

## Sticking to principles and anticipating outcomes

TOM JEFFERSON<sup>1</sup>

<sup>1</sup>Senior Associate Tutor, University of Oxford.

Received and accepted: august 21st 2017.

**Summary.** The publication of *Unanticipated outcomes*, the personal story of Jerome P. Kassirer, former editor-in-chief of the *New England Journal of Medicine*, gives the opportunity to consider the ethical principles of biomedical and scientific publishing. Conflict of interests, reporting, and fraud affect the credibility of medical communication, which rests on the robustness and transparency of its processes. Not all is yet lost, but we must be guided by strong moral principles and to a consistent framework of values.

About a decade ago two of us decided to estimate the value added by the logo of the *New England Journal of Medicine* (*NEJM*) to a 10-page reprinted report of a randomised controlled trial (RCT). We followed a simple procedure. One of us wrote to the *NEJM* circulation department requesting an itemised estimate for 5000 reprints of the latest RCT. This had to be published in the *NEJM* and have a paper length of 10 pages. Next, we asked our local printer for an estimate to print 5000 copies of the same length and material quality as the *NEJM* reprints, with covers and text of the same length and complexity provided by us. We deducted postage and packing expenses when we compared the two estimates we had obtained.

The result was that the *NEJM* reprints were twenty times more expensive. As the printed content was the same, the difference to the buyer could only be due to administration costs that our local printer did not incur and the quality certification offered by the *NEJM* “brand”. The scientific quality seal could not be offered by the printer, but that offered by the *NEJM* would have included selection of probably the most attractive RCTs on offer at the time, the value added by the editorial process and the dissemination of the work by countless outlets worldwide. Even allowing for the value added by a “good” RCT, as certified implicitly by publication on the *NEJM*, the *NEJM* logo added a ten to fifteen-fold value to the product.

As quality is in the eye of the beholder, a big reprint order with a cost way outside the means of any researcher I know, gives a very rough estimate of the value of the *NEJM* logo to anyone wanting such a lot of paper. And they must want it badly to pay such inflated premiums.

*Unanticipated outcomes* is the personal story of Jerome (Jerry) Kassirer<sup>1</sup>, a nephrologist and academic who for eight crucial years was top dog at the *NEJM*. Kassirer described himself as the guardian of a na-

**Riassunto** La pubblicazione di *Unanticipated outcomes*, la storia personale di Jerome P. Kassirer, ex direttore del *New England Journal of Medicine*, offre l'opportunità di considerare i principi etici dell'editoria biomedica e scientifica. Il conflitto di interessi, le dichiarazioni e la frode influenzano la credibilità della comunicazione medica, che poggia sulla robustezza e sulla trasparenza dei suoi processi. Non tutto è ancora perduto, ma dobbiamo essere guidati da forti principi morali e da un quadro coerente di valori.

tional treasure and fought an apparently ultimately unsuccessful battle with the journal owners (the Massachusetts Medical Society or MMS) to preserve the ethics and independence of his ward. Kassirer was appointed in the summer of 1991 and was fired 8 years later. By this time he had successfully scuppered plans by the MMS to debase the name of the *NEJM* by launching specialist journals (like *NEJM Oncology*) with papers rejected by the *NEJM*, turn the *NEJM* into a publishing group (which eventually came about), move his editorial offices into the “corporate offices” of the MMS and antagonise a number of very powerful bodies such as the American Medical and the National Rifles Associations.

It is interesting and a mark of Kassirer's mental focus on his job that at the time he did not realise that some of the AMA officials were also MMS officers.

Most of all, Kassirer managed to keep clear the distinction between medical ethics and business ethics, making it quite clear that his *NEJM* was written for physicians (a claim modestly confined to New England and possibly American physicians) and was not a marketplace. The terms of Kassirer's firing are vile, for example the MMS insisted on Kassirer not using the term “firing” and tried to stop even Kassirer's family speaking to the media.

As you would expect from a former *NEJM* editor in chief, the book is well written and highly readable, but is also deeply depressing as it charts Kassirer's increasing disagreements with the MMS, as the ending that researchers of my generation well know looms in sight. It is also the story of a human being that implicitly regards his tenure at the *NEJM* as the pinnacle of his professional life. My depression lifted at the very end of my read, when Kassirer clearly explains why the current publishing ethics are failing.

In the last few years we have seen a steady accumulation of evidence from a variety of sources, rang-

“ We still have a little time before medicine, publishing, science and those who work in them are swallowed up by the marketplace and we must all do what he has done. ”

ing from litigation to public campaigns, to freedom of information requests, that the reports of clinical trials published in journals' condensed and compressed form are likely to be (in the rosier cases) datasets which could be subject to explanations alternative to those drawn by the authors. That is, if the data reported in the journals were in sufficient detail to allow alternative explanations to be drawn. Often they are not and my rosy scenario does not take into account the evidence of selection and distortion of methods and results of experiments on humans and our increasingly feeble efforts to purify medicine from fraud<sup>2-25</sup>.

In a situation where publication in famous journals is worth so much extra and our methods for detecting fraud, distortions, poor quality and unnecessary (in one word unethical) research are failing, the value of a journal rests on its credibility. This in turn rests on the ethics and reputation of its editors and the robustness and transparency of its processes. The current editor of the *NEJM* has acquiesced or instigated a lurch towards industry, the only body that can afford the eye-watering reprint charges (and profit from them). The *NEJM* is estimated to have made around \$ 700,000<sup>26</sup> from the reprint business from the VIGOR study of Vioxx, a careful piece of marketing which has still not been retracted.

By this stage my few readers will have recognised all the practices obstructed by Kassirer as currently commonplace in one or the other of the big biomedical journals. Which brings me to the conclusion: by making a stand and paying for his principles with his job, Kassirer is showing us that not all is yet lost. We still have a little time before medicine, publishing, science and those who work in them are swallowed up by the marketplace and we must all do what he has done. Stick to principles.

If we do not, the merchants and money changers will have taken over the Temple for good.

*Conflicts of interest:* no potential conflicts of interest relevant to this article should be disclosed.

## Reference

- Kassirer JP. Unanticipated outcomes: a medical memoir. Canton, MA: Sherman Printing Company, 2017.
- Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. *BMJ Open* 2013; 3: e002496.
- Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials. *JAMA* 2004; 291: 2457-65.
- Chan A-W, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014; 383: 257-66.
- Dunn AG, Arachi D, Hudgins J, et al. Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza. An analysis of systematic reviews. *Ann Intern Med* 2014; 161: 513-8.
- Dwan K, Altman DG, Arnaiz JA, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS ONE* 2008; 3: e3081.
- Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev* 2009; 1: MR000006.
- Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326: 1167-70.
- Lundh A, Sismondo S, Lexchin J, Busuioic OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2012; 12: MR000033.
- McGauran N, Wieseler B, Kreis J, Schüler Y-B, Kölsch H, Kaiser T. Reporting bias in medical research: a narrative review. *Trials* 2010; 11: 37.
- Yank V, Rennie D, Bero LA. Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study. *BMJ* 2007; 335: 1202.
- Coyne DW. The health-related quality of life was not improved by targeting higher hemoglobin in the Normal Hematocrit Trial. *Kidney Int* 2012; 82: 235-41.
- Eyding D, Lelgemann M, Grouven U, 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.
- Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med* 2013; 158: 890-902.
- Köhler M, Haag S, Biester K, et al. Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports. *BMJ* 2015; 350: h796.
- Hughes S, Cohen D, Jaggi R. Differences in reporting serious adverse events in industry sponsored clinical trial registries and journal articles on antidepressant and antipsychotic drugs: a cross-sectional study. *BMJ Open* 2014; 4: e005535.
- Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012; 1: CD008965.
- Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015; 351: h4320.
- Maund E, Tendal B, Hróbjartsson A, et al. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. *BMJ* 2014; 348: g3510.
- Rodgers MA, Brown JVE, Heirs MK, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. *BMJ* 2013; 346: f3981.
- Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *BMJ* 2014; 349: g6501.

22. 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.
23. Vedula SS, Li T, Dickersin K. Differences in reporting of analyses in internal company documents versus published trial reports: comparisons in industry-sponsored trials in off-label uses of gabapentin. *PLoS Medicine* 2013; 10: e1001378.
24. Wieseler B, Kerekes MF, Vervoelgyi V, McGauran N, Kaiser T. Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. *BMJ* 2012; 344: d8141.
25. Wieseler B, Wolfram N, McGauran N, et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. *PLoS Med* 2013; 10: e1001526.
26. Wilson M. The New England Journal of Medicine: commercial conflict of interest and revisiting the Vioxx scandal. *Indian J Med Ethics* 2016; 1NS: 167-71.

---

Corresponding author:  
Dr Tom Jefferson  
Senior Associate Tutor  
University of Oxford  
Oxford OX2 6GG



**www.recentiprogressi.it**

Indicizzata su Medline e Scopus.  
Ricerca su PubMed.  
Accessibile online dagli operatori  
delle aziende sanitarie e ospedaliere  
di diverse Regioni italiane.  
Strumento di consultazione del personale  
di gran parte degli IRCCS del nostro Paese.

**Ma anche utile e indipendente.**

Per di più, sul sito della rivista trovi

- **videointerviste** collegate con i contenuti pubblicati dalla rivista
- **infografiche** di approfondimento.

**Puntuale,  
credibile, italiana.**