Note on the reasons why the BMJ papers by Abramson et al and by Malhotra, along with their subsequent correspondence, should be retracted

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As explained in each of my four previous letters (dated 31 March, 14 April, 25 April and 28 April 2014: attached) to the Editor of the BMJ following the meeting that I arranged with her in December 2013 to discuss this issue, the problem with these papers is straightforward: a "statin-related adverse event" – as was studied by Zhang et al in the report that is cited – is not necessarily caused by, or a side-effect of, a statin. Hence, Abramson et al and Malhotra seriously misrepresent the evidence from Zhang et al by repeatedly claiming that that study showed that the rate of side-effects due to statin therapy is about 20%.

Such serious misrepresentations of the evidence seem likely to lead to people who are at elevated risk of heart attacks and strokes stopping their statin therapy or not starting it in the first place. As a consequence, this may well result in unnecessary heart attacks, strokes and vascular deaths. With regard to the issue of offering statins to people who are at the lower end of the risk spectrum, such misinformation about side-effect rates would prevent them from making a properly informed choice, although the impact is likely to be less catastrophic. (It is, however, important not to allow the argument about recommendations to lower the level of risk at which statins are offered to be confused with this issue of misrepresentation.)

For these reasons, although the correction that the BMJ has finally agreed to publish is a step forward, that should have been done much more promptly after the misleading nature of these claims had been drawn to the journal's attention (in accordance with the guidelines of the Committee on Publication Ethics [COPE]) – rather than refusing to do so for 6 months (see attached emails) – and both papers now need to be prominently retracted in order to avoid repeated reference to these misleading claims and to mitigate the damage caused.

Serious misrepresentation of evidence about rate of side-effects caused by statins

In the paper by Abramson et al (BMJ October 2013), the authors state that statin therapy *"has about an 18% risk of causing side effects that range from minor and reversible to serious and irreversible"*. Also, in a text box, they state that "*The side-effects of statins … occur in about 20% of people treated with statins"*. Zhang et al is the only reference that is given as the basis of this claim about the magnitude of the rate of side-effects with statins.

Similarly, Malhotra (BMJ October 2013) states that: *"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".* Zhang et al is the only reference given as the basis of this claim about the magnitude of the harm. [As well as misrepresenting the rate of side-effects, it should be noted that this list of alleged side-effects also misrepresents Zhang et al since not all of them were reported in it.]

Deliberate repeated misrepresentation of the evidence about the rate of side-effects

When the basis of these claims of the rate of side-effects was challenged in a letter to the BMJ from Dr Amrit Takhar in November 2013 and by me in March 2014, the BMJ allowed both Abramson et al and Malhotra to repeat their misrepresentations of the evidence:

Abramson et al (BMJ November 2013): *"We …disagree with the opinion that we have 'overstated the case against statins' … the incidence of side effects may have been under-reported…". "…the incidence of statin-related side effects reported by Zhang et al was, in fact, 'approximately one-fifth' …. the finding that many of the patients who experienced statin-related side effects could tolerate statin therapy on rechallenge does not negate the fact they experienced a drug-related side effect".* [Given the authors' experience as experts in litigation related to statins, they presumably chose to use "side effect" with care.]

Abramson also wrote an article for the New York Times in November 2013 referencing his BMJ article, and stating that *"18 percent or more of this group would experience side effects, including muscle pain or weakness, decreased cognitive function, increased risk of diabetes (especially for women), cataracts or sexual dysfunction".* He continued to repeat this serious misrepresentation of the evidence from the paper by Zhang et al in the media (for example, in an interview published in the Sunday Express in March 2014).

Malhotra (BMJ March 2014): *"The Zhang paper reported that almost 1 in 5 (17.4%) or 18,778 out of 107,835 patients treated with a statin … had a 'statin-related adverse event documented'. The most commonly documented side effect was myalgia or myopathy ….." "… of 11,124 patients who at least temporarily discontinued their medication because of side-effects...There is a clear discrepancy between side effects reported in clinical trials and real world experience".* Dr Malhotra was also quoted in the Guardian (March 2014) saying *"up to 20% of people suffer disabling side-effects that result in discontinuation of the drug"*.

Given that the nature and seriousness of this misrepresentation of the evidence had been clearly explained to these authors, their refusal to withdraw these claims and, indeed, their decision to repeat them, would seem to indicate a deliberate intent to mislead the medical profession and the public despite the potential for harm to patients.

Summary of the paper by Zhang et al (Ann Intern Med 2013)

The evidence in the paper by Zhang et al does not support these claims 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 "statin-related events", which were defined as *"clinical events or symptoms believed to have been caused by statins"*. One of the stated aims of that study 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 had discontinued a statin and were re-challenged were taking a statin 12 months later, the authors concluded that *"many of the statin-related events may have other causes…"*. Moreover, since the proportions of people not taking statins who would have reported such events cannot be determined, it is wrong to conclude that this study can show that statins cause side-effects in 18-20% of patients.

The most common category of statin-related events in Zhang et al was musculoskeletal pain. Other observational studies (such as those reported by Buettner et al and Mansi et al) have reported high rates of musculoskeletal pain among both statin users and non-users, so those investigators have concluded that pain occurring during statin use may be unrelated to statin use. In addition, they have noted that residual confounding and ascertainment bias (as well as the impact of advice given to patients that statins can cause muscle problems due to the risk, albeit rare, of myopathy) prevent such observational studies from determining a causal association between statins and myalgia (or, indeed, other common outcomes).

In correspondence with the BMJ on this issue, it is clear that there has been confusion about other aspects of the study by Zhang et al and what can be concluded from it. For example:

- As well as not dealing with the misleading claims by Abramson et al and Malhotra that side-effects are caused by statins in 18-20% of patients, the BMJ's proposed corrections in the Editor's email of 23 April misrepresent the statement in the paper by Zhang et al that *"as many as 87% of statin discontinuations among patients with documented statin-related events could have been due to these events"*, which refers to the discontinuations being potentially due to these events, and not to whether these events are necessarily being caused by the statin (which is what is implied by the proposed correction).

- During discussions with the Editor on 8 May 2014, a reference in Zhang et al to "*the 5% to 10% rate [of reported statin-related events] usually described in randomized, placebo-controlled, trials"*, which relates to the findings of a meta-analysis of the randomised trials (Kashani et al; Circulation 2006), was interpreted as being the side-effect rate with statins in the randomised trials. Instead, this was the rate of attributed events among the patients allocated active therapy in the trials, but with similar rates having been reported among the patients who had been allocated placebo in these blinded trials (as shown below). Again, this illustrates the magnitude of the bias inherent in observational studies in which not only are the patients who take statin and those who do not different from each other (which cannot be reliably taken into account by adjusted analyses), but also knowledge that a patient has received a particular treatment impacts materially on attribution.

[Note: My comments about the misrepresentation of the evidence by Abramson et al and by Malhotra should not be taken as a criticism of the paper by Zhang et al, which is a clear and nuanced report of what appears to have been a carefully conducted study.]

Evidence against the magnitude of the side-effect rate claimed in the BMJ articles

In the November 2013 letter from Abramson et al, it is noted that rates of adverse events based on spontaneous reporting – which is all that is typically available for observational studies – are likely to be less reliable than rates based on events determined prospectively by structured interview. By contrast with the observational studies, the randomised placebo-controlled trials of statins have typically recorded such events systematically (for example, the fact of stopping study treatment and reasons for doing so; muscle pain and weakness [in order not to miss myopathy]; serious adverse events [SAE] and, in some trials, all adverse events [AE]). Consequently, the trials do provide robust assessments of the effects of statins on adverse events that are not biased by systematic differences between the patients who are given statins and those who are not in their baseline risks of adverse events (due to randomisation) or in the recording of events that occur in them (due to blinding).

As is stated in the published protocol for the Cholesterol Treatment Trialists' [CTT] meta-analysis (Am J Cardiol 1994), which was finalised before any of the statin outcome trials had reported, the aim was to detect any moderate beneficial or adverse effects on cause-specific mortality, on major vascular events and on site-specific cancer. (The information sought for each randomised patient is listed in Table III of the protocol paper: Abramson et al should have checked it before alleging that the CTT collaboration was withholding analyses of data on all SAEs.) Detailed analyses of the effects of allocation to statin on all of these outcomes have been reported in a series of CTT papers, including the most recent paper looking at people at different levels of baseline risk (Lancet 2012), demonstrating beneficial reductions in vascular morbidity and mortality for a wide range of patients (including those at lower risk than those in whom statins are currently recommended) without evidence of adverse effects on any particular non-vascular cause of death or on any site-specific cause of cancer.

For the reliable detection of larger effects of statins on common outcomes (for example, reasons for stopping treatment, myalgia) – such as those claimed by Abramson et al and Malhotra – it is not necessary to have data on every outcome from all of the trials (which is why, for example, some trials only recorded serious AEs and not all AEs). Instead, meta-analyses of the available data would suffice to provide sufficiently reliable evidence for such effects: for example, Kashani et al (Circulation 2006) showed that there were similar rates of discontinuations due to any adverse event (5.6% statin versus 6.1% placebo; p=0.80) and of myalgias (15.4% statin versus 18.7% placebo; p=0.37) among the patients allocated active therapy and those allocated placebo. A more recent meta-analysis by Finegold et al (Eur J Prev Cardiol 2014) of the published data confirms the findings of Kashani et al for muscle-related outcomes and extends the range of outcomes assessed to some extent (although more complete data on vascular outcomes, site-specific cancer and cause-specific mortality are provided by the CTT meta-analyses). In addition, particularly detailed assessments in

individual trials of specific outcomes (such as repeated measures of cognitive function in the PROSPER trial of 5 years of pravastatin) have been able to demonstrate that statins do not have adverse effects on such outcomes. Moreover, some of the randomised trials of statins have obtained extended follow-up beyond the 5-year trial treatment period: for example, the WOSCOPS trial in primary prevention linked the patients to their health records and have reported 15 year follow-up, with increasing benefit emerging beyond the treatment period and no evidence of adverse effects of statin therapy (NEJM 2007 & EHJ 2014).

These carefully conducted randomised trials and meta-analyses of trials (along with meta-analyses of relevant observational studies; for example, Macedo et al; BMC Medicine 2014) 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 (about 1 per 10,000 per annum) – not to be confused with myalgia (as both Abramson and Malhotra do in what they write), for which there is little good evidence of any causal association – and of diabetes (a 10% proportional increase detected by a meta-analysis of the randomised trials to test the hypothesis generated by the post hoc observation in the JUPITER trial of rosuvastatin).

There have been a number of assertions in the BMJ that potential conflicts of interest have biased the assessment of the evidence on side-effects in the randomised trials of statins. Coordination of the CTT collaboration has been funded by the Medical Research Council, British Heart Foundation, Cancer Research UK, EC Biomed Programme, Australian National Health and Medical Research Council, and National Heart Foundation (Australia), without commercial funding. With regard to the individual trials, most (if not all) received support from the statin manufacturers, although not exclusively. More relevantly, however, many of these trials were conducted independently of their funders (for example, CTSU's trials were designed, coordinated, analysed, interpreted and reported entirely independently by us). 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"*.

Centrality of the misleading claims about side-effect rates to these papers

In the most recent correction proposed by the BMJ for the article by Abramson et al (email dated 12 May), it is asserted by the authors in the final paragraph that the (long-overdue) withdrawal of their claim that statins cause side-effects in 18-20% of patients does not impact on *"the primary finding in our article – that CTT data fail to show reduction in overall risk of mortality by statin therapy for people with <20% risk of CVD over the next 10 years".* This is an entirely specious argument.

About half of the paper by Abramson et al relates to claims about harms caused by statins. As indicated at the end of the second paragraph, the authors *"argue that the evidence does not show that the benefits of statins in low risk patients outweigh the harms"*. This message is repeated on the second page when the authors state, based on the outcomes of all-cause mortality and all SAEs combined (see issues below), that *"the net-benefit harm equation has zero overall benefit… and ignores the clear evidence of harm that has been demonstrated"* [quoting Zhang et al]. Withdrawal of these exaggerated claims about the size of the harms of statin therapy changes this balance materially and invalidates the overall conclusions.

There are a number of other errors of fact or interpretation in the paper by Abramson et al that contribute to invalidating its conclusions (although the principal reason for retracting it is the deliberate and repeated misrepresentation of the magnitude of the harms of statins):

- ***All-cause mortality is not the best way to assess effects of treatment on survival:*** It is not entirely clear what Abramson et al mean when they say that all-cause mortality is the *"most encompassing"* endpoint. In any case, Abramson et al mis-calculated the result

for all-cause mortality in the low-risk groups by using Figure 3 in the CTT paper (despite the legend to that figure indicating why that should not be done) and, it seems, by over-looking the results that were reported for all-cause mortality in webfigure 8 of the paper. As a consequence the results in Table 1 of their paper are incorrect. Leaving that simple error aside, the outcome of all-cause mortality is not only insensitive to any reductions in vascular mortality with statins, but also to any increases in particular causes of death (and the lack of such adverse effects in the published CTT analyses is generally reassuring). Moreover, effects of treatment on cause-specific mortality are more readily generalizable to different circumstances (e.g. primary versus secondary populations) where proportions of deaths from different causes may differ. (The example of a trial of a vaccine may help to illustrate this point: it would not be very sensible to use all-cause mortality in assessing whether a vaccine prevented deaths from some particular infection or, indeed, might have off-target adverse effects on some other causes of death.)

- ***All SAEs combined is not a good way to assess efficacy or safety:*** Similarly, the assertion by Abramson et al that *"The best indication of the net effect of a treatment on overall health is the total number of serious adverse events"* sounds smart but, in reality, is not at all wise. By combining the effects of a treatment that potentially go in different directions, an outcome of "all SAEs combined" would not only be insensitive to benefits but, importantly, it would tend to obscure any adverse effects of treatment on specific outcomes (such as the small increase in diabetes detected by meta-analyses of the statin trials and the possible small increase in haemorrhagic stroke noted in the CTT paper: see webfigure 4). Again, the effects of a treatment on specific SAEs rather than on all SAEs are likely to be more readily generalised to different circumstances (as with the example in the CTT paper about the absolute effect on haemorrhagic strokes in Asian populations where the underlying rates are higher). There would seem to be a logical disconnect in Abramson et al's argument that the lack of a reduction in all SAEs combined (based on JUPITER, ASCOT and LIPID) means that there is no benefit, but that other evidence shows there is an *"18% risk of causing side effects that range from minor and reversible to serious and irreversible".* Would not their argument based on all SAEs equally mean that there is no serious harm associated with statin therapy; or does it just support the argument above that the approach of using all SAEs combined is not that wise?

- ***Misleading comparisons of myopathy and myalgia rates:*** Under the sub-title "Myopathy", Abramson et al state that *"The excess risk of myopathy associated with statins reported in the CTT meta-analysis is 0.5 per 1000 patients over five years – number need to harm (NNH) is 2000. However [based on an observational study]… increase in muscle pain is 100 times greater than that reported in clinical trials – 53/1000 patients, NNH=19".* It is a serious concern that Abramson et al decided to confuse readers deliberately (see their 20 December BMJ letter) by directly comparing rates of "myopathy" (based on the definition referenced in the CTT paper of muscle symptoms plus blood creatine kinase levels >10 x upper limit of normal) with rates of reports of musculoskeletal pain of any severity (which is what was recorded in the observational study cited). The randomised trials have reported rates of myopathy (as defined above) and of less severe muscle symptoms separately: for example, in the HPS trial, 33% of patients in both the active and placebo groups reported muscle pain or weakness at some time during the 5-year trial treatment period. (In that regard, the authors of the observational study stated *"It is important to note the prevalence of pain was high among both statin users and nonusers. Therefore, pain occurring during statin use may be unrelated to statin use…".*) Huffman et al commented on the misleading nature of this comparison between rates of myopathy and less severe muscle symptoms in their letter to the BMJ of 27 November and, as with their repeated refusal to accept that adverse events are not necessarily side-effects [see above], Abramson et al just assert in their 20 December response that myalgia is the same as myopathy, which is not correct (as is shown above) and is a further misrepresentation of the evidence on statin side-effects.

- ***Other claims of hazards are not reliable:*** On the second page of the article, there is a subsection entitled *"Others"* in the section entitled *"Known harms".* However, the adverse events that are listed are not known harms of statin therapy; consequently, this claim is also misleading. Indeed, the meta-analyses of both randomised trials and observational studies that are cited above provide compelling evidence against there being any causal association of statin therapy with these outcomes. (For example, in the meta-analysis of the observational studies including the hypothesis-generating study, the relative risk for cataract is 1.01 with a 95% confidence interval of 0.86-1.19; Macedo et al 2014.)

- ***Comments about minimising adverse effects in trials are ill-informed:*** By contrast with the assertion on the third page of this paper, exclusion from the trials of patients with co-morbidities that are relative contra-indications for using statin therapy in routine care would, by definition, yield results that are directly relevant to normal practice. Moreover, where it might be appropriate to consider such therapy in some of these groups in special circumstances, trials have been conducted (e.g. the SHARP trial in renal disease) and demonstrated both safety and benefit. With regard to the comment about the use of pre-randomisation run-in periods on active drug, the published safety report on the HPS trial showed that similar proportions of patients stopped their study treatment during the placebo and active drug pre-randomisation phases (BMC Clin Pharm 2009; 9:6). As discussed above at some length, the randomised trials typically sought and recorded all SAEs and reasons for stopping study treatment systematically, and some also sought and recorded all AEs or specific outcomes (including cognitive changes, by contrast with Abramson et al's assertion), while some even linked the participants to national health registries to supplement and extend follow-up, so the claim about under-ascertainment is unfounded. As for the claim of 10% drop out rates, most (if not all) of the statin trials had high rates of follow-up of all randomised patients, even when they stopped taking their study treatment (allowing unbiased intention-to-treat analyses). In lifting this text largely unchanged from the paper by Mansi et al (reference 23), Abramson et al failed to lift the related reference which might have alerted readers (and reviewers) to the fact that this last claim of high drop-out rates was based on trials of antipsychotic drugs (not statins)!

- ***Limitations of cost-effectiveness comments:*** It is unclear why a paper in the British Medical Journal published the prices of statin therapy in US$ and, moreover, why it used prices derived from the USA. By contrast with the quoted price of *"up to $1/day or more per person"*, the UK price of generic simvastatin or atorvastatin is about £2 per month. Again, specious arguments about the use of completely different and, most probably, far more expensive agents (such as PCSK9 inhibitors) are introduced for no good reason (other than, perhaps, to mislead readers further).

Reasons for recommending retraction of articles containing such misleading claims

In section 12 of the guidelines of the Committee on Publication Ethics (COPE) – which the BMJ helped to establish – it states that: *"Errors, inaccurate or misleading statements must be corrected promptly and with due prominence".* In addition, with respect to retractions, these guidelines 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, these claims of a side-effect rate of 18-20% with statin therapy are not supported by the evidence that is cited. Nor do meta-analyses of the relevant randomised trials and observational studies provide support for an excess rate of side-effects with statins of this magnitude. The adverse public health impact of these misleading claims may well be substantial (and, indeed, far greater than that of the MMR vaccine and autism claims which led to Wakefield being struck off) since they seem likely to lead to people at high risk of heart

attacks and strokes stopping their statin therapy or not starting it in the first place, resulting in many heart attacks, strokes and vascular deaths that would otherwise have been avoided.

Despite this clear misrepresentation of the evidence and its public health importance, the BMJ refused to correct the scientific record promptly and prominently. Indeed, even after the misleading nature of those claims had been pointed out explicitly to the BMJ, it still allowed Abramson et al and Malhotra to reiterate their misleading claims, compounding its original error in publishing these reports. The alleged rates of side-effects of about 20% are being repeated elsewhere, increasing the damage that has been caused by these BMJ papers.

Clearly it is now no longer possible for the BMJ to comply with the COPE requirements to correct these errors promptly (since they were published more than 6 months ago) and, in order to demonstrate its commitment to maintaining the integrity of the scientific record, it should now retract the original papers by Abramson et al and by Malhotra, along with the related correspondence in which they repeat their misrepresentation of the evidence. (Just publishing a correction does not suffice to demonstrate the public health significance of this serious error or to ensure that these misleading claims do not continue to be repeated.)

Potential conflicts of interest: The CTSU conducts, analyses and interprets its clinical trials (for which it serves as the regulatory sponsor) and other research independently of industry and other funders, with the datasets held by the CTSU rather than by the funders. In accordance with our long-term policy, honoraria, consultancies or other payments have not been received directly or indirectly from industry, either personally by me or by the University (except for reimbursement of travel and accommodation for taking part in relevant scientific meetings). I am attaching a list of all of the grants to Oxford University for any CTSU trials and all other commercially-funded research over the past 20 years.

It would also seem appropriate for the panel to be provided with similarly detailed information about all potential conflicts of interest of the authors of those papers. Dr Malhotra declared that he has no such conflicts at all, while Dr Abramson and colleagues have declared taking payments for lectures and serving as experts in litigation about statin therapy. It is not clear whether undeclared sales related to the book "Overdosed America" are relevant, although Dr Abramson's services as a speaker are advertised based on that book; for example, see: www.curtisbrown.co.uk/john-abramson/. (Based on Scopus, his other academic contribution is a total of 9 citations over the past 10 years, consisting entirely of commentaries and letters on other people's work.) However – as was the case with Andrew Wakefield in his claims about a link between the MMR vaccine and autism – the size of the income from litigation and any other work that could benefit from making misleading claims about the rate of side-effects due to a treatment is relevant in deciding whether to retract a paper in order that the scientific integrity of the academic record is maintained and the public's health is protected.

Attached:

Letters to BMJ dated 31 March, 14 April, 25 April and 28 April 2014
Emails to/from BMJ Editor starting in October 2013
List of CTSU grants