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31 March 2014

Dr Fiona Godlee
Editor, BMJ
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Dear Fiona

NOT FOR PUBLICATION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,

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)?

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14 April 2014

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Dear Fiona

NOT FOR PUBLICATION

Thank you for responding so rapidly to my letter of 31 March, but unfortunately the key points that I raised have not been addressed properly either by the letters from Abramson et al and Malhotra or by your response of 1 April.

I can assure you that this issue is not at all personal. As indicated previously, it seems highly likely that the misleading claims that have been reported by the BMJ about side-effect rates with statins will lead to large numbers of unnecessary heart attacks, strokes and premature deaths because patients at elevated risk will be dissuaded from taking statins. My concern is with the BMJ's failure to correct promptly and prominently such a serious mistake when it has major public health implications.

As I explained to you when we met, the evidence cited by Abramson et al and Malhotra does not support their claims that statins cause side-effects in 18-20% of patients. For the sake of clarity, a "statin-related adverse event" (which is what was studied in the paper by Zhang et al that is being cited) is not necessarily caused by, or a side-effect of, a statin. Consequently, it is a serious misrepresentation of the evidence for Abramson et al and Malhotra to state that it is. As was the case with the claims of a link between the MMR vaccine and autism, the most serious problem with these papers is the magnitude of the effect for which the claim is made that a causal link has been demonstrated – and the BMJ has now compounded the problem by reiterating this misleading claim in the recent letters by Abramson et al and Malhotra, despite the error having been pointed out explicitly.

In section 12 (*"Ensuring the integrity of the academic record"*) of the COPE guidelines for Journal Editors, it states: *"12.1. Errors, inaccurate or misleading statements must be corrected promptly and with due prominence.*" When I met with you on 2 December, I explained my concerns about these two papers, and very specifically highlighted the problem with their claims about the magnitude of the rate of side-effects with statins. But, although you wrote in your email of 2 December that you took seriously the concerns that I had raised and would discuss with your colleagues what the BMJ should do, the BMJ has done nothing to correct the record. Indeed, as noted above, when this issue was raised again explicitly in a letter to the journal, Abramson et al were allowed to reiterate this unjustifiable claim. So, instead of correcting a seriously misleading statement when it is pointed out both verbally in a meeting set up to discuss these concerns and in writing, the BMJ has instead repeated it.

It would seem that this situation is explicitly covered by the COPE guidelines on retractions which state that *"Journal editors should consider retracting a publication if: they have clear evidence that the findings are unreliable, either as a result of misconduct (e.g. data fabrication) or honest error (e.g. miscalculation or experimental error)".* As indicated above, the finding by Abramson et al and by Malhotra of a side-effect rate of 18-20% is clearly unreliable (and this is reinforced by meta-analyses of relevant observational studies and randomised trials which refute those claims). Moreover, the adverse public health impact of this misrepresentation of the evidence is likely to be substantial (and, as I've indicated previously, far greater than that of the MMR vaccine and autism claims). Given that this is the case, please would you explain why the BMJ is still refusing to correct these misleading statements prominently and to retract these papers in accordance with the COPE guidelines?

When I first wrote to you about the problems with these two papers, you indicated that their quality had been assured by the BMJ's peer-review process. Given your public commitment to transparency, I had anticipated that you would want to demonstrate that the BMJ's peer review process was sufficiently rigorous and unbiased (which seems not to have been the case given the egregious nature of these errors). Again, this would appear to be covered by the COPE guidelines (for example, sections 7 and 8 on peer review). The identities of the reviewers is not relevant, but I again ask that you make available their anonymised comments, as well as those of the editors, for both papers so that it might be possible to understand how these errors of judgement could have occurred.

My previous letter was rather long and, as a consequence, you may well have missed the request in its postscript (since you have not responded to it). Please would you let me have the details of all conflicts of interest for Abramson et al and Malhotra, including the amounts of any payments that they have received for any statin-related work? This is information that should quite properly be in the public domain. In a spirit of reciprocity, I have attached the details of all grants from industry to CTSU for our research covering the past 20 years and more, along with CTSU's policy on honoraria and other payments from industry (which involves us not taking such payments, directly or indirectly, personally or to the institution, except for reimbursement of travel and accommodation to take part in relevant scientific meetings).

I do hope that it will be possible to move forward constructively with the BMJ to have these papers and their misleading claims withdrawn in the interests of public health. If you think that it might be helpful for us to speak about these points or any other issues then I would, of course, be delighted to do so either by phone or face-to-face in Oxford or London. In which case, please do let me know when would be convenient.

Yours sincerely

Rory Collins

Enclosed: Grants and CTSU policy

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25 April 2014

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Dear Fiona

Thank you for your email of 23 April.

I first drew this issue to your attention at the end of October 2013, and again on a number of subsequent occasions, but only 6 months later have you finally accepted that claims made by Abramson et al and by Malhotra in the BMJ misrepresented the scientific evidence. By contrast, you are requiring me to respond to your email within 2 days. I am doing so, but chiefly to ask that you reflect more carefully on the content of my previous letters before the BMJ compounds its error further.

Although the BMJ should properly have corrected such serious misrepresentations of the evidence promptly (in accordance with the COPE guidelines, and indeed all appropriate scientific and medical conventions), clearly that cannot now be achieved. However, it is still possible to do so clearly and prominently. Instead, what you are proposing to do is not at all adequate to redress the likely damage to public health that has been caused by the BMJ publishing these misleading claims and not promptly retracting them (but instead repeating them) when advised to do so.

In particular, I would ask that you consider more carefully my previous letters:

- *Continued misrepresentation:* Both Abramson et al and Malhotra do not confine their comments to (as you put it in your email and proposed "correction") rates of "statin-related adverse events", but instead claim that statins cause side-effects in 18-20% of patients. As indicated in my previous letters, a "statin-related adverse event" (as studied by Zhang et al) is not necessarily caused by, or a side-effect of, a statin. Moreover, both observational studies and randomised trials demonstrate that the alleged size of such effects is not scientifically sustainable. In any correction of the scientific record, these distinctions should be made absolutely clear, rather than attempting to excuse these misrepresentations and further misinform readers. (The parallels with the MMR vaccine story are being increased by this editorial reluctance to accept that a serious error has been made and to correct it.)

- *Prominent correction:* Although it is now too late for the BMJ to act promptly, it is still possible to comply with the COPE guidelines to correct such errors with *"due prominence*." Instead, not only are you proposing not to correct the record clearly but also seem to be proposing to do so without the level of prominence to which the BMJ gave the original misleading claims. For example, you wrote an editorial that drew special attention to the paper by Abramson et al. Consequently, not only should any correction be an accurate one, but it should be given equal prominence; for example as an editorial comment. I should be happy to work with you to ensure that what the BMJ says represents a clear and prominent correction of these misleading claims.

- *Retraction of these reports*: Given the seriousness of the misrepresentation of the evidence and the public health significance, it would be appropriate for the BMJ to retract these papers formally (again in accordance with the COPE guidelines). By doing so, you would demonstrate not only the seriousness of the error, but also the BMJ's commitment to correcting the scientific record in such circumstances. (Accepting that one has made a mistake is a sign of strength not weakness.)

- *Conflicts of interest:* Both in your editorial comment on the paper by Abramson et al and in the paper itself, it is implied that conflicts of interest have resulted in trials conducted by academic researchers producing misleading information. It is not unreasonable, therefore, to request that the BMJ makes publicly known the extent of the potential conflicts of interest of the authors who are making such allegations. As is the case for the misleading claims about the size of the risk of side-effects with statins, the size of such personal financial conflicts of interest is relevant. (You will, I am sure, recall that the size of the payments made to Wakefield for legal work in litigation related to the MMR vaccine was considered highly relevant.)

- *Proper peer review:* Thank you for agreeing to ask the two peer reviewers of the paper by Abramson et al for permission to make their comments public. However, it was not clear if you planned to do likewise with the peer reviewers of Malhotra's article. It may be that I've misunderstood your email, but if not then please could you also arrange for those reviewers' comments to be made public. Opening up the BMJ's review process in this way, may help to avoid such serious errors from slipping through in the future.

Please do not make a bad situation worse by compounding the BMJ's original error in publishing and promoting these papers: this should not involve point scoring or sophistry, but instead should be about correcting the scientific record in order not to mislead the medical profession further and adversely affect the public's health.

Again, I repeat my offer to meet with you to discuss what the BMJ should now do to help undo the harm that has been caused.

Yours sincerely

Rory Collins