

Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review

Emmanuel Stamatakis^{*,†}, Richard Weiler[‡] and John P.A. Ioannidis^{§,¶}

^{*}Department of Epidemiology and Public Health, University College London, London, UK, [†]Prevention Research Collaboration, School of Public Health, University of Sydney, Sydney, NSW, Australia, [‡]University College London Hospitals NHS Foundation Trust, London, UK, [§]Stanford Prevention Research Center, Department of Medicine and Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA, [¶]Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, CA, USA

ABSTRACT

Background Expenditure on industry products (mostly drugs and devices) has spiraled over the last 15 years and accounts for substantial part of healthcare expenditure. The enormous financial interests involved in the development and marketing of drugs and devices may have given excessive power to these industries to influence medical research, policy, and practice.

Material and methods Review of the literature and analysis of the multiple pathways through which the industry has directly or indirectly infiltrated the broader healthcare systems. We present the analysis of the industry influences at the following levels: (i) evidence base production, (ii) evidence synthesis, (iii) understanding of safety and harms issues, (iv) cost-effectiveness evaluation, (v) clinical practice guidelines formation, (vi) healthcare professional education, (vii) healthcare practice, (viii) healthcare consumer's decisions.

Results We located abundance of consistent evidence demonstrating that the industry has created means to intervene in all steps of the processes that determine healthcare research, strategy, expenditure, practice and education. As a result of these interferences, the benefits of drugs and other products are often exaggerated and their potential harms are downplayed, and clinical guidelines, medical practice, and healthcare expenditure decisions are biased.

Conclusion To serve its interests, the industry masterfully influences evidence base production, evidence synthesis, understanding of harms issues, cost-effectiveness evaluations, clinical practice guidelines and healthcare professional education and also exerts direct influences on professional decisions and health consumers. There is an urgent need for regulation and other action towards redefining the mission of medicine towards a more objective and patient-, population- and society-benefit direction that is free from conflict of interests.

Keywords conflict of interests, evidence-based medicine, health care, healthcare industry, medication, pharmaceutical industry.

Eur J Clin Invest 2013

Introduction

A universal characteristic of most healthcare systems in developed countries is the heavy focus on pharmacological approaches for treating and preventing chronic disease and the considerable expenditure on high-tech medical equipment, devices and technologies. This focus is often linked to astonishing financial interests, such as the \$130 billion a single drug (Lipitor) generated over 14 years [1], an amount that is higher than the 2010 gross domestic product of 129 of the 184 countries in the world [2]. Besides traditional drugs, biologics and

devices can also produce huge revenue. For example, the manufacturers of anti-TNF biological drugs and therapies have created a \$10 billion annual market [3,4] even though these agents are used for indications with rather modest, incremental benefits. The market for drug-eluting stents for coronary artery disease is \$4-6 billion per year in the United States alone [5], even though a large share of the indications for which these stents are used (e.g. stable coronary disease) has no supporting evidence [6-9]. This excessive financial capacity and the

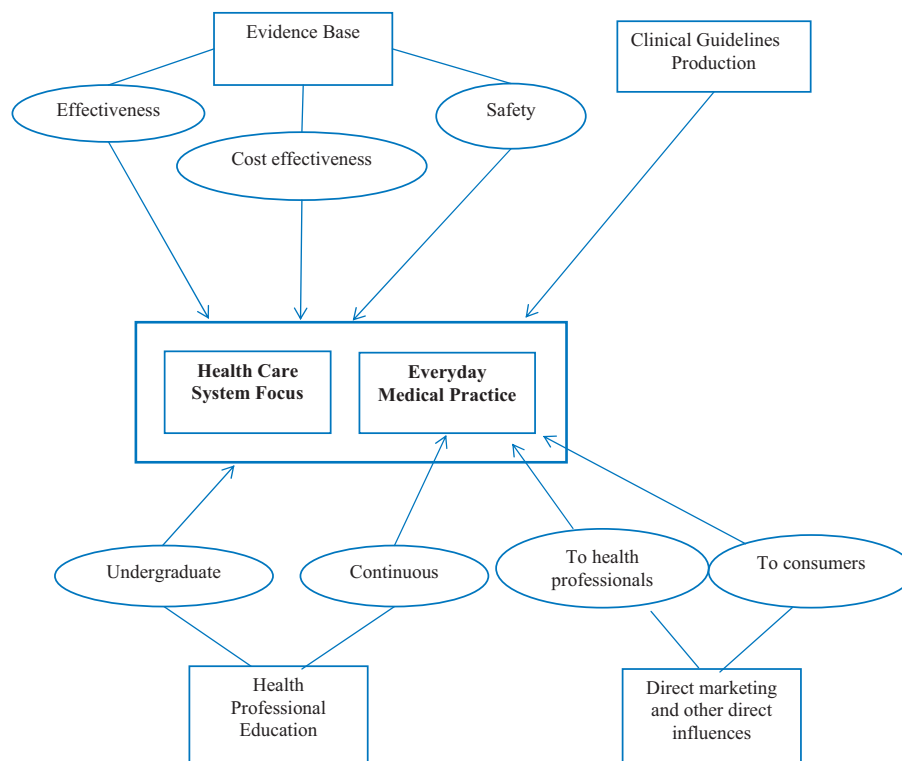


Figure 1 An outline of the main pathways through which the industry influences medical practice and the focus of the healthcare systems.

associated political and lobbying power allow the industry to dictate the rules of the healthcare game to serve its interests at several levels. The industry's interests are often at stark contrast to those of the patients and the society. In this article, we try to analyse the multiple complex pathways through which the industry has directly or indirectly infiltrated healthcare systems including strategic direction, expenditure, research, medical education and daily clinical practice.

How the industry influences healthcare research, strategy, expenditure and practice

The industry has created means to intervene in all steps of the processes that influence healthcare research, strategy, expenditure and practice. These include evidence base production, evidence synthesis, understanding of harms issues, cost-effectiveness evaluation, clinical guidelines formation, healthcare professional education and direct influences on healthcare professional decisions (Fig. 1).

Evidence base production

Industry funds and often designs and controls a large portion of the most influential medical studies. Trials funded by for-

profit organizations are on average 4 times more likely than trials sponsored by non-for-profit organizations to favour the sponsored drug [10,11]. Empirical evidence suggests that while methodological quality is the same in industry-sponsored and other trials [10], industry-sponsored trials are more likely to compare the sponsored intervention against an inactive or straw man comparator [3,10]. An evaluation of over 600 trials registered in clinicaltrials.gov shows that with few exceptions, single trials address only products of a single company [12]. However, for most conditions, there exist many possible interventions, including lifestyle changes and products manufactured by diverse companies. Finally, for many years now, the public sector has largely abandoned the conduct of randomized trials to the industry and thus, not surprisingly, the most cited trials are almost always industry sponsored, often exclusively so [12]. These trials then also guide the conduct of other clinical research. Medical research is doomed to navigate only questions posed by the industry and their extensions. There is increasing direct evidence about the manipulation of reported results in industry-sponsored trials, which demonstrate favourable results and the avoidance of inconvenient findings, as in the case of gabapentin for off-label use [13]. In addition to these direct biases, the industry has a major impact

on which research is published in the most influential medical journals through ghost authorship [14,15], (i.e. raising the status of trial results by listing academically affiliated investigators as first or second authors in manuscripts) written by company staff or professional medical writers paid by the companies. It is possible that major journals have often undisclosed conflict of interests from publishing industry trials. Journals also have conflicts themselves, because such industry trials generate considerable revenue from offprints and can boost the journal's impact factor by as much as 15% [16].

Evidence synthesis

Systematic reviews that summarize trials addressing the wrong questions (as above) will simply reinforce the wrong messages [17], unless meta-analysts are astute to diagnose the problems in the generation of the evidence, let alone publication and other selection biases. Access to raw data of clinical trials to date has been limited, and integration in systematic reviews of the data that are readily available may perpetuate and solidify the biases of the primary literature [18]. Moreover, as systematic reviews and meta-analyses have grown in prestige and influence, the industry has also infiltrated this type of research. A systematic review comparing the methodological quality of meta-analyses of the same drugs by source of funding (industry-funded versus nonindustry funded) [19] concluded that the former type of study is of lower methodological quality and considerably more likely to omit reporting bias-relevant details (e.g. descriptions of the excluded patients/studies). Although the estimated treatment effects were similar on average, 100% of industry-funded meta-analyses had conclusions recommending the experimental drug without reservations compared with 0% of the (independent) Cochrane reviews [19]. In meta-analyses of antihypertensive drugs, financial ties to a pharmaceutical company were not associated with favourable results, but were linked to four times higher odds to report favourable conclusions [20]. Furthermore, conflict of interests in the original studies included in meta-analyses are usually silenced and unreported [21]. For example, a recent study revealed that only 2 of 29 pharmacological meta-analyses reported the funding sources of the trials and none of them reported author–industry ties in the primary trials [21]. Finally, content experts who co-author systematic reviews and meta-analyses may often distort the phrasing of the research questions, the results and the interpretation of these reviews in favour of industry products [22].

Understanding of harms issues

Licensing for new products or indications requires demonstration of effectiveness and absence of major harms. However, the whole process allows plenty of room for serious harms to be unrecognized by the time licensing is granted. Many interven-

tions are withdrawn or acquire black boxes years after they are licensed and after they have already cost a fortune to the health-care system [23]. Recent drug withdrawals suggest that financial ties with the pharmaceutical industry can determine the orientation of the authors of trials and meta-analyses in drug safety issues. Rosiglitazone, a multibillion selling drug for type 2 diabetes, was approved and prescribed to millions of patients worldwide for 10 years despite limited evidence on its benefits and, especially, safety [24]. Rosiglitazone potentially increases the risk of cardiovascular disease and comorbidities such as weight gain and increases blood lipids. It has recently been withdrawn from both the EU and New Zealand markets, and its indications have been severely restricted in the United States [25]. Among the many similar revelations, perhaps the best known case is rofecoxib (Vioxx), a blockbuster nonsteroidal anti-inflammatory drug that nearly doubled the chances of both myocardial infarction and stroke [26]. Data revealed during a litigation case suggested the manufacturer intentionally distorted the presentation of trial safety data [27] and trained its sale representatives to tactfully avoid physician questions on safety [28].

Cost-effectiveness evaluation

Cost-effectiveness of therapies is a major criterion when allocating scarce public resources and is directly influenced by commercial pricing strategies. Most published analyses report favourable incremental cost-effectiveness ratios, and studies funded by industry are more likely to report ratios below required thresholds on cost-effectiveness [29]. Studies funded by industry are more than twice as likely to report cost-effectiveness ratios below \$20 000 per quality-adjusted life year compared with studies funded by other sources [30]. There are many different methods by which industry-sponsored cost-effectiveness analyses can achieve more favourable results, including but not limited to biased assumptions about the intervention, its comparators (e.g. underestimating the sensitivity/specificity of the standard Pap test for analyses of HPV vaccines or HPV DNA tests for cervical cancer prevention) [31] or other parameters that need to be modelled (e.g. extent of indirect effects for vaccines) [32].

Clinical practice guidelines

Clinical practice guidelines are supposed to be based on best evidence. They are endorsed by recognized authorities, and to a large extent, they define daily medical practice. Integrity, objectivity and independence are of paramount importance for a correct translation of the evidence into clinical guidelines. These three crucial attributes are difficult to safeguard. Most (56%) scientists involved in the 17 most authoritative US cardiovascular clinical practice guidelines released between 2004 and 2008 received research grants, honoraria for speeches in drug-promoting events, stocks (shares) or consultancy fees by

pharmaceutical and related industries [33]. Over 80% of the committee chairs had such conflict of interests. Over 50% of guideline panel members in the United States and Canada have conflict of interests while the respective figure for guidelines sponsored by nongovernment sources approaches 70% [34]. Overall, between 56 and 87% of clinical practice guidelines, authors have been found to have at least a conflict of interest (consultancies, research support, equity/stock ownership) [35]. There is substantial margin for the members of these committees to input their subjective views through 'expert opinion' (evidence level C), which represented nearly half of all major US cardiovascular clinical care guidelines published between 1984 and 2008 [36]. Even higher levels of interaction were noted between the authors of 44 clinical guidelines and the pharmaceutical industry in a previous publication [37]. Given that the boundary between industry and academia has become so vague, it is hardly surprising that clinical practice guidelines often are heavily focused on new costly interventions and only loosely follow the available evidence. For example, current guidelines still advocate tight pharmacological glycaemic control for patients with type 2 diabetes, despite the best available evidence suggesting that there is no major benefit for patients [38] and possibly even deterioration of quality of life [39]. Declarations of the conflict of interests of expert panels and researchers are thought to guarantee transparency and integrity in the evidence base and clinical recommendation generation process. Nevertheless, there appears to be a gap between the intended purpose and practice as financial conflict of interests are severely under-reported in drug trial meta-analyses and panel guidelines [34] and practitioners very rarely discount for such conflicts when evaluating the evidence base [40]. Besides clinical guidelines formation, narrative review and editorials by key opinion leaders also have a major impact on clinical practice decisions and the medical community in general [41,42]. An example of the influence of the conflict of interests of key opinion leaders is that although evidence does not support that brand-name drugs are superior to generic drugs [43], editorials often counsel against the interchangeability of generic drugs [43].

Healthcare professional education

Intense exposure to pharmaceutical marketing commences during undergraduate medical education for future prescribers. A study showed that third-year medical students are exposed to one industry-sponsored gift or activity per week and almost (93%) all have been asked or required to attend at least one industry-sponsored lunch [44]. The large majority (67–92%) of medical students acknowledge that education from industry sources is biased and that pharmaceutical industry pressures increase over the course of medical school [45]. This exposure brainwashes medical students' attitudes towards the

marketed products [46]. In the USA, 60% of medical school chairs have some form of personal relationship with industry (e.g. consultant, a member of a scientific advisory board, a paid speaker, an officer, founder or member of the board of directors) [47]. Continuing medical education (CME) is an essential part of the development for practicing health professionals. In the United States, industry support for CME increased from \$301 million per year in 1998 to \$1.2 billion per year in 2007 accounting for approximately 60% of the total accredited CME costs (including advertising/exhibit payments) [48]. Although there are signs of a reversing trend (due to regulatory restrictions and the economic trends), industry-funded CME still accounted for approximately half of all CME by 2010 [48]. Industry sponsors have substantial influence over the content of education programmes, which often involve heftily paid prominent medical figures presenting information about the company's latest products, often using slides provided by the company [49]. Sponsored CME leads to increases in prescription rates by the attendant physicians of the promoted medication [50]. In the UK, most hospital educational 'grand rounds' and many other medical education meetings are sponsored by the industry, with lunches provided in return for sales and marketing opportunities. In primary care, many staff events are sponsored by the pharmaceutical industry in return for a lunch and 'educational' opportunities on pharmaceutical products. Postgraduate education departments foster strong relationships with sales representatives, and educational meetings and conferences are nearly always industry financed [51].

Direct influences on healthcare professional decisions

Direct marketing pressures by sales representatives are substantial, for example, a US cardiologist meets with sales representatives nine times a month on average [52]. In 2004, over a third of the \$57 billion that pharmaceutical companies spent on promotional activities went on visiting doctors to promote new drugs and establish relationships with health professionals in community or academic settings [53]. Regular interactions with sales representatives increases the chances to add the drug company to a hospital's formulary by over 300%, and the combination of the physician receiving honoraria leads to even greater increases [54]. The culture of industry-offered 'gifts' or equipment, educational textbooks, sponsorship or luxury travel [55] and free meals has been common across the entire spectrum of health practitioners. In many countries, most industries have a trade association representing their profit-orientated members, for example, the UK Association of the British Pharmaceutical Industry (ABPI) with 150 members, which has set up the Prescription Medicines Code of Practice authority to administer the pharma-

ceutical industries' own code of practice. However, there has been a recent exodus of ABPI members, with even fewer companies choosing to follow even this largely voluntary code [56]. Surveyed patients consider the financial ties between practitioners and drug companies unacceptable and a compromise to their quality of care [57]; however, patients are rarely aware of their doctor's ties with the industry, which may have biased their care plan.

Direct-to-consumer advertising

In the United States, where such marketing practices are permitted by law, direct-to-consumer advertising (DTCA) is a major force of rising pharmaceutical costs [58]. Industry spending on DTCA for pharmaceuticals alone increased from \$11 billion to \$30 billion within the 1996–2005 decade [59], about the same period of time when the total costs of prescription drugs were rising at a rate higher than 30% a year [60]. Besides inflated costs for patients and healthcare providers [58], DTCA is linked to concerns over the aptitude of the lay public to understand risks and benefits through a 30-s TV or a one-page magazine advertisement. DTCA typically commences one year after release of a new drug [59], which is a very short time frame for many unwanted side effects to become apparent. The US Senate has previously considered legislation prohibiting such advertising for at least two years [61].

Conclusions

Given that many of the problems discussed above are closely linked to financial interests, we would argue that there is an urgent need to better deal with conflict of interests in medicine and healthcare. The Institute of Medicine has published a comprehensive set of recommendations on how to deal with conflict of interests in medicine so that the undue industry influences we describe above are eliminated [62]. These recommendations cover general policy measures, medical research, undergraduate and continuous medical education, medical practice, as well as clinical guideline formation. The evidence we presented highlights the case for tighter regulation on how the healthcare industry designs, conducts, disseminates and publicizes their research, markets their products and interacts with medical students, health professionals and researchers. Currently, industry expenditure influences and determines medical practice and attitudes at various levels (Fig. 1) at the expense of patients' health, healthcare budgets and medicine's integrity. There are positive signs of action taken in both United States and Europe, for example, the Sunshine Act in the United States that requires drug companies to declare all payments and hospitality or gifts they give to doctors. In Denmark, companies have been required to declare their payments to doctors since 2008, in Scotland, doctors have to declare such transactions themselves,

and France is currently preparing such legislation. The New England Journal of Medicine banned cost-effectiveness evaluations sponsored by product manufacturers almost two decades ago. These are some indicative steps towards redefining the mission of medicine towards a more objective and patient-, population- and society-benefit direction that is free from conflict of interests.

Acknowledgements

ES is supported by a Career Development Fellowship (ES) provided by the National Institute for Health Research. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS or the National Institute for Health Research or the Department of Health.

Conflict of interests

None of the authors have any conflict of interest to declare.

Address

Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK. (E. Stamatakis); School of Public Health, Prevention Research Collaboration, University of Sydney, Sydney, NSW 2006, Australia (E. Stamatakis); University College London Hospitals NHS Foundation Trust, 235 Euston Road, London, NW1 2BU, UK (R. Weiler); Stanford Prevention Research Center, Department of Medicine and Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA 94305, USA (J. P. A. Ioannidis); Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, CA 94305, USA (J. P. A. Ioannidis).

Correspondence to: Emmanuel Stamatakis, University College London, Department of Epidemiology and Public Health, 1-19 Torrington Place, London, WC1E 6BT, UK. Tel.: +44 (0) 20 76791721; fax: +44 (0) 20 78130242; e-mail: e.stamatakis@ucl.ac.uk

Received 15 February 2013; accepted 24 February 2013

References

- 1 The Lancet (in-house editorial). Lessons from Lipitor and the broken blockbuster drug model. *Lancet* 2011;**378**:1976.
- 2 International Monetary Fund. World Economic Outlook Database [Internet]. Nominal GDP list of countries for the year 2010. 2011. Available at: www.imf.org/external/pubs/ft/weo/2011/02/weodata/index.aspx. updated on 24 January 2012.
- 3 Ioannidis JPA, Karassa FB. The need to consider the wider agenda in systematic reviews and meta-analyses: breadth, timing and depth of evidence. *BMJ* 2010;**341**:c4875. doi:10.1136/bmj.c4875.
- 4 Abbott. 2009 Annual Report [Internet] 2009. Available at: http://www.abbott.com/annual-reports/2009/downloads/Editorial_section_only.pdf. cited on 12 February 2013.

- 5 MassDevice staff. MassDevice Blog: Abbott Labs and Boston Scientific together make up about 64 percent of U.S. drug eluting stent market [Internet]. c2011. Available at: <http://www.massdevice.com/news/abbott-and-boston-scientific-dominate-46-billion-drug-eluting-stent-market>. cited on 12 February 2013.
- 6 Prasad V, Cifu A, Ioannidis JPA. Reversals of established medical practices: evidence to abandon ship. *JAMA* 2012;**307**:37–8.
- 7 Katritsis DG, Ioannidis JPA. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease. *Circulation* 2005;**111**:2906–12.
- 8 Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–16.
- 9 Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;**172**:312–9.
- 10 Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;**326**:1167–70.
- 11 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.
- 12 Lathyris DN, Patsopoulos NA, Salanti G, Ioannidis JPA. Industry sponsorship and selection of comparators in randomized clinical trials. *Eur J Clin Invest* 2010;**40**:172–82.
- 13 Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 2009;**361**:1963–71.
- 14 Ross JS, Hill KP, Egilman DS, Krumholz H. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA* 2008;**299**:1800–12.
- 15 Sismondo S. Ghosts in the Machine. *Soc Stud Sci* 2009;**39**:171–98.
- 16 Lundh A, Barbateskovic M, Hróbjartsson A, Gøtzsche PC. Conflicts of interest at medical journals: the influence of industry-supported randomised trials on journal impact factors and revenue – cohort study. *PLoS Med* 2010;**7**:e1000354.
- 17 Ioannidis JPA. Meta-research: the art of getting it wrong. *Res Synth Methods* 2010;**1**:169–84.
- 18 Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. *BMJ* 2012;**344**:d7898.
- 19 Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *BMJ* 2006;**333**:782.
- 20 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.
- 21 Roseman M, Milete K, Bero LA, Coyne JC, Lexchin J, Turner EH *et al.* Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA* 2011;**305**:1008–17.
- 22 Gøtzsche PC, Ioannidis JP. Content area experts as authors: helpful or harmful for systematic reviews and meta-analyses? *BMJ* 2012;**345**:e7031.
- 23 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;**287**:2215–20.
- 24 Cohen D. Rosiglitazone: what went wrong? *BMJ* 2010;**341**:c4848.
- 25 Wang AT, McCoy CP, Murad MH, Montori VM. Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. *BMJ* 2010;**340**:c1344.
- 26 Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K *et al.* The adenomatous polyp prevention on Vioxx trial investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;**352**:1092–102.
- 27 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.
- 28 Berenson A. For Merck, Vioxx paper trail won't go away. *New York Times*. 2005 Aug 21; Sect A:1.
- 29 Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D *et al.* Bias in published cost effectiveness studies: systematic review. *BMJ* 2006;**332**:699–703.
- 30 Miners AH, Garau M, Fidan D, Fischer AJ. Comparing estimates of cost effectiveness submitted to the National Institute for Clinical Excellence (NICE) by different organisations: retrospective study. *BMJ* 2005;**330**:65.
- 31 Polyzos NP, Valachis A, Mauri D, Ioannidis JP. Industry involvement and baseline assumptions of cost-effectiveness analyses: diagnostic accuracy of the Papanicolaou test. *CMAJ* 2011;**183**:E337–43.
- 32 Rozenbaum MH, Hoek AJ, Hak E, Postma MJ. Huge impact of assumptions on indirect effects on the cost-effectiveness of routine infant vaccination with 7-valent conjugate vaccine (Prevnar). *Vaccine* 2010;**28**:2367–9.
- 33 Mendelson TB, Meltzer M, Campbell EG, Caplan AL, Kirkpatrick JN. Conflicts of interest in cardiovascular clinical practice guidelines. *Arch Intern Med* 2011;**171**:577–84.
- 34 Neuman J, Korenstein D, Ross JS, Keyhani S. Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study. *BMJ* 2011;**343**:d5621.
- 35 Norris SL, Holmer HK, Ogden LA, Burda BU. Conflict of interest in clinical practice guideline development: a systematic review. *PLoS One* 2011;**6**:e25153.
- 36 Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009;**301**:831–41.
- 37 Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA* 2002;**287**:612–7.
- 38 Montori VM, Fernandez-Balsells M. Glycemic control in type 2 diabetes: time for an evidence-based about-face? *Ann Intern Med* 2009;**150**:803–8.
- 39 Yudkin JS, Richter B, Gale EA. Intensified glucose lowering in type 2 diabetes: time for a reappraisal. *Diabetologia* 2010;**53**:2079–85.
- 40 Silverman GK, Loewenstein GF, Anderson BL, Ubel PA, Zinberg S, Schulkin J. Failure to discount for conflict of interest when evaluating medical literature: a randomised trial of physicians. *J Med Ethics* 2010;**36**:265–70.
- 41 Moynihan R. Key opinion leaders: independent experts or drug representatives in disguise? *BMJ* 2008;**336**:1402–3.
- 42 Meffert JJ. Key opinion leaders: where they come from and how that affects the drugs you prescribe. *Dermatol Ther* 2009;**22**:262–8.
- 43 Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK *et al.* Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA* 2008;**300**:2514–26.

- 44 Sierles FS, Brodkey AC, Cleary LM, McCurdy FA, Mintz M, Frank J *et al.* Medical students' exposure to and attitudes about drug company interactions. *JAMA* 2005;**294**:1034–42.
- 45 Austad KE, Avorn J, Kesselheim AS. Medical students' exposure to and attitudes about the pharmaceutical industry: a systematic review. *PLoS Med* 2011;**8**:e1001037.
- 46 Grande D, Frosch DL, Perkins AW, Kahn BE. Effect of exposure to small pharmaceutical promotional items on treatment preferences. *Arch Intern Med* 2009;**169**:887–93.
- 47 Campbell EG, Weissman JS, Ehringhaus S, Rao SR, Moy B, Feibelmann S *et al.* Institutional academic industry relationships. *JAMA* 2007;**298**:1779–86.
- 48 Steinman MA, Landefeld CS, Baron RB. Industry support of CME — are we at the tipping point? *N Engl J Med* 2012;**366**:1069–71.
- 49 Avorn J, Choudhry NK. Funding for medical education: maintaining a healthy separation from industry. *Circulation* 2010;**121**:2228–34.
- 50 Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA* 2000;**283**:373–80.
- 51 Brody H. Pharmaceutical Industry financial support for medical education; benefit, or undue harm? *J Law Med Ethics* 2009;**37**:451–60.
- 52 Campbell EG, Gruen RL, Mountford J, Miller LG, Cleary PD, Blumenthal D. A national survey of physician-industry relationships. *N Engl J Med* 2007;**356**:1742–50.
- 53 Gagnon M-A, Lexchin J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLoS Med* 2008;**5**:e1.
- 54 Chren MM, Landefeld CS. Physicians' behavior and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary. *JAMA* 1994;**271**:684–9.
- 55 Giannakakis IA, Ioannidis JPA. Arabian nights—1001 tales of how pharmaceutical companies cater to the material needs of doctors: case report. *BMJ* 2000;**321**:1563–4.
- 56 Norgine MP, Martin P. Norgine's reply to ABPI. *BMJ* 2010;**340**:c1869.
- 57 Licurse A, Barber E, Joffe S, Gross C. The impact of disclosing financial ties in research and clinical care: a systematic review. *Arch Intern Med* 2010;**170**:675–82.
- 58 Law MR, Soumerai SB, Adams AS, Majumdar SR. Costs and consequences of direct-to-consumer advertising for clopidogrel in Medicaid. *Arch Intern Med* 2009;**169**:1969–74.
- 59 Donohue JM, Cevasco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. *N Engl J Med* 2007;**357**:673–81.
- 60 Kaiser Family Foundation [Internet]. Prescription Drug Trends. Menlo Park, California; c2010. Available at: <http://www.kff.org/rxdrugs/upload/3057-08.pdf>. cited on 12 February 2013.
- 61 Shuchman M. Drug risks and free speech: can congress ban consumer drug ads? *N Engl J Med* 2007;**356**:2236–9.
- 62 Institute of Medicine. Chapters 3–8. In: Lo B, Fields MJ, editors. *Conflict of Interest in Medical Research, Education, and Practice*. Washington, DC: National Academy of Sciences; 2009: pp. 62–229.