bmj.com/podcasts
Birte Twisselmann talks to Beate Wieseler about IQWiG and reboxetine

Drug studies: a tale of hide and seek

Beate Wieseler, **Natalie McGauran**, and **Thomas Kaiser** use their experience with the assessment of reboxetine to illustrate how publication bias affects health policy decisions and offer some solutions

The antidepressant reboxetine, a selective noradrenaline (norepinephrine) reuptake inhibitor, has been approved in several European countries (including the United Kingdom and Germany) since 1997. However, approval was declined in the United States in 2001. The German Institute for Quality and Efficiency in Health Care (IQWiG) report on the benefit and harm of newer antidepressants concluded in 2009 that, overall, reboxetine was both ineffective and potentially harmful.[1 2]

Data from the IQWiG report are published in the accompanying systematic review of reboxetine versus placebo and selective serotonin reuptake inhibitors for acute treatment of major depression, which includes previously unpublished data.[3] An additional analysis of published versus both published and unpublished evidence shows that published evidence overestimates the benefit of reboxetine, while underestimating harm. These typical effects of publication bias have been identified (and in part quantified) not only in other research on antidepressants[4 5] but in a wide range of treatments.[6 7]

Biased evidence may form part of a marketing strategy. Analyses of litigation documents, which are available at the Drug Industry Document Archive (http://dida.library.ucsf.edu), have shown how trials and journal publications are used as marketing tools to promote drug use.[8 9] A striking example is the promotion of the off-label use of gabapentin,[9] which was heavily supported by the dissemination of literature that reported only selected outcomes.[10]

Problems in obtaining data for health technology assessment

To minimise the influence of publication bias and increase transparency, IQWiG requests manufacturers of drugs under assessment to sign a voluntary agreement requiring submission of a list of all sponsored published and unpublished trials; submission of CONSORT compliant documents (generally the clinical study reports) on all relevant trials selected by IQWiG; and permission for publication of all previously unpublished relevant data in the assessment report. Unlike other health technology assessment bodies, IQWiG does not accept "commercial in confidence" data.

IQWiG publishes a preliminary report on its website, which is open to comments from all interested parties.[11] The retrieval of comprehensive evidence on reboxetine for the preliminary report on newer antidepressants was hampered by the fact that the manufacturer, Pfizer, although providing a list of published trials and European submission documents, did not submit a complete list of unpublished trials as requested by IQWiG.


PAUL VISMARA/GETTY IMAGES

Secondary publications suggested that there were unpublished studies. The literature search showed that reboxetine was tested in at least 16 trials including about 4600 patients. However, sufficient data were published on only about 1600 of these patients. In June 2009, IQWiG therefore issued the preliminary conclusion that because of the high risk of publication bias, no meaningful assessment of reboxetine was possible and thus no benefit of the drug could be proved.[12-14] Pfizer immediately publicly claimed "We provided IQWiG with sufficient data: those data that from our point of view are suited for a benefit assessment of Edronax (active ingredient: reboxetine), also in comparison with other drugs" [authors' translation].[15] However, Pfizer then decided to provide most of the missing data. The subsequent assessment showed that, overall, reboxetine had no benefit.[2] As a result of the IQWiG report, the Federal Joint Committee, the statutory health insurance system's main decision making body, plans to stop reimbursement for the drug.

Disparate standards for approval and post-approval decisions

It is generally agreed that regulatory authorities need to have access to the complete data on drugs, and extensive regulation guarantees this access. In contrast, there is insufficient regulation on the evidence required to make health policy decisions after approval, even though these decisions have a considerable effect on the treatment of patients. Furthermore, although regulatory authorities hold the relevant trial data, they often cite confidentiality laws as a reason for denying policy makers and other parties access. Beyond current legislation making trial data publicly available in results databases (see below), there is no legal obligation for manufacturers to provide data for post-approval evaluations by health technology assessment bodies. Consequently, health policy decision makers often have to rely mainly on published information.

Role of regulatory agencies

Reboxetine was approved in several European countries in 1997. In 1999, the Food and Drug Administration granted preliminary approval on the basis of trials primarily conducted outside the US; however, after the results of later US and Canadian trials had been submitted,[16] the FDA declined final approval in 2001 because of "a lack of compelling evidence of efficacy."[17] The new trial results and the FDA's decision had no effect on the European approval status. Post-approval regulatory reviews of drugs have generally focused on safety data; evaluation of new efficacy data (for example, after different approval decisions in other markets) has not been the primary focus.

Authorising bodies will inevitably make decisions at different times, and often new evidence will be available to the body that makes the decision later. If different approval decisions are made, there

is no system in place that triggers a review by the body that made the first decision. Of course such a re-evaluation would increase the regulatory workload, and a structured approach would be required to ensure the efficient use of resources—for example, the quantification of the effect of new evidence and an analysis of the reasons for differences in approval decisions. (Discrepant decisions may not necessarily be caused by new evidence; other reasons, such as the availability of alternatives in the respective market may also have a role.) Some regulatory agencies such as the FDA and European Medicines Agency (EMA) are already cooperating closely with each other—for example, the FDA opened an office in Brussels in 2009 and has staff members located at EMA in London.[18] Although extended cooperation and additional regulatory resources would be required, the example of reboxetine shows that re-evaluations may improve the quality of treatment for patients.

Legal changes

The US FDA Amendments Act of 2007 solves part of the problem surrounding publication bias in drug research.[19] The act requires standardised data on protocol and results to be publicly posted at clinicaltrials.gov for clinical trials (except phase 1) of drugs subject to FDA regulation.[20] In general, results must be posted within one year after completion of study. Non-compliance with the law results, among other things, in penalties of up to $10 000 (£6500; €7900) a day.

However, the act has loopholes: it does not cover trials completed before 27 September 2007 or trials of drugs that were never approved.[21] Thus although comprehensive information will in future be available on newer drugs, published information on older drugs will remain biased, resulting in an unfair comparison of old and new treatment options. It also means that negative findings on drugs never approved may not be made public, even if the drug is approved elsewhere, as in the case of reboxetine.

In addition, posting of results for trials of approved drugs tested in new, unapproved indications can be delayed for two years (if approval is not granted in the new indication, results must still be posted).[21] Finally, existing regulations are insufficient to tackle the problem of reporting selected outcomes; this requires registration of full study protocols, including any amendments,[10 22] and of plans for statistical analysis.

Similar legislation to the FDA Amendments Act is under way in Europe with the mandatory public disclosure of data from the clinical trials database EudraCT.[23 24] These laws should be expedited and also close the loopholes that the FDA experience shows can be critical.

What is IQWiG?

- An independent non-government and non-profit foundation (www.iqwig.de)
- Established in 2004 as part of German healthcare reform
- Mainly funded by a levy on inpatient and outpatient services
- Produces health technology assessments on diagnostic or therapeutic interventions and health economic evaluations for the Federal Joint Committee (G-BA)—the statutory health insurance system's main decision making body
- Publishes evidence based consumer health information (www.informedhealthonline.org)
- Appraises clinical practice guidelines

Recommendations

Current regulations on the publication of trial results are clearly insufficient. The reboxetine case shows that in order to provide patients, clinicians, and health policy makers with unbiased and verified evidence on which to base decisions the following measures are required:

- Extension of the FDA Amendments Act to include drugs for which approval was declined and worldwide implementation of this type of legislation
- Public access to regulatory databases containing trials of older drugs not covered by current law[21 25]
- Greater data sharing between regulatory authorities, as well as re-evaluation of a drug if approval is declined elsewhere
- Legal obligation for manufacturers to provide all requested data to health technology assessment bodies without commercial restrictions to publication.

Implementation of all four measures, which should cover trials of both drug and non-drug interventions, would close the information gaps for post-approval decisions and enable adequate decision making in health care.

Beate Wieseler deputy head of department of drug assessment
Natalie McGauran researcher
Thomas Kaiser head of department of drug assessment,
Institute for Quality and Efficiency in Health Care, Dillenburger Strasse 27, 51105 Cologne, Germany
Correspondence to: B Wieseler **beate.wieseler@iqwig.de**

Accepted: 16 August 2010

We thank Hilda Bastian for her helpful comments on the first draft of the manuscript.

Contributors and sources: BW and NMcG conceived the paper and drew up the first draft. TK critically reviewed and revised the first draft. All the authors reviewed and revised the following drafts and approved the final version. BW is the guarantor.

Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any company for the submitted work; the authors are employed by IQWiG and support the mandatory worldwide establishment of trial registries and study results databases.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Institute for Quality and Efficiency in Health Care. [Bupropion, mirtazapine, and reboxetine in the treatment of depression: final report; commission A05-20C.][German]. 2009. www.iqwig.de/download/A05-20C_Abschlussbericht_Bupropion_Mirtazapin_und_Reboxetin_bei_Depressionen.pdf.
2 Institute for Quality and Efficiency in Health Care. Antidepressants: benefit of reboxetine not proven. Press release, 24 Nov 2009. www.iqwig.de/antidepressants-benefit-of-reboxetine-not-proven.981.en.html.
3 Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010;341:c4737.
4 Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363:1341-5.
5 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358:252-60.
6 Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010;14:1-193.
7 McGauran N, Wieseler B, Kreis J, Schüler YB, Kölsch H, Kaiser T. Reporting bias in medical research: a narrative review. *Trials* 2010;11:37.
8 Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med* 2008;149:251-8.
9 Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med* 2006;145:284-93.
10 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.
11 Institute for Quality and Efficiency in Health Care. General methods: version 3.0. 2008. www.iqwig.de/download/IQWiG_General_methods_V-3-0.pdf.
12 Institute for Quality and Efficiency in Health Care. [Bupropion, mirtazapine, and reboxetine in the treatment of depression: preliminary report; commission A05-20C.][German]. 2009. www.iqwig.de/download/A05-20C_Vorbericht_Bupropion_Mirtazapin_und_Reboxetin_bei_Depressionen.pdf.
13 Stafford N. German agency refuses to rule on drug's benefits until Pfizer discloses all trial results. *BMJ* 2009;338:b2521.
14 Institute for Quality and Efficiency in Health Care. Bupropion, mirtazapine and reboxetine in the treatment of depression: executive summary of preliminary report; commission A05-20C. 2009. www.iqwig.de/download/A05-20C_Executive_summary_preliminary_report_Bupropion_mirtazapine_and_reboxetine_in_the_treatment_of_depression.pdf.
15 Pfizer Pharma. [Pfizer rejects allegations by IQWiG.] [German]. Press release, 10 Jun, 2009. www.medikamente-und-arznei.de/Pfizer_weist_IQWiG-Vorwuerfe_zurueck.570.0.html.
16 Page ME. The promises and pitfalls of reboxetine. *CNS Drug Rev* 2003;9:327-42.
17 Preskorn SH. Reboxetine: a norepinephrine selective reuptake pump inhibitor. *J Psychiatr Pract* 2004;10:57-63.
18 Food and Drug Administration. Improving the safety of imported food and medical products. 2010. www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM187246.pdf.
19 Food and Drug Administration. FDA Amendments Act of 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf.
20 ClinicalTrials.gov Protocol Registration System: PRS and US Public Law 110-85. 2010. http://prsinfo.clinicaltrials.gov/fdaaa.html.
21 Wood AJJ. Progress and deficiencies in the registration of clinical trials. *N Engl J Med* 2009;360:824-30.
22 Krleza-Jeric K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (part 1). *BMJ* 2005;330:956-8.
23 Regulation (EC) no 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *Official J Eur Commun* 2004;47:L1-33.
24 Regulation (EC) no 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending regulation (EEC) no 1768/92, directive 2001/20/EC, directive 2001/83/EC and regulation (EC) no 726/2004. *Official J Eur Commun* 2006;49:L1-9.
25 Turner EH. Closing a loophole in the FDA Amendments Act. *Science* 2008;322:44-6.

Cite this as: *BMJ* 2010;341:c4942

See EDITORIAL, p 787, RESEARCH, p 816

Free the data

Several recent examples show the problems of trusting drug companies to provide the complete picture about the clinical trials they sponsor. **Robert Steinbrook** and **Jerome P Kassirer** propose that investigators and journal editors have full access to data

Concerns about the reliability of the data in the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial[1 2] have once again raised an uncomfortable question—what criteria should medical journals use when they consider reports of industry sponsored clinical trials for publication? As published, the open label RECORD trial, which was sponsored by GlaxoSmithKline, showed that the addition of rosiglitazone (Avandia) to metformin or sulfonylurea was not inferior to treatment with a combination of these drugs for a composite endpoint of cardiovascular events and death, and was inconclusive about any possible effect on myocardial infarction.[2] However, during the course of the review of the study by the United States Food and Drug Administration (FDA), a reviewer who audited the raw data found that potential bias and omissions in the adjudication of cardiovascular endpoints had downplayed the risk of myocardial infarction associated with taking rosiglitazone.[3 4] Another FDA official said of the reviewer's report, " I think you could sum [the review] up in one word, and the word is truth. Can we trust the sponsor with the results of RECORD?"[5] In September 2010, regulatory agencies announced that medicines containing rosiglitazone would be taken off the market in Europe and their use substantially restricted in the United States.[6 7]

In some ways, the rosiglitazone story is the story of rofecoxib (Vioxx) all over again.[8] In 2005, concerns were raised about important safety data that were not included in the report of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which was sponsored by Merck. The concerns about the omission of three myocardial infarctions in the group assigned to rofecoxib and other relevant safety data were raised after the release of data by the FDA and documents obtained through litigation.[9 10]

Companies have financial interests in the outcome of the studies they sponsor; they own the data, and set the rules for access to the data. Unfortunately, they cannot be relied on to consistently provide dispassionate evaluations of their own drugs and medical devices.[11] Moreover, many investigators have notable financial interests with the same sponsors. According to the voluntary principles of the Pharmaceutical Research and Manufacturers of America, "As sponsors, we are responsible for receipt and verification of data from all research sites for the studies we conduct; we ensure the accuracy and integrity of the entire study database, which is owned by the sponsor."[12] These obligations may be appropriate, but it has become impossible to assess which industry studies are trustworthy.

JONATHAN EVANS/GETTY IMAGES

Some regulatory agencies, such as the FDA, have legal authority to independently scrutinise the data. For example, when the FDA restricted access to rosiglitazone, it acknowledged that the RECORD data were not reliable and required that the sponsor convene an independent group of scientists to readjudicate the endpoints at the patient level.[7] Journal editors, however, have no such legal authority.

Clinical trial investigators are caught in an awkward catch-22. The uniform requirements for manuscripts submitted to biomedical journals specify that when a study is "funded by an agency with a proprietary or financial interest in the outcome," the authors should attest that "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."[13] Yet the principles of the Pharmaceutical Research and Manufacturers of America include vague statements such as "we seek to provide investigators with meaningful access to clinical data from the studies in which they participate" and "investigators will be given access to any tables, figures, and reports they need from the study that are related to the hypothesis being tested or explored or which are needed in order to understand the results of the study."[12] These principles do not include provisions for full and unrestricted access to the trial database as determined by the researchers, not the company. Thus investigators may be unable to examine the data independently, confirm findings, and conduct their own analyses.[14] Without such unfettered access, investigators cannot guarantee that they have met journals' standards for the conduct and reporting of research. Parenthetically, it may be important to distinguish between trials that are funded and sponsored by industry and those that receive industry funding but are sponsored by medical research agencies and conducted by investigators who are independent of industry.

A desirable situation would be for considerably more clinical trials to be sponsored, funded, and conducted by organisations that are independent of industry[11 15] and for considerably fewer investigators to have financial associations with industry other than research support and bona fide consulting related to research. However, companies will continue to sponsor trials and it is unrealistic to expect that journals will stop publishing them. But a lesson from

rosiglitazone and rofecoxib is that it is time for journals to tighten their standards further.[14]

Of the possible approaches, we highlight three. First, journals should explicitly define "full access to all of the data," for example, as "unrestricted access to the trial database, as determined by the researchers, the ability to examine the primary data independent of the sponsor, including the conduct or confirmation of statistical and other analyses, and control over the decision to publish." Second, an author who is independent of a sponsor with a proprietary or financial interest in the outcome—that is, one that has no recent, current, or pending financial association with such a sponsor other than research support administered by the investigator's institution or employer—should serve as principal investigator and take responsibility for the integrity of the study data and the accuracy of the data analysis. Third, the responsible author should be prepared and able to provide the data to the journal, if requested, before acceptance and for a specified period of time after publication, perhaps five years.

These standards should apply to all trials, and journals should decline studies that do not meet them. If concerns about data integrity arise after publication, editors should promptly pursue appropriate actions, such as an independent review of the data, corrections, retractions, and expressions of concern.[13] We anticipate that editors would ask to see the primary data rarely and only for well-defined reasons, but the mere requirement of availability of data for independent examination by journals would be an important safeguard. Some journals have taken noteworthy steps in the directions we suggest,[16 17] but higher standards are needed across the board. Trust in the medical literature, not just in industry sponsored trials, is at stake.

Robert Steinbrook adjunct associate professor
Jerome P Kassirer professor, Tufts University School of Medicine, Boston, MA, United States
rsteinbrook@attglobal.net

Contributors: RS is a former deputy editor and national correspondent of the *New England Journal of Medicine*. JPK is a former editor-in-chief of the *New England Journal of Medicine*. RS and JPK have longstanding professional interests in the integrity of the medical literature and improving the quality of medical journals. Both contributed to developing the concepts, writing, and revising all drafts of the manuscript. RS is the guarantor.

Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned, externally peer reviewed.

1 Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007;357:28-38.
2 Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. *Lancet* 2009;303:2125-35.
3 Marciniak TA. Cardiovascular events in RECORD, NDA 21-071/S035. June 14, 2010. In: FDA briefing document, advisory committee meeting for NDA 21071 Avandia (rosiglitazone maleate) tablet. 2010. www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218491.htm.
4 Cohen D. Rosiglitazone: what went wrong. *BMJ* 2010;341:c4848.
5 Unger E. Transcript for the July 13, 2010 joint meeting of the endocrinologic and metabolic drugs advisory committee and the drug safety and risk management advisory committee. www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm199874.htm.
6 European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. 2010. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
7 Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. *N Engl J Med* 2010;363:10.1056/NEJMp1010788.
8 Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from Vioxx? *BMJ* 2007;334:120-3.
9 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* 2005;353:2813-4.
10 Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. *N Engl J Med* 2006;354:1193.
11 Angell M. Industry-sponsored clinical research: a broken system. *JAMA* 2008;300:1069-71.
12 Pharmaceutical Research and Manufacturers of America. Principles on conduct of clinical trials and communication of clinical trial results. Revised April 2009. www.phrma.org/clinical_trials.
13 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. www.icmje.org.
14 Steinbrook R. Gag clauses in clinical-trial agreements. *N Engl J Med* 2005;352:2160-2.
15 Smith R. Medical journals are an extension of the marketing arm of pharmaceutical companies. *PLoS Med* 2:e138.
16 DeAngelis, CD, Fontanarosa PB. Ensuring integrity in industry-sponsored research primum non nocere, revisited. *JAMA* 2010;303:1196-8.
17 Annals of Internal Medicine. Information for authors. 2010. www.annals.org/site/misc/ifora.xhtml.

Cite this as: *BMJ* 2010;341:c5391

See EDITORIAL, p 787

COMMENTARY

Journals must facilitate criticism

Steinbrook and Kassirer's analysis article (p 811)—which suggests that medical journals should require full access to data for industry sponsored trials—broaches many questions, but it is not clear that it advances our thinking. The first question raised is whether the authors truly comprehend the nature of large scale randomised trials. Trials are a major industry; complex, costly, and bureaucratic. Good chairs of steering committees do check carefully that things are done properly, at least to the extent that they are able, but such scrutiny is fundamentally, in the context of drug development and safety, the responsibility of the regulators.

The RECORD trial[1] suffered from a number of methodological challenges, in particular unacceptably high levels of loss to follow-up.[2] It is not surprising that some of the judgments of a blinded endpoints committee were contestable. The reason we have such committees is because a simple algorithm cannot provide an answer and a judgment is required. We blind the committees so they can make decisions untrammelled by the knowledge of the treatment a participant received. That said, one of the reasons the US Food and Drug Administration and others have favoured all cause mortality as an outcome measure in cardiovascular trials for many years is because of the objective nature of that outcome.[3] RECORD shows no excess risk for rosiglitazone on that outcome.

The authors propose that more trials should be conducted by independent organisations, but problems in quality and timeliness often arise in trials undertaken by academics, which has led to the rise of the commercial clinical research organisations.[4] Additionally, we must not forget the very positive endeavours that industry has been involved in—such as trials of treatments for heart failure, which have substantially affected patients' lives.[5]

It is when considering the role of journals that the authors have exceptional experience. However, their analysis says rather little beyond implicitly recommending the *JAMA* guidelines.[6] Access to original data for a journal editor would be very troublesome; to get to grips with a trial dataset is very time consuming and requires special skills that editors generally do not have. Furthermore, the locked trial dataset would not answer questions about the manner in which those data were derived; such questions require source verification and substantial extra work

and resources. But in the context of drug development and safety, verifying these issues is the responsibility of the regulatory agencies. Surely what we need is for the regulators to do their jobs properly, and ensure that resulting publications of clinical trials are reliable and the data pass scrutiny?

The FDA take a special role in ensuring that marketing for pharmaceutical products is limited to that supported by the scientific data. They have taken steps to ensure that their processes adapt to criticism and avoid allowing sponsors opportunities for unfounded claims (for example, through tightening up loopholes around composite outcomes). Should the regulators have a greater responsibility for what trialists can say in articles? This may fall outside their remit, but transparent processes are essential so that we can see how and why they came to their decisions (the FDA is much better than the European Medicines Agency in this regard).

But what is the role of a medical journal? Obviously to publish scientific work, but also to engage in scrutiny and debate on the validity and interpretation of that work. Rather than simply bashing the companies (which may be deserved, but does not progress us very far) surely journals should encourage and communicate debate that will help prescribers decide what to do in such circumstances? Public criticism acts as a check and a balance on future activities—it seems unlikely that a company would run an unblinded safety study in future, for example. As a ringside observer of this episode, it seems that the truth is hard to call, and risks if they exist seem marginal. It is such circumstances that breed controversy, and it is a journal's job to help us steer a safe course through such controversy.

Nick Freemantle professor of clinical epidemiology and biostatistics, School of Health and Population Sciences, Edgbaston, Birmingham B15 2SP, UK

N.Freemantle@bham.ac.uk

Competing interests: The author has completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; funding for research, travel, and consulting from Novo Nordisk, Sanofi Aventis, Johnson and Johnson, and Eli Lilly; and no other relationships or activities that could appear to have influenced the submitted work.

1 Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125-35.
2 Freemantle N. What can we learn from the continuing regulatory focus on the thiazolidinediones? *BMJ* 2010;341: c4812.
3 Temple R, Pledger GW. The FDA's critique of the anturane reinfarction trial. *N Engl J Med* 1980;303:148892.
4 Freemantle N, Stocken D. The commercialisation of clinical research: who pays the piper, calls the tune? *Family Practice* 2004;21:335-6.
5 NICE. Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care. NICE clinical guideline no 108. 2010. www.nice.org.uk/nicemedia/live/13099/50514/50514.pdf.
6 JAMA. *JAMA* authorship responsibility, financial disclosure, acknowledgment, and copyright transfer/publishing agreement. 2010. http://jama.ama-assn.org/misc/auinst_crit.pdf.

Cite this as: *BMJ* 2010;341:c5397

COMMENTARY

Applying the criteria to the RECORD study

Studies such as RECORD[1] highlight the difficulties of assessing the safety profile of medicines for the treatment of long term conditions. Our response should be measured and recognise the complex issues involved in the design, conduct, and evaluation of studies that explore risks and benefits of treatments. It is too simplistic to assert that collusion between sponsors, investigators, authors, and data and safety monitoring boards is the root cause.

With regards to Steinbrook and Kassirer's (p 811) first criterion, it is hard to imagine any institution—whether academic, industry, or governmental—allowing unfettered analyses of their research data. Many institutions support data release for exploratory research and meta-analyses, protected by formal agreements for data use and storage, appropriate acknowledgments, review, and publication. These agreements stipulate defined research protocols and formal collaboration agreements. In RECORD[1] the data and safety monitoring board met twice a year and "had full access to the interim data" and "were responsible for the decision to publish the results, and wrote the manuscript."

The second criterion of having an independent author taking responsibility for the integrity of the data was met in this study. Philip Home was chair of the steering group for the trial and all fees he receives are donated to the institutions with which he is associated (Newcastle University, Worldwide Initiative for Diabetes Education, and the International Diabetes Federation).[1] This study highlights some important issues regarding decisions that balance safety and efficacy. The FDA committee[2] agreed that rosiglitazone was clearly associated with an increased cardiac ischaemic risk but voted 22 to 1 that it should remain available to patients. By contrast, the European Union has withdrawn the medicine from the market. So although concerns were raised about the study design, two regulatory agencies came to different conclusions based on the same data.

The third and fourth criteria regarding the author justifying the data and journals ensuring that they pursue any inaccuracies have merit but should apply to all studies regardless of the sponsor. For example the principal author could provide the data on which the manuscript is based for a limited period during peer review. Institutions will, however, have legitimate concerns about data integrity and the precise definition of what data are being released. Equally, most reputable journals already pursue corrections and retractions.

However, these measures alone will not prevent a repeat of the problems that arose in the RECORD trial. Post-marketing studies evaluate the safety of a medicine in patient populations many times larger and more heterogeneous than those used to register the drug. These patients represent the real world of prescribing. The concepts of observational post marketing surveillance and specific aspects of the design of the RECORD trial were subsequently criticised by the FDA committee.[2] More rigorous and binding pre-approval of post-marketing studies by regulatory agencies, including the FDA,[3] would be beneficial. Finally, steering groups and data and safety monitoring boards must also play a vital part in ensuring trials are appropriately designed and reported.

Gordon Coutts chief executive, Colchester Hospital University Foundation Trust, Colchester CO4 5JL, UK

Gordon.Coutts@colchesterhospital.nhs.uk

Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; GC has formerly been vice president and managing director at Schering Plough and at Lilly; no other relationships or activities that could appear to have influenced the submitted work.

1 Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. *Lancet* 2009;303:2125-35.
2 Marciniak TA. Cardiovascular events in RECORD, NDA 21-071/S035. June 14, 2010. In: FDA briefing document, advisory committee meeting for NDA 21071 Avandia (rosiglitazone maleate) tablet. July 12 and 14, 2010. www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218491.htm.
3 FDA. Guidance for industry. Postmarketing studies and clinical trials—implementation of section 505(o) of the Federal Food, Drug, and Cosmetic Act. Draft guidance. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.

Cite this as: *BMJ* 2010;341:c5409

COMMENTARY

Journals as police officers?

A timely paper from Robert Steinbrook and Jerome P Kassirer (p 811) takes the position that journals should increase the rigour required to address bias in data offered for publication from industry sponsored trials. In particular (1) the definition (currently ambiguous) of "full access to data" for the authors should be cleared up; (2) one author in the team should be truly independent of any pecuniary interest in the product and act as guarantor; (3) data must be available to editors in case of future concern, (something hopefully rarely exercised); and finally (4) there would be consequences after publication if data were found to have been misleadingly provided (presumably retractions and public disgrace). The problem is illustrated by the rosiglitazone and rofecoxib scandals; these examples could be supplemented by recent *BMJ* investigations of the drug industry's influences on the response to the A/H1N1 influenza pandemic.[1] Some will argue with this approach.

Is it true that journals will be willing to act as police officers in this regard? Widespread criticism of some of the "big five" implies that journals themselves are influenced by the financial returns of drug companies, through the purchase of millions of reprints to be used in publicity. Nor will journal editors relish having to try and sort out data mismatches—this can be a daunting task worthy of a whole piece of research in its own right. Journal editors may thus have a right to look at primary data that is never exercised because there is such a strong disincentive to do so. And drug companies may be very good at burying any investigation with tons of documents.

Is it easy to find a truly unbiased author? For one thing, mere money is not necessarily the only influence. Getting published in a big journal may be very helpful for the academic's career, in which case being squeaky clean from a financial point of view may not be enough to guarantee objectivity.

Even when the editor is alerted to serious concerns about blatant fraud in a paper they have published, it can be almost impossible to redress it: a paper on cardioprotective diet published in the *BMJ*[2] and outed decades later is a good example. The editor demanded the primary data, to be told it had been eaten by white ants. Ghostwriting is another issue that has not been discussed in this context. Much is made of the problem, but is it also a serious cause of bias? Perhaps regularly drawing the world's attention to these scandals in order to maintain the outrage is the most important duty of journals.

Is Steinbrook and Kassirer's analysis too one-sided? Not for my tastes, but perhaps the drug industry will want to have its say in what could be an interesting debate.

Chris Del Mar professor of primary care research, Bond University, Gold Coast, Queensland 4229, Australia
cdelmar@bond.edu.au

Competing interests: None declared.

1 Cohen D, Carter P. WHO and the pandemic flu "conspiracies." *BMJ* 2010;340:c2912.
2 Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R, Ghosh S, Niaz MA. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. *BMJ* 1992;304:1015-9.

Cite this as: *BMJ* 2010;341:c5406

FROM BMJ.COM

From health kick to goal at the European Health Forum, Gastein

I didn't really know what to expect from the session, so when the five main speakers jogged in to the sound of a referee's whistle dressed in blue and black striped football shirts and shorts, I had an inkling that this wasn't going to be your average boring business lunch.

The entire discussion was peppered with flavourful football terms and references to fouls, yellow cards, dribbles, and offlines. And, they all made sense. Use of the ref's whistle was limited to speakers going off the point or exceeding their time limit.

It was a fun discussion all the way through, though the topics were covered in a serious and professional manner. This is what public health should be like—fun, interesting, focused, and useful—a different take. Why shouldn't top notch ideas be generated in a relaxed, comfortable environment?

Sharp, pointed questions were addressed to pharmaceutical company representatives regarding their expressed commitment to actually improving health, particularly since they are seen by certain patient and health professional groups as "the devil incarnate."

There is a feeling out there that pharmaceutical companies are playing around with existing drugs which they know will make it to clinical trials, rather than engaging in truly novel research which can lead to bigger breakthroughs. Is this excessively cynical? What do you think?

"Health in all policies" was a recurrent topic brought up by various speakers and participants. The fact that policies from other parts of the EU (economic, social, etc) can influence health, and that the health of populations will in turn play an important role in shaping future policies, is both an encouraging and sobering thought.

Gender discrimination in research, women's health, and the biological differences that exist between men and women which are still not yet fully appreciated by companies, were brought up. As was the issue of the difference in longevity between men and women ("Do women kill men?"), and the fact that although women live longer, they do so plagued by chronic illness and disability.

More research and political clout should be aimed at increasing the number of healthy, functional life years, rather than simply addressing biological age. To achieve this, it is imperative for different organisations, patient groups, health professionals, NGOs etc to team up and act synergistically: socioeconomic factors and changing life circumstances hit people, and hit them hard. When life hits, women get poorly, and men die. In Russia and Glasgow, the average male life expectancy is 54 years.

Towards the end of the session, an interesting point made by the minister of health for Cyprus provided a suitable conclusion: "Every minister in every ministerial cabinet is a minister of health. Pressure needs to be made on other ministers as well, in order to achieve lasting and concrete health change. Before becoming minister of finance, one should be the minister of health."

Dan Cauchi is currently reading for a masters degree in public health at the University of Maltaand blogged for the *BMJ* while attending the European Health Forum in Gastein, Austria, earlier this month.

You can read more blogs from the young Gasteiners on www.ehfg.org