Bad karma

Stephen Senn

Competence Center for Methodology and Statistics
CRP Santé, Strassen Luxembourg

Correspondence to:

Stephen Senn
Competence Center for
Methodology and Statistics
CRP-Santé, L-1445 Strassen
Luxembourg
stephen.senn@crp-sante.lu

Abstract

Bad Pharma provides a hyper-critical account of the pharmaceutical industry's approach to conducting, publishing and using clinical research and development. However, its attack on the drug regulators is unfair and its examination of the medical press uncritical. In consequence, it fails to provide the appropriate solution to making results of trials more widely available. This is to make the rigour of drug regulation available to all, rather than extending the use of that mediocre medium, the medical press.

Keywords: Missing data, Drug development, Publication bias

Gone missing

All who carry out a Cochrane Collaboration (CC) meta-analysis are warned of the importance of identifying all relevant trials. Missing trials are a problem, not just because they represent a loss of information but in particular because the information that is missing may systematically differ from that which is not. Amongst the many sins of which Ben Goldacre accuses the pharmaceutical industry in *Bad Pharma*[1] is that of failing to publish negative studies. However, his critical faculties, ever present when it comes to the pharmaceutical industry, have gone missing when it comes to others. The consequences of his unfair criticisms of drug regulators (the only characters in the book who have a chapter to themselves with the adjective 'bad') and his eagerness to accept whatever journal editors and the CC tell him are that he misdiagnoses the problem and doesn't see the solution.

As one who has dealt with regulators and regularly reviewed for medical journals, I see the difference like this. Regulators are professional, thorough and expert. The FDA, in particular, has played an important role in promoting the study of many methodological issues affecting analysis and interpretation of clinical trials, whether directly by its own staff or by encouraging, and in some cases commissioning, others to do so. In particular, bioequivalence, non-inferiority, multiplicity, and missing data[2] are all subjects that have greatly benefitted from regulatory input. Statisticians working for the pharmaceutical industry have also made important methodological contributions to drug development science. Furthermore, the International Conference on Harmonisation E9 guideline on statistical analysis[3] is much superior to the alternatives that the journals have to offer. The net result is that the quality of review provided by the regulator far exceeds that provided by journals. The regulators also get to see all the studies, or at least, all the studies for any product seeking a license.

The problem, however, is that it is not only regulators who have to make decisions about pharmaceuticals but also reimbursers, physicians, and patients. Journals provide a visible forum for exchanging results and findings between researchers and for discussing and disseminating them. It is true that peer review makes only a weak contribution to quality but there is not much point lauding the superiority of studies that aren't seen. The first place that any independently based meta-analyst will look for studies is in the medical press. It is thus unacceptable that studies are only seen by the regulators. In a paper I wrote in 2000 entitled 'Statistical quality in analysing pharmaceutical clinical trials'.[4] I put it like this 'No sponsor who refuses to provide end-users with trial data deserves to sell drugs' (p. 26).

Not surprisingly, the Evidence Based Medicine (EBM) movement has railed against the fact that regulatory studies are not always published. Goldacre suggests that it must be made mandatory for studies to be published within 12 months of completion, 'in summary table form if academic publication has not occurred' (p. 98). Certainly any system that relies on academic publication is unworkable, principally because the medical press is not a single authority but a collection of

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competing interests, none of which can be made responsible for publishing any given paper. However, I think that Goldacre underestimates the difficulties. The journals cannot be part of the solution. They are part of the problem. As long as they are seen as being the most prestigious route for dissemination of results, it will be difficult to get all results in a timely manner.

Pluses and minuses

Furthermore, it is quite possible that journals are prejudiced in favour of positive studies. Goldacre dismisses this, describing the journals as 'blameless' (p. 34) but his analysis is inadequate and biased. Contrary to what he claims, the experimental evidence, that is to say from studies in which positive and negative versions of the same paper have been submitted to journals, seems to show quite strongly that there is a bias in favour of positive studies. Goldacre sums up this evidence by saying, 'overall though, even if there are clearly rough edges in some domains, these results don't suggest that the journals are the main cause of the disappearance of negative results' (p. 36). However, he is relying on a 'method' here, noting that some studies were not significant, that the whole EBM movement rejects. This is not how the CC proceeds. A formal summary of studies is needed and it is not given by Goldacre.

When it comes to the observational studies, then Goldacre accepts uncritically what the EBM movement has concluded, despite the fact that in the paper he deals with in most detail,[5] it is editors concluding that they are doing a good job. A number of studies have found that if submissions to journals are classified by whether the findings were 'positive' or 'negative' the acceptance rate is similar. Goldacre then concludes that there is no editorial bias in accepting or rejecting. The fallacy is simple. Goldacre implicitly assumes that the quality of studies submitted is equal. If, instead, authors were submitting by estimated probability of acceptance, not bothering to submit unless this were higher than some threshold, then we might see no difference in this probability but a difference in quality instead, with negative submitted studies having higher quality.[6,7]

Is there any evidence for this? We all occasionally cite papers only having read the abstract and some perhaps only read the title but here it seems that Goldacre has cited a paper without even having read the title! This paper was, 'Commercially funded and United States-based research is more likely to be published; good-quality studies with negative outcomes are not'.[8] You would have thought that the curious association of 'quality' and 'negative studies' in the title would have encouraged reading of the abstract, in which one could have discovered, 'Studies with a negative outcome were of higher quality ($P = 0.003$) and included larger sample sizes ($P = 0.05$)'. In fact, the first of these findings was the most significant one in the article. However, Goldacre seems to have left the 'mental horsepower' – that in his chapter Bad Trials he warns the reader will be needed (p. 172) – placidly munching hay in the stable.

In other words, to claim that journal editors are not biased against negative studies is like claiming that there is no bias against women in higher education because the same percentage of either sex applying to be promoted to professor is successful, overlooking the higher qualifications of women applicants. An explanation then would be that women were not applying because they knew that the system was biased against them and there was no point applying unless their qualifications were exemplary.

Pious bias

Goldacre's bias against the drug developers and regulators regularly misleads him and his readers. How many readers, I wonder, not knowledgeable about drug regulation, would learn from reading Goldacre's section 'Dodgy subgroup analysis' (pp. 205–210) that such are outlawed in regulatory submissions[9] but scarcely policed by the journals? Much of the consulting I do for the industry is concerned with designing watertight, pre-specified analyses to control the type I error rate. (See Senn and Bretz[10] for an example of some methodological considerations.) On the other hand, never in reviewing for the medical press have I been provided with the statistical analysis plan.

In fact, most of Chapter 4 'Bad trials' is pretty much irrelevant to what happens in drug development. Goldacre concedes right at the beginning of the chapter, 'we should also remember that many bad trials…are conducted by independent academics', and even admits that when it comes to studies of trial quality '…industry trials often come out better…' (p. 171), but he dismisses all this as irrelevant '…for one simple reason: independent academics are bit players in this domain' (p. 172). Nothing is offered here by way of argument and explanation beyond appealing to pharmaceutical industry dominance. He does not examine the quality scores of studies comparing industry and academic trials. He doesn't list any indicators

of quality to which he is objecting. Instead he rushes on to discuss bad trials as if they were particularly an industry phenomenon, whereas one could more plausibly argue the reverse is the case.

Goldacre writes, 'Research reviewing a long series of FDA votes found that experts are slightly more likely to vote in a company's interest if they have a financial tie to that company' (p. 126). How many readers will realise that the cited paper stated, 'excluding advisory committee members and voting consultants with conflicts would not have altered the overall vote outcome at any meeting studied'[11] (p. 1921), and that at an individual level a 'paradoxical' association was found between conflict of interest for the competitor drug and voting for the index drug?

Future imperfect

Thus, my view is that *Bad Pharma* has contributed to bringing bad karma to a debate in which drug developers, drug regulators, journals, and, indeed, the CC should have been learning from each other. For what it is worth, my proposal for openness is as follows:

- Sponsors should be self-publishing of the results of trials.
- They should produce, as part of the regulatory submission process, a publication plan.
- A license to market should be given only once the plan is fulfilled.

However, there are many difficult details to be worked out in any plan. In particular

- What level of detail should be provided and how in practice will confidentiality be guaranteed?
- In an attempt to control problems of data-dredging, should we require those who want access to data in order to conduct an independent analysis, to pre-specify this analysis?

It is unhelpful to regard either of these last two points as being symptoms of resistance to progress by the pharmaceutical industry. I predict that we will find mistakes made with inadvertent disclosure of confidential data and that we won't see the EBM movement or the CC coming to the rescue of the industry when this happens. If we don't do something to address the problem of pre-specification, how will we deal with the problem of missing analyses? And must we require that every researcher requesting data publishes the pre-specified analysis? If not how can we guard against the problem of selective analyses? How will we police this?

Prosecutor not judge

To return to Bad Pharma, my view is that you should regard it as a case for the prosecution with all the bias and selective choice of evidence from such a case that you would expect. That's fair enough. There is a place for such cases. Unfortunately, however, many commentators seem to have mistaken it for the judge's summing up. One lesson from *Bad Pharma* is clear: the chattering classes are easily deceived.

Declarations

I consult regularly for the pharmaceutical industry and my career is furthered by publishing. I maintain a full declaration of interest here: http://www.senns.demon.co.uk/Declaration_Interest.htm. The views expressed in this article are mine alone and should not be ascribed to any other party.

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Author information

Stephen Senn is head of the Competence for Methodology and Statistics at CRP Santé in Luxembourg. He has worked for the NHS and the Swiss pharmaceutical industry and held chairs at University College London and the University of Glasgow. He is the author of *Statistical Issues in Drug Development* (1997 & 2007) and *Dicing with Death* (2003).

New ICMJE guidelines for authorship

Revised guidelines for authorship have now been published by the International Committee of Medical Journal Editors (ICMJE).[1] As of August 2013, authorship now requires:

1. Substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The last point is the new part – and will be the most difficult one for authors to comply with. In their commentary,[2] the ICMJE further insists that 'Each author of a paper needs to understand the full scope of the work, know which co-authors are responsible for specific contributions, and have confidence in co-authors' ability and integrity'. This was added because of issues of author misconduct due to authors denying responsibility.

Whether all contributors will be willing or able to comply with these revised guidelines is another story. In my experience, it is already difficult to get most of them to comply with the first three points. Regardless, it is our responsibility as professional medical writers to maintain the highest ethical standards, which includes informing our clients on content and ethics guidelines like those of the ICMJE.

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Phillip Leventhal
4Clinics, Paris, France
pleventhal@4clinics.com