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Dear Fiona

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NOT FOR PUBLICATION

You wrote in your email of 2 December that you took seriously the concerns that I raised at our meeting that day about two papers published in the BMJ, and that you would discuss with your colleagues what the journal should do in the light of those concerns.

Subsequently, however, you have not indicated that you had any plans to rectify the serious problems that have been caused by the BMJ publishing the misleading claims in those articles (despite being prompted to do so). It is also disappointing that you did not take the opportunity to retract those claims publicly when given the opportunity to do so recently (and, again, despite being prompted specifically to do so).

I am, therefore, writing to request that the BMJ formally retracts the articles by Abramson et al (BMJ 2013; 347: f6123) and by Malhotra (BMJ 2013; 347: f6340) because of the serious misrepresentation of the evidence that they cite in support of their claims. As I explained when we met, there are a number of problems with these papers (some of which have also been drawn to your attention in the 27 November 2013 letter from Huffman et al), but my particular concern is with the claims that are made in them about the magnitude of the risk of adverse effects caused by statin therapy.

For example, in Abramson et al, it is stated that *"A retrospective cohort study found that 18% of statin treated patients had discontinued therapy (at least temporarily) because of statin-related adverse events"*, and it is then asserted that *"Statin therapy ... has about an 18% risk of causing side effects that range from minor and reversible to serious and irreversible"*. Similarly, in Malhotra's paper it is stated that: *"A recent 'real world' study of 150,000 patients who were taking statins showed 'unacceptable' side effects – including myalgia, gastrointestinal upset, sleep and memory disturbance, and erectile dysfunction – in 20% of participants, resulting in discontinuation of the drug"*. Subsequently, he has been quoted as saying that *"... up to 20% of people suffer disabling side-effects that result in discontinuation of the drug"* (Guardian 22 March 2014).

The paper cited in support of these claims was by Zhang et al (Ann Intern Med 2013; 158: 526-34). As I pointed out to you when we met, the evidence in that paper does not support the claims of Abramson and Malhotra that statins cause side-effects in 18-20% of patients,

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and nor is that the conclusion of its authors. Instead, this retrospective cohort study involved analyses of events that had been attributed to statin therapy, and one of its aims was to determine whether misattribution of symptoms was likely to be resulting in inappropriate or unnecessary discontinuation of statins. Based on the observation that over 90% of patients who discontinued a statin and were then re-challenged were taking a statin 12 months later, the authors concluded that *“many of the statin-related events may have other causes...”*. In any case, since it is not known what proportion of these events would have occurred in people not taking statins, it is wrong to conclude based on this study (as Abramson and Malhotra do) that it shows statins cause side-effects in 18-20% of patients. (As you should now be aware, carefully conducted analyses of the relevant observational studies and randomised trials have shown that there is nothing like a 20% absolute excess risk of adverse events caused by statin therapy; instead, they find only small excesses of myopathy – not to be confused with myalgia, for which there is little good evidence of any causal association – and of diabetes.)

My specific concern is that the misleading claim that 18-20% of patients who receive statins will have *“side effects that range from minor and reversible to serious and irreversible”* or will *“suffer disabling side-effects”* seems very likely to lead to people at elevated risk of heart attacks and strokes stopping their statin therapy or not starting it in the first place. As a consequence, it is not unreasonable to conclude that such misinformation may well result in unnecessary heart attacks, strokes and vascular deaths. (I do understand that your concern relates to people at the lower end of the risk spectrum, but – even for them – such misinformation prevents them from making an informed choice, although the impact is likely to be less catastrophic.) Given the egregious nature of these errors, it is surprising that they were not picked up during the peer-review of either of the papers. In order that it might be possible to understand better how they might have slipped through without correction, please could you provide the reviewers’ and editors’ comments on the two papers?

You clearly do not like my analogy with the MMR vaccine and autism story. However, it does not seem that different; in both cases, seriously misleading claims of adverse effects of treatment were made that were not supported by the evidence put forward in their support, and the published peer-reviewed claims were further exacerbated by claims made in the media. With respect to the impact on unnecessary death and disability, it seems quite probable that the adverse effect of patients at elevated risk not taking statins is likely to be far greater than the effect of reduced take up of MMR vaccine (which, of course, is not to diminish the adverse impact of such loss of herd immunity).

I know that you take seriously such issues (as was illustrated by the coverage that the BMJ gave to the MMR vaccine story), so I would welcome your consideration of my request that these papers be withdrawn for the sake of public health. If you think that it would be better to have this request considered independently by the Committee on Publication Ethics rather than by the journal then please do let me know.

Yours sincerely



Rory Collins

P.S. Conflicts of interest: There have been a number of comments in the BMJ and elsewhere about potential conflicts of interest in this area, so it may be helpful to provide you with some background. CTSU’s coordination of the Cholesterol Treatment Trialists’

Collaboration (CTTC) has been funded by the Medical Research Council and British Heart Foundation, without any commercial funding. With regard to the individual trials contributing to the CTTC, most (if not all) have received support from the statin manufacturers, although not exclusively (for example, CTSU's MRC/BHF Heart Protection Study was funded by the MRC and BHF, as well as by Merck and the vitamin manufacturer Roche). More relevantly, however, many of these trials were conducted independently of their funders (for example, CTSU's trials were designed, run, analysed, interpreted and reported independently, and the unblinded data have not been shared with the companies). It is, therefore, not appropriate for the BMJ to publish that *"the large discrepancies between the frequency of adverse events reported in commercially funded randomised controlled trials included in CTT meta-analyses and non-commercially funded studies show that determination of harms cannot be left to industry alone"*.

As we are all aware, a range of potential conflicts of interest exist and it is important that there is transparency (as, for example, with the BMJ's advertising and sponsorship revenue from vaccine manufacturers which it inadvertently omitted to report when commenting on the MMR vaccine and autism story). With respect to CTSU, we have had a policy for more than 20 years of not accepting honoraria, consultancy or other payments directly or indirectly from industry, except for research grants and reimbursement of travel and accommodation to take part in scientific meetings (see attached). In the case of Wakefield, it is clear that one of the major issues was that the nature and the extent of his conflicts of interest (including the amounts paid for litigation-related work) were not made apparent when the paper was submitted. Please could you let me have details of all conflicts of interest that have been declared by the authors of the Abramson and Malhotra papers (including the size of all payments that they have received for any statin-related work)?