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BMJ panel considering retraction of papers
by Abramson et al and by Malhotra

Dear Chair and Panel Members

We are writing to draw your attention to serious and extensive errors in a letter sent by Dr Aseem Malhotra and others to NICE and the Secretary of State for Health, as well as to the media with a press release (see attached email from Dr Malhotra to a journalist.)

Although you have been tasked with considering errors in the papers that were published in the BMJ by Abramson et al and by Malhotra (along with their related BMJ Rapid Response correspondence in which they repeat their misleading claims), the nature of the errors in this letter to NICE and the way in which they have been widely disseminated are relevant to considering retraction of the papers.

In particular, it would seem that the failure to deal promptly and properly with the misleading claims in those two BMJ papers during the review process and subsequently (including, for example, in the Rapid Response letter to the BMJ from the Cochrane statin group) has emboldened Dr Malhotra to misrepresent the evidence further. Similarly, Dr Abramson recently reiterated (1 July BMJ: attached) his misleading comparison of the small excess of myopathy with statin therapy in the randomised trials versus non-randomised data for musculoskeletal pain of any severity, which was challenged during the peer review process and by the Cochrane statin group because the outcomes being compared are entirely different (an error repeated in the letter to NICE: see below).

The consequence is that confusion about the effects of statins has been increased, which may well lead to patients at elevated risk of heart attacks and strokes stopping statins or not starting them, thereby substantially increasing their risks of death and disability from such events.

There are two major types of scientific error in the evidence presented in this open letter to NICE:

1. **Errors of interpretation**: Much is made in that letter about differences in the rates of adverse events that were recorded in different statin trials. However, it is not scientifically appropriate – as has been done in the letter from Malhotra and colleagues to NICE – to make non-randomised comparisons between trials of the rates of events that are defined very differently in different trials (which also involved different types of patient with different underlying risks of adverse

events). For example, rates of adverse events that are given as the reasons for discontinuation should not be compared with rates of all adverse events or with rates of discontinuation for any reason (as has been incorrectly done in the letter to NICE: see below). Moreover, since the results quoted relate to the numbers of events that occur during a particular trial (and should more properly be referred to as "cumulative incidence" rather than "rates"), they will also be affected by differences in the duration of different trials.

By contrast, it would have been entirely appropriate to make direct comparisons of event rates between randomised groups within each trial since these are based on the unbiased blinded assessment of events defined in the same way for both the patients allocated active statin treatment and those allocated placebo treatment within any particular trial. The similarity of the rates in the statin versus placebo groups within each of these randomised, blinded and controlled comparisons reported in the letter provides robust unbiased evidence of a lack of adverse effects of statin therapy on each of these different adverse event measures.

2. **Misrepresentation of the evidence:** In comparing the rates in the placebo groups of these trials in section 2 of the letter to NICE, it is not made clear what is meant by "effects" (by contrast with "events" used earlier in the letter), but it seems to be – given the rates quoted for some of the trials – something along the lines of "adverse events that led to discontinuation of the active or placebo study treatment". It is claimed in the letter to NICE that these *"placebo adverse effect rates range from 2.7% to 80.4%, a thirty fold difference"*. As noted above such comparisons are not scientifically appropriate, but the statement is also incorrect.

   In particular, it is stated in the letter to NICE that "Total adverse effects" occurred in 80.4% of the placebo-allocated patients in the METEOR trial, whereas this is actually the rate of "Total adverse events" (see JAMA 2007; 297: 1344-53: relevant section highlighted in attached paper). It is misleading to compare the rate of "Total adverse events" in METEOR versus subsets of the adverse events in the other trials, such as those that led to discontinuation of study treatment (i.e. so called "effects"). Published results for the rates of the comparable outcome of "adverse events leading to discontinuation" in METEOR are 11% rosuvastatin vs 8% placebo, and those results are entirely compatible with those reported for similar outcomes in the other trials, given that the precise definitions used in those trials differed, and so too did the types of patient that were included and the duration of study treatment.

   Another major error in the letter relates to the misrepresentation of the results from the WOSCOPS trial. At the top of the second page, it is stated that *"the cumulative incidence of myalgia was 0.06% in the statin arm, and 0.06% in the placebo arm"*. However, in the paper referenced in support of that claim (see N Engl J Med 1995; 333: 1301-7: relevant section highlighted in attached paper), it is reported that "myalgia" was recorded in 20 of the 3302 patients allocated pravastatin and 19 of the 3299 patients allocated placebo: these numbers translate into percentages of 0.6% vs 0.6% (i.e. a 10-fold error in the letter sent to NICE and disseminated widely to the media).

   Moreover, in addition, it was reported in the same section of the WOSCOPS paper that another 97 statin versus 102 placebo patients reported other muscle aches, yielding an overall rate of 3.5% versus 3.7%. The METEOR trial classified adverse events using the MedDRA coding system, which includes all muscle aching in the definition of myalgia. Consequently, comparison of the rates of myalgia defined more similarly in METEOR of 12.1% and in WOSCOPS of 3.7% yields a

difference that is not 200-fold (as claimed in the letter to NICE), but is only about 3-fold (i.e. more than a 60-fold error in the letter sent to NICE).

This error was drawn to the attention of one of the signatories of the letter by us, and Dr Kendrick did then send an email to NICE (see attached) in which he wrote: *"It was stated that the cumulative incidence of myalgia in the WOSCOPS study was 0.06%. This was an error, as the cumulative incidence was 0.6%. This means that the difference in the rate of myalgia between the WOSCOPS and METEOR studies was 20 fold, not 200 fold."* However, despite it having been explicitly pointed out (see relevant extract from email to Dr Gerada: attached), he did not take into account the other muscle aching reported in WOSCOPS in correcting this comparison.

These errors invalidate one of the main points made in the letter to NICE, undermining conclusions that were widely disseminated but that have not been publicly corrected.

Relevance to the panel's remit

A debate about whether or not to lower the risk threshold at which statins can be offered by the NHS (as is being considered by NICE) is entirely appropriate. However, in making the case against such a change, it is not at all appropriate to misrepresent evidence in ways that mislead doctors, patients and the wider public.

As indicated above, the failure to deal promptly and properly with serious misrepresentations of the evidence on the safety and efficacy of statin therapy in the papers by Abramson et al and Malhotra would appear to be encouraging repetition and extension of those misleading claims. The reckless disregard for accuracy in the presentation of the evidence, as demonstrated by the errors in the attached letter to NICE which was widely disseminated (as well as by the BMJ papers, and related correspondence and public statements, by Drs Abramson and Malhotra), puts patient safety at risk and brings the medical profession into disrepute.

For these reasons, this misleading letter to NICE would seem relevant to your considerations.

Yours sincerely

Jane Armitage Colin Baigent Rory Collins

Attached

Email with press release sent by Dr Malhotra to The Times
Repetition of misleading claim about myopathy rates by Abramson (BMJ; 1 July 2014)
Open letter to NICE with annotations indicating errors in interpretation and fact
Emails to Dr Gerada and from Dr Kendrick regarding one of the errors in the letter to NICE
Folder containing reports for relevant studies with relevant sections highlighted