): 279–85
DOI: 10.3238/arztebl.2010.0279

Influence on many different aspects of a clinical drug trial can affect the results, from the purpose via the planning and conduct of the study all the way to its evaluation and publication (5).

The authors of the present systematic review set out to assess whether recently published studies reveal a connection between financing of drug trials by pharmaceutical companies and results favorable to these companies' products. Part 1 investigates whether and, if so, how the type of funding affects study protocol and quality. Part 2 identifies and depicts the aspects of clinical drug trials that can be influenced by financial support from the pharmaceutical industry.

Methods

Systematic literature review

The criteria for the selection of systematic investigations into the effects of financing on study results were oriented on the above-mentioned reviews (7, 8). The literature search was carried out in the PubMed database. The most important MeSH terms and search terms, combined by means of Boolean operators, were "conflict of interest", research support as topic", clinical trials as topic", "commerce", "drug industry", "authorship", "publication bias", and "financial support".

The following limits, among others, were imposed: "publication date", "clinical trial", "meta-analysis", and "randomized controlled trial".

Searches were carried out on 26 May 2008 (for the period 1 November 2002 to 26 May 2008), 4 December 2008 (for 26 May 2008 to 3 December 2008), and 16 December 2009 (for 1 October 2008 to 16 December 2009).

Publications in all languages were included. Two of the authors (G. Schott, U. Limbach) independently selected suitable studies on the basis of the inclusion and exclusion criteria (see below). In the case of disagreement, consensus was achieved by discussion with a third author (K. Lieb). The reference lists of all selected articles were inspected for further relevant publications (9).

Inclusion and exclusion criteria

The criteria for inclusion were:

- Publication between 1 November 2002 and 16 December 2009 (i.e., directly following on from the period analyzed by Bekelman et al. [7])
- Description of the methods employed
- Provision of empirical data as to whether and how financing by pharmaceutical companies affects various aspects of clinical trials (e.g., protocol, conduct, results, conclusions, or publication).

Commentaries, editorials, and abstracts were excluded.

Some studies were found to combine clinical drug trials and analyses of, for example, surgical interventions, medical devices, or preclinical investigations. In such cases the study was included as long as the results of clinical drug testing were described separately.

Evaluation of the literature

The basic characteristics, purpose, and principal findings of each of the studies reviewed were recorded (*eTable*). The quality of the studies' methods was not systematically evaluated, because there is no validated, reliable instrument for quality assessment that can be applied to all of the various study designs (including systematic reviews, meta-analyses, case studies, and cross-sectional studies).

In the effort to ensure comprehensive portrayal of the various ways in which influence could be exerted, a descriptive approach was chosen; no hypotheses were advanced or statistical analyses performed. The studies were arranged by topic according to their results.

Results

The search of the PubMed database yielded 1705 publications. After inspection of reference lists, 57 publications that satisfied the inclusion and exclusion criteria were evaluated (*Figure*). The results of this evaluation are described in Parts 1 and 2 of the present study.

The publications included were primarily studies performed with the expressed goal of comparing clinical trials funded by pharmaceutical companies with clinical trials that had not received financial support from such companies, e.g., with regard to the results or conclusions. These studies were accompanied by a number of publications that investigated the consequences of financing of a study by pharmaceutical companies. These included, for example, articles in which information from the files of the US licensing authority (Food and Drug Administration, FDA) was compared with data from publications in medical journals, and case studies on individual substances.

Two systematic reviews carried out for much the same reason as the present review were excluded on the grounds that their principal primary studies had already been included (10, 11). The results of the publications covered in the present review are based largely on clinical drug trials conducted principally in the Anglo-American countries. A few publications also analyzed studies performed in Germany. The most recent studies whose data were taken into account in the papers covered were published in November 2008. The publications evaluated concern various areas of medicine, but it cannot be completely ruled out that original data from a small number of drug trials were included more than once. A few studies dealt with several aspects.

Connection between type of funding and results of drug trials

Twenty-six of the 57 publications analyzed sought to ascertain whether the results and/or conclusions of drug trials depended on the type of funding or on financial conflicts of interest on the part of the authors (*eTable*).

These investigations dealt with various medical topics and disciplines (among them oncology [e1, e2], cardiovascular diseases [e3], and psychiatry [e4]) and featured different study designs (e.g., systematic review, meta-analysis, case study).

Altogether, 23 of these 26 studies came to the conclusion that there was a positive correlation between the financing of a study by pharmaceutical companies and/or conflicts of interest on the part of the authors and results or conclusions that were favorable to the sponsor. The statistical significance of this finding was investigated in 22 cases and confirmed in 20.

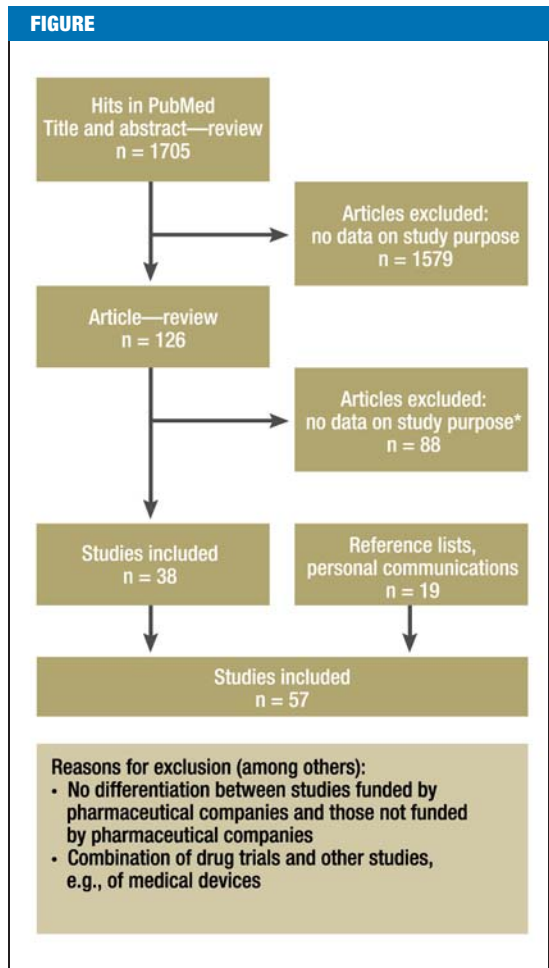
In 4 cases it was apparent that the findings were interpreted favorably towards the pharmaceutical concern that had funded the study, independent of the results (e5–e8).

In 3 investigations there was no clear association between the funding of a study by pharmaceutical companies and findings that favored the sponsors (e9–e11). In one of these, a urological study (e11), very few publications were analyzed (n = 24); furthermore, the author disclosed “Speakers’ Bureau—Pfizer” as a conflict of interest. Another study investigated the connection between the conclusions and the source of financial support in clinical trials that had appeared in 5 influential medical journals over a period of 20 years (e10). Most trials yielded positive results for the drug in question regardless of the funding source, but this study also revealed a trend over the course of time towards more positive findings in industrially financed trials than in trials supported by non-profit organizations (e10). The third study compared the results (but not the interpretations or conclusions) of clinical trials of drugs used in pain management, some of them long available as generics (e9).

Study protocol

Five of the 57 studies analyzed investigated whether funding by pharmaceutical companies affected the design of the study protocol (Table 1). The use of placebos was shown to be significantly more common in RCTs of drugs for psoriasis that were financed by such companies than in those with funding from other sources (e12). Moreover, several studies of treatment for premature ejaculation that were sponsored by a pharmaceutical company were found to have disregarded the relevant objective endpoint (e13). In an investigation of inhaled corticosteroids, significant differences in the frequency of adverse drug reactions (ADR) between the probands and the control group occurred only half as often when the study had been funded by the manufacturers (see also Part 2). The differences could be attributed wholly to the study design. For example, studies financed by pharmaceutical companies used lower dosages.

A further study revealed that an RCT of rofecoxib was a “seeding trial,” i.e., a clinical study that claims to be testing a scientific hypothesis but in reality has the purpose of making the drug known to prescribing physicians and thus increasing sales (e14). Examination of confidential internal documents that became public in the context of legal proceedings revealed that the study had been designed and conducted by the marketing department of the pharmaceutical company concerned. However, there were also signs of other irregularities.



Literature review flowchart

TABLE 1

Investigations into the influence of pharmaceutical companies on the study protocol of drug trials

Authors	Purpose	Result
Hill et al. 2008 (e14)	Description of seeding trial "Assessment of Differences between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE)" using Merck & Co. documents from the years 1998 to 2006	Study protocol designed and all data processed in marketing department of Merck & Co. Aim of study (sales promotion) withheld from participating patients and physicians and members of institutional review board.
Katz et al. 2006 (e12)	Calculation of prevalence of placebo controls in RCTs on psoriasis published from 2001 to 2005; identification of factors associated with use of placebos	Active controls used in 85 studies (61%) comprising 8171 patients, placebos in 52 studies (38.5%) with 11 406 patients. Significantly more frequent use of placebos in studies funded by pharmaceutical companies (OR 2.61, 95% CI 1.19–5.73, p = 0.02; adjusted for study location and funding source).
Nieto et al. 2007 (e19)	Evaluation of differences in results regarding ADRs and their interpretation between 275 studies on inhaled corticosteroids financed by pharmaceutical manufacturers and 229 such studies not funded by pharmaceutical manufacturers; studies published between 1993 and 2002	Compared with studies not funded by pharmaceutical companies, those financed by pharmaceutical companies significantly more often employed parallel design and lower dosages. For this reason, statistically significant differences in ADRs were significantly less frequent in studies financed by pharmaceutical manufacturers than in studies not funded by pharmaceutical manufacturers (34.5% vs. 65.1%; prevalence ratio 0.53, 95% CI 0.44–0.64).
Procyshyn et al. 2004 (e15)	Assessment of blinding, placebo use, comparative medication, and sample size in 372 studies on clozapine, risperidone, and olanzapine published between 1990 and 2001	In studies from two pharmaceutical companies, blinding, placebo control, and comparison with another atypical antipsychotic were more frequent than in studies not funded by pharmaceutical companies or in studies from a third pharmaceutical company.
Waldinger et al. 2008 (e13)	Comparison of studies of dapoxetine sponsored by pharmaceutical companies and studies of conventional SSRIs in men with premature ejaculation	Studies with dapoxetine focused on patients' subjective perceptions, neglected the objective parameter "intra vaginal ejaculation latency time (IELT)", presented data as arithmetic, not geometric, mean (inadequate), and had no correct recording of ADRs.

RCTs, randomized controlled trials; ADRs, adverse drug reactions; OR, odds ratio; 95% CI, 95% confidence interval; SSRIs, selective serotonin reuptake inhibitors

TABLE 2

Investigations into the influence of type of funding on the quality of the methods employed in drug trials

Authors	Instrument for quality assessment	Result
Jorgensen et al. 2006 (e6)	Validated assessment procedure (Oxman and Guyatt index)	Cochrane Reviews had higher-quality methods than reviews funded by pharmaceutical companies (investigation of eight pairs of studies on the same drug, $p < 0.01$), reviews with non-declared financing, and reviews without support or funded by organizations with no commercial interests.
Montgomery et al. 2004 (e18)	Validated assessment procedure (Jadad score)	Non-significant trend towards lower average Jadad scores in studies funded by pharmaceutical companies ($p = 0.07$)
Perlis et al. 2005 (e17)	Validated assessment procedure (Jadad score)	Average Jadad score higher in studies with than in those without funding by pharmaceutical companies (3.65 vs. 2.68; $p = 0.0001$).
Yuen et al. 2008 (e16)	Five-point scale based on CONSORT Statement	Assessment of the evidential power of RCTs on the treatment of systemic lupus erythematosus without renal involvement published between 1975 and 2007 showed that studies funded by pharmaceutical companies had a significantly higher number of participants ($p < 0.001$) and tended to exhibit better study quality.

RCTs, randomized controlled trials

The target group of prescribers (family doctors) was determined at the outset, and only then was the study protocol formulated. Neither ethics committees nor participants were informed of the true goal of the study, namely promotion of the drug. To make this marketing as successful as possible and pitch the product to a large number of doctors, the study was carried out in 600 centers. Such a high number of centers would not have been required for the official purpose of the study (comparison of the gastrointestinal tolerability of rofecoxib and naproxen). Indications of increased cardiovascular morbidity among those taking rofecoxib were not pursued. The article describing the study was written by employees of the manufacturer of rofecoxib, but appeared under another researcher's name. This was thus a case of guest authorship (see Part 2). The pharmaceutical company concerned investigated the marketing effect of the study, finding that participating physicians did indeed prescribe rofecoxib significantly more often than non-participants in its first 6 months on the market.

In contrast, differences in study protocol among investigations of atypical antipsychotics could not be attributed to the type of funding (e15). The protocols of 3 pharmaceutical companies and of studies not supported by the pharmaceutical industry were compared. Blinding, placebo controls, and use of an atypical antipsychotic for comparison were found more frequently in the protocols of two of the pharmaceutical companies than in those of the third company or the studies without industrial financing.

Connection between type of funding and quality of study methods

Altogether, 4 publications concerned themselves with the methodological quality of drug trials in relation to financial support (Table 2). Various instruments were employed to assess quality: for RCTs the Jadad scale (12) and a scale based on the CONSORT Statement (e16), both of which ask, for example, about blinding and randomization; for systematic reviews, the Oxman and Guyatt index, which for instance asks about search strategies and avoidance of selection bias (13).

In 2 investigations the quality of the methods of the clinical trials financed by pharmaceutical companies was comparable to or even better than when funding came from a sponsor without commercial interests (e16, e17), and in only one study did it tend to be worse (e18). Comparison of industrially financed meta-analyses and Cochrane Reviews showed that the latter displayed higher quality (e6); search strategies and randomization methods were described more often, for example, and literature searches were more comprehensive.

Discussion

The results of clinical drug trials that are funded by pharmaceutical companies or whose authors have financial conflicts of interest are favorable to the products of the sponsoring company far more frequently than studies whose funding comes from other sources. Furthermore, interpretation of the data in the conclusions of industrially financed trials more often

favors the sponsor. This was shown by the present systematic review and analysis of investigations, published between 1 November 2002 and 16 December 2009, into various diseases, study types (e.g., RCTs and observational studies), and drugs. The results confirm the conclusions of 2 systematic reviews, both published in 2003, conducted with similar intent (7, 8). The principle of equipoise, i.e., uncertainty which of the alternative approaches benefits the patient most, forms the ethical foundation of clinical studies in which the probands receive various treatments (14). This principle seems to be violated in many studies funded by pharmaceutical companies.

There are numerous reasons why studies financed by pharmaceutical manufacturers more often yield positive results. Four investigations found evidence that pharmaceutical companies influence the study protocol to their advantage (e12–e14, e19), e.g., by more frequent use of placebos in control groups than in independently funded studies (e12). Although the responsible authorities sometimes demand placebo-controlled trials as a condition of licensing, they also request active controls (15). Further factors leading to higher frequency of results favorable to the sponsor in trials funded by pharmaceutical companies are described in Part 2 of this review.

Trials financed by pharmaceutical concerns displayed no signs of poorer methodological quality. On the contrary, two studies showed superior quality (e16, e17). It must be taken into account, however, that some factors that serve to assess the quality of the instruments used in a study were not determined, among them the clinical relevance of the target parameters. In oncology, for instance, there are currently major defects in the protocols of industrially sponsored clinical trials, e.g., deficiencies in the definition of patient-relevant endpoints and in the selection of suitable substances for the control arm of RCTs (16–19). Moreover, clinical trials in oncology are often discontinued after preliminary analysis (20), with the result that only a short time after the licensing of a drug its additional benefits and the safety of new substances can frequently no longer be evaluated, preventing any benefit/risk analysis (21).

This work was supported by funds from the Initiative for Health Services Research (Förderinitiative Versorgungsforschung) of the German Medical Association (Bundesärztekammer, BÄK). The 110th German Medical Assembly tasked the BÄK with investigating, in the framework of the Initiative for Health Services Research, the influence of sponsors on the scientific results of drug trials.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 29 May 2009, revised version accepted on 23 February 2010.

Translated from the original German by David Roseveare.

REFERENCES

1. Djulbegovic B, Lacey M, Cantor A, Fields KK, Bennett CL, Adams JR, et al.: The uncertainty principle and industry-sponsored research. *Lancet* 2000; 356: 635–8.

2. Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennett CL: Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA* 1999; 282: 1453–7.

3. Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, et al.: A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994; 154: 157–63.

4. Yaphe J, Edman R, Knishkowsky B, Herman J: The association between funding by commercial interests and study outcome in randomized controlled drug trials. *Fam Pract* 2001; 18: 565–8.

5. Bero LA, Rennie D: Influences on the quality of published drug studies. *Int J Technol Assess Health Care* 1996; 12: 209–37.

6. Flanagan A, Carey LA, Fontanarosa PB, Phillips SG, Pace BP, Lundberg GD, et al.: Prevalence of articles with honorary authors and ghost authors in peer-reviewed medical journals. *JAMA* 1998; 280: 222–4.

7. Bekelman JE, Li Y, Gross CP: Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003; 289: 454–65.

8. Lexchin J, Bero LA, Djulbegovic B, Clark O: Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326: 1167–70.

9. Rensing M, Blettner M, Klug SJ: Systematic literature reviews and meta-analyses: part 6 of a series on evaluation of scientific publications [Systematische Übersichtsarbeiten und Metaanalysen: Teil 6 der Serie zur Bewertung wissenschaftlicher Publikationen]. *Dtsch Arztebl Int* 2009; 106: 456–63.

10. Sismondo S: Pharmaceutical company funding and its consequences: a qualitative systematic review. *Contemp Clin Trials* 2008; 29: 109–13.

11. Golder S, Loke YK: Is there evidence for biased reporting of published adverse effects data in pharmaceutical industry-funded studies? *Br J Clin Pharmacol* 2008; 66: 767–73.

12. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al.: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.

13. Oxman AD, Guyatt GH: Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991; 44: 1271–8.

14. Freedman B: Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317: 141–5.

15. EMA, CHMP: Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 3) on haematological malignancies: www.ema.europa.eu/pdfs/human/ewp/52008808en.pdf. London, 20. November 2008; Doc. Ref. EMEA/CHMP/EWP/520088/2008. Last accessed on 8 February 2010.

16. Apolone G, Joppi R, Bertele V, Garattini S: Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. *Br J Cancer* 2005; 93: 504–9.

17. Bertele V, Banzi R, Capasso F, Tafuri G, Trotta F, Apolone G, et al.: Haematological anticancer drugs in Europe: any added value at the time of approval? *Eur J Clin Pharmacol* 2007; 63: 713–9.

18. Johnson JR, Williams G, Pazdur R: End points and United States Food and Drug Administration approval of oncology drugs. *J Clin Oncol* 2003; 21: 1404–11.

19. van Luijn JC, Gribnau FW, Leufkens HG: Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. *Br J Clin Pharmacol* 2007; 63: 159–62.

20. Trotta F, Apolone G, Garattini S, Tafuri G: Stopping a trial early in oncology: for patients or for industry? *Ann Oncol* 2008; 19: 1347–53.

21. Ludwig W-D, Fetscher S, Schildmann J: Teure Innovationen in der Onkologie – für alle? *Der Onkologe* 2009; 15: 1004–14.

Corresponding author

Dr. med. Gisela Schott
Arzneimittelkommission der deutschen Ärzteschaft
Herbert-Lewin-Platz 1
10623 Berlin, Germany
gisela.schott@akdae.de



For e-references please refer to:
www.aerzteblatt-international.de/ref1610

eTable available at:
www.aerzteblatt-international.de/article10m0279

ORIGINAL ARTICLE

The Financing of Drug Trials by Pharmaceutical Companies and Its Consequences

Part 1: A Qualitative, Systematic Review of the Literature on Possible Influences on the Findings, Protocols, and Quality of Drug Trials

Gisela Schott, Henry Pachi, Ulrich Limbach, Ursula Gundert-Remy, Wolf-Dieter Ludwig*, Klaus Lieb*

E-References

- e1. Peppercorn J, Blood E, Winer E, Partridge A: Association between pharmaceutical involvement and outcomes in breast cancer clinical trials. *Cancer* 2007; 109: 1239–46.
- e2. Booth CM, Cescon DW, Wang L, Tannock IF, Krzyzanowska MK: Evolution of the randomized controlled trial in oncology over three decades. *J Clin Oncol* 2008; 26: 5458–64.
- e3. Ridker PM, Torres J: Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000–2005. *JAMA* 2006; 295: 2270–4.
- e4. Tungaraza T, Poole R: Influence of drug company authorship and sponsorship on drug trial outcomes. *Br J Psychiatry* 2007; 191: 82–3.
- e5. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL: Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA* 2003; 290: 921–8.
- e6. Jorgensen AW, Hilden J, Gotsche PC: Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *BMJ* 2006; 333: 782–5.
- e7. Yank V, Rennie D, Bero LA: Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study. *BMJ* 2007; 335: 1202–5.
- e8. Gilstad JR, Finucane TE: Results, rhetoric, and randomized trials: the case of donepezil. *J Am Geriatr Soc* 2008; 56: 1556–62.
- e9. Barden J, Derry S, McQuay HJ, Moore RA: Bias from industry trial funding? A framework, a suggested approach, and a negative result. *Pain* 2006; 121: 207–18.
- e10. Buchkowsky SS, Jewesson PJ: Industry sponsorship and authorship of clinical trials over 20 years. *Ann Pharmacother* 2004; 38: 579–85.
- e11. Tulikangas PK, Ayers A, O'Sullivan DM: A meta-analysis comparing trials of antimuscarinic medications funded by industry or not. *BJU Int* 2006; 98: 377–80.
- e12. Katz KA, Karlawish JH, Chiang DS, Bognet RA, Probert KJ, Margolis DJ: Prevalence and factors associated with use of placebo control groups in randomized controlled trials in psoriasis: a cross-sectional study. *J Am Acad Dermatol* 2006; 55: 814–22.
- e13. Waldinger MD, Schweitzer DH: Premature ejaculation and pharmaceutical company-based medicine: the dapoxetine case. *J Sex Med* 2008; 5: 966–97.
- e14. Hill KP, Ross JS, Egilman DS, Krumholz HM: The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med* 2008; 149: 251–8.
- e15. Procyshyn RM, Chau A, Fortin P, Jenkins W: Prevalence and outcomes of pharmaceutical industry-sponsored clinical trials involving clozapine, risperidone, or olanzapine. *Can J Psychiatry* 2004; 49: 601–6.
- e16. Yuen SY, Pope JE: Learning from past mistakes: assessing trial quality, power and eligibility in non-renal systemic lupus erythematosus randomized controlled trials. *Rheumatology (Oxford)* 2008; 47: 1367–72.
- e17. Perlis CS, Harwood M, Perlis RH: Extent and impact of industry sponsorship conflicts of interest in dermatology research. *J Am Acad Dermatol* 2005; 52: 967–71.
- e18. Montgomery JH, Byerly M, Carmody T, Li B, Miller DR, Varghese F et al.: An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia. *Control Clin Trials* 2004; 25: 598–612.
- e19. Nieto A, Mazon A, Pamies R, Linana JJ, Lanuza A, Jimenez FO, et al.: Adverse effects of inhaled corticosteroids in funded and non-funded studies. *Arch Intern Med* 2007; 167: 2047–53.
- e20. Baker CB, Johnsrud MT, Crismon ML, Rosenheck RA, Woods SW: Quantitative analysis of sponsorship bias in economic studies of antidepressants. *Br J Psychiatry* 2003; 183: 498–506.
- e21. Bero L, Oostvogel F, Bacchetti P, Lee K: Factors associated with findings of published trials of drug-drug comparisons: why some statins appear more efficacious than others. *PLoS Med* 2007; 4: e184.
- e22. Bhandari M, Busse JW, Jackowski D, Montori VM, Schunemann H, Sprague S, et al.: Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ* 2004; 170: 477–80.
- e23. Etter JF, Burri M, Stapleton J: The impact of pharmaceutical company funding on results of randomized trials of nicotine replacement therapy for smoking cessation: a meta-analysis. *Addiction* 2007; 102: 815–22.
- e24. Finucane TE, Boulton CE: Association of funding and findings of pharmaceutical research at a meeting of a medical professional society. *Am J Med* 2004; 117: 842–45.
- e25. Fries JF, Krishnan E: Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. *Arthritis Res Ther* 2004; 6: R250-5.
- e26. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S: Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry* 2006; 163: 185–94.

- e27. Kelly RE, Jr., Cohen LJ, Semple RJ, Bialer P, Lau A, Bodenheimer A, et al.: Relationship between drug company funding and outcomes of clinical psychiatric research. *Psychol Med* 2006; 36: 1647–56.
- e28. Liss H: Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship. *Isr Med Assoc J* 2006; 8: 451–4.
- e29. Moncrieff J: Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. *Br J Psychiatry* 2003; 183: 161–6.
- e30. Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA: Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. *Am J Psychiatry* 2005; 162: 1957–60.
- e31. Vlad SC, LaValley MP, McAlindon TE, Felson DT: Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum* 2007; 56: 2267–77.

eTABLE

Investigations into the connection between the type of funding and the results of drug trials

Authors	Subject	Result
Als-Nielsen et al. 2003 (e5)	Connection between type of funding and results on basis of treatment effects or ADRs in 370 RCTs, used in Cochrane Reviews; researched in Cochrane Library 2001	Significantly higher likelihood of recommendation of drug investigated in studies funded by pharmaceutical companies than in studies financed by non-commercial bodies (OR 5.3, 95% CI 2.0–14.4).
Baker et al. 2003 (e20)	Association between funding source and quantitative results in pharmaco-economic studies of antidepressives in all identifiable publications with quantitative results; published between 1987 and 2001	Significant association between funding by pharmaceutical companies and results favorable to pharmaceutical sponsor.
Barden et al. 2006 (e9)	Connection between funding by pharmaceutical companies and results favorable to the sponsor in 176 meta-analyses on acute pain and migraine from five previous reviews	Investigation could not be conducted as planned, because only 2 of 176 studies were funded by organizations that did not pursue commercial interests (unspecified: n = 31). Therefore, comparison of results for a drug depending on its use as test substance or comparative medication. With one exception, no differences.
Bero et al. 2007 (e21)	Connection between type of funding, characteristics of study design, and other factors affecting results in 192 RCTs that compared different statins; published between 1999 and 2005	Funding by pharmaceutical companies is significantly associated with positive results (OR 20.16, 95% CI 4.37–92.98; p<0.001) and conclusions (OR 34.55, 95% CI 7.09–168.4; p<0.001). Statistically significant results are less likely in adequately blinded studies.
Bhandari et al. 2004 (e22)	Connection between funding by pharmaceutical companies and statistically significant results in 158 RCTs; published in five major journals between 1999 and 2001	Significant association between funding by pharmaceutical companies and results favorable to company (OR 1.6, 95% CI 1.1–2.8).
Booth et al. 2008 (e2)	Changes in study design, funding, and results of 321 RCTs in oncology during three decades (1975 to 2004)	Independently from one another, funding by pharmaceutical companies and significant study results were associated with recommendation of the experimental treatment (OR 3.5, 95% CI 1.6–7.5 and OR 19.6, 95% CI 8.9–43.1, respectively). Distinct increase over study period in proportion of studies funded by pharmaceutical companies (from 4% to 57%). Potencies unchanged with time, but increase in recommendations of experimental treatment.
Buchkowsky et al. 2004 (e10)	Characterization of 500 randomly selected clinical trials: funding, reporting, sources; investigation of links between author and pharmaceutical companies; description of trends in results over 20-year period (1981 to 2000)	Independently of funding source, majority of studies favored study medication: 74% of studies with unspecified funding source, 67% of studies funded by organizations that did not pursue commercial interests, 73% of studies funded by pharmaceutical companies, and 81% of studies financed by two or more sponsors (p = 0.159). Increase in results favorable to pharmaceutical companies over time.
Etter et al. 2007 (e23)	Influence of funding on results of 105 studies on nicotine replacement therapy	Studies funded by pharmaceutical companies more frequently had a statistically significant result (OR 3.70, 95% CI 1.46–9.35)
Finucane et al. 2004 (e24)	Correlation between funding and results in 48 abstracts of drug trials at a congress	Significant association between funding by pharmaceutical companies and results favorable to companies (p = 0.0007)
Fries et al. 2004 (e25)	Frequency of adherence to uncertainty principle (equipose) in 45 abstracts of RCTs funded by pharmaceutical companies; presented at a rheumatology congress in 2001	All study results were positive for pharmaceutical sponsor, so that result could have been predicted from knowledge of sponsor alone (p<0.0001).
Gilstad et al. 2008 (e8)	Comparison of wording at five points in text of publications on all 18 RCTs on donepezil in patients with Alzheimer's disease; published up to November 2007 in studies funded by pharmaceutical companies versus studies not funded by pharmaceutical companies	Distinct favoring of active ingredient in 13 studies funded by pharmaceutical companies (15 publications); in studies not funded by pharmaceutical companies, effect of donepezil described as slight or absent. Results of RCTs broadly identical; different wordings not explained by differences in results.
Heres et al. 2006 (e26)	Association between type of funding and results in 30 head-to-head studies in psychiatry; published between 1966 and 2003	Result favored sponsor's product in 90% of studies (p<0.001). Contradictory results for individual active ingredients depending on study sponsor.
Jorgensen et al. 2006 (e6)	Comparison of quality and conclusions of Cochrane Reviews (published in 2003) with those of meta-analyses funded by pharmaceutical companies (24 pairs)	In contrast to Cochrane Reviews, conclusions of meta-analyses funded by pharmaceutical companies recommend study drug without reservation (p = 0.02).
Kelly et al. 2006 (e27)	Correlation between funding and results in 542 studies in psychiatry; published in 1992 and 2002	Significant association between funding by pharmaceutical companies and results favorable to companies. Proportion of favorable results similar in 1992 and 2002.
Liss et al. 2006 (e28)	Influence of funding on results of 100 studies of drugs used in pulmonology or allergology; published between October 2002 and September 2003	Results favorable to pharmaceutical company more frequent in studies funded by pharmaceutical companies (62/63 [98%] vs. 12/37 [32%]; p<0.05).

Authors	Subject	Result
Moncrieff et al. 2003 (e29)	Reassessment of evidence on clozapine (10 studies); identification of reasons for heterogeneity; published between 1998 and 2003	Funding by pharmaceutical companies significantly associated with positive result for clozapine. No clinically relevant advantage for clozapine in large current studies conducted without support from pharmaceutical companies.
Montgomery et al. 2004 (e18)	Influence of funding source on results of 86 RCTs in psychiatry; literature search carried out in 2002 with no limitation on year of publication	Results of studies funded by pharmaceutical companies significantly favor second-generation antipsychotics over first-generation drugs.
Peppercorn et al. 2007 (e1)	Correlation between funding source, study design, and results of 140 clinical trials on breast cancer; published in 2003, 1998, 1993	On joint analysis of all studies from 1993, 1998, and 2003, no significant difference in proportion of positive results between studies funded by pharmaceutical companies and those not funded by pharmaceutical companies ($p = 0.14$). In studies from 2003: results more frequently positive in the case of funding by pharmaceutical companies (84% vs. 54%; $p = 0.02$).
Perlis C. et al. 2005 (e17)	Determination of extent and consequences of financial conflicts of interest in 179 clinical trials in dermatology; published between 2000 and 2003	Significant association between study funding by pharmaceutical companies and results favorable to pharmaceutical companies (adjusted OR 4.5, 95% CI 1.2–17.1).
Perlis R. et al. 2005 (e30)	Determination of extent and consequences of funding by pharmaceutical companies and financial conflicts of interest in 162 RCTs in psychiatry; published between 2001 and 2003	In the case of financial conflict of interest on part of author, 4.9 times higher likelihood of positive results. Difference statistically significant only in studies funded by pharmaceutical companies.
Procyshyn et al. 2004 (e15)	Prevalence and results of studies funded by pharmaceutical companies among 372 studies on clozapine, risperidone, and olanzapine; published between 1990 and 2001	No negative results in studies funded by pharmaceutical companies
Ridker et al. 2006 (e3)	Association between funding source and study results in 205 RCTs on cardiovascular topics; published between 2002 and 2005	Proportion of studies that favor new treatment significantly higher among those funded by pharmaceutical companies ($p = 0.002$)
Tulikangas et al. 2006 (e11)	Dependence of results on type of funding in 24 studies in urology; published between 1966 and 2003	No correlation
Tungaraza et al. 2007 (e4)	Influence of funding by pharmaceutical companies on results of 190 drug trials in psychiatry; published between 2000 and 2004	Higher likelihood of reporting negative results in independently funded studies than in studies financed by pharmaceutical companies (16/44 [36%] vs. 22/146 [15%]; $p = 0.004$). Correlation particularly strong when authors include employee of pharmaceutical company.
Vlad et al. 2007 (e31)	Identification of factors that explain heterogeneity of results in 15 studies on glucosamines; published between 1966 and 2006	Magnitude of effect smaller in studies without involvement of pharmaceutical companies than in those with involvement of pharmaceutical companies (0.05–0.16 vs. 0.47–0.55).
Yank et al. 2007 (e7)	Association between financial links to a pharmaceutical company and positive results or conclusions in 124 meta-analyses of antihypertensive drugs; published up to 2004	Financial links to a pharmaceutical company not associated with positive results, but associated with positive conclusions (OR 4.09, 95% CI 1.30–12.83).

ADRs, adverse drug reactions; RCTs, randomized controlled trials; OR, odds ratio; 95% CI, 95% confidence interval