**Annotations showing errors in interpretation and fact in this letter by Thompson and colleagues (highlighted versions of the papers referred to in the annotations are available at [http://www.ctsu.ox.ac.uk/research/meta-trials/ctt/list-of-supporting-references])**

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cc. The Right Honourable Jeremy Hunt, MP
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Department of Health
Richmond House
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London, SW1A 2NS

10th June. 2014

## Concerns about the latest NICE draft guidance on statins

**Introduction:**

We are concerned about your draft guidance on CV risk for discussion and debate. We would ask for a delay until our concerns are addressed. Whilst we agree with much of the guidance, our concerns focus on six key areas: **medicalization of healthy individuals**, **true levels of adverse events, hidden data, industry bias, loss of professional confidence, and conflicts of interest**

The draft guidance recommends offering statin treatment for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD.

**1. Medicalisation of five million healthy individuals.**

Firstly, we believe that the benefits in a low risk population do not justify putting approximately five million more people on drugs that will then have to be taken lifelong.

The important questions for clinicians and for patients include: (1) does treatment of elevated cholesterol levels with statins in otherwise healthy persons decrease mortality or prevent other serious outcomes? (2) What are the adverse effects associated with statin treatment in healthy persons? (3) Do the potential benefits outweigh the potential risks? Recent papers have **suggested that statin therapy should not be recommended for men with elevated cholesterol who are otherwise healthy.**[2]

Furthermore, Atorvastatin 20mg is also recommended as the first-line treatment. This appears counter intuitive, as Atorvastatin has never been demonstrated to reduce mortality for primary prevention any clinical study. (3b)

**2. Conflicting levels of adverse events**

In emphasising the cost per Quality Adjusted Life Year (QALY), NICE is clearly making a major assumption that the key issue is mortality reduction, and that statins lead to very few adverse effects. We would question this very strongly.

The levels of adverse events reported in the statin trials contain worrying anomalies. For example, in the West of Scotland Coronary Prevention Study (WOSCOPS, the first primary prevention study done), the cumulative incidence of myalgia was 0.06% in the statin *arm, and 0.06% in the placebo arm*[3].[Error: Actually 0.6% vs 0.6% for "myalgia" as defined in WOSCOPS, or 3.5% vs 3.7% for "myalgia plus muscle aching" in WOSCOPS: see note]

*However, the METEOR study found an incidence of myalgia of 12.7% in the Rosuvastatin arm, and 12.1% in the placebo arm*[4]*. Whilst it can be understood that a different formulation of statin could cause a different rate of myalgia, it is difficult to see how the placebo could, in* one study, cause a rate of myalgia of 0.06%, and 12.1% in another. This is a two hundred fold difference in a trial lasting less than half as long. [Error: Actually 3-fold, not 200-fold, difference]

Furthermore, the rate of adverse effects in the statin and placebo arms of all the trials has been almost identical. Exact comparison between trials is not possible, due to lack of complete data, and various measures of adverse effects are used, in different ways. [Scientifically flawed argument: see note and cover email] However, here is a short selection of major statins studies.

AFCAPS/TEXCAPS: Total adverse effects losartan 13.6%: Placebo 13.8%

4S: Total adverse effect simvastatin 6%: Placebo 6%

CARDS: Total adverse effects atorvastatin 25%: Placebo 24% [Error: The correct values for the outcome of "effects" used in this letter are probably 8.5% vs 10.3%: see note]

HPS: Discontinuation rates simvastatin 4.5%: Placebo 5.1% [Error: These rates are of "effects", not discontinuations, but with a small numerical error: see note]

METEOR: Total adverse effects rosuvastatin 83.3%: Placebo 80.4% [Error: The correct values for "effects" are 11% vs 8%: see note]

LIPID: Total adverse effects 3.2% Pravastatin: Placebo 2.7%

JUPITER: Discontinuation rate of drug 25% Rosuvastatin 25% placebo. Serious Adverse events 15.2% Rosuvastatin 15.5% placebo [Error: The correct values for "effects", as defined elsewhere, are 1.6% vs 1.8%: see note]

WOSCOPS: Total adverse effects. Pravastatin 7.8%: Placebo 7.0% [Possible error: The values for "effects" appear to be 9.2% vs 9.1%: see note]

Curiously, the adverse effect rate of the statin, it is always very similar to that of placebo. However, placebo adverse effect rates range from 2.7% to 80.4%, a thirty fold difference. [Error: Range is only from about 2% to 14%; i.e. 7-fold, not 30-fold, difference: see note]

**3. Hidden data**

Without access to the raw data, it is difficult to understand how statin related adverse events, and placebo related adverse events can mirror each other so precisely, whilst the absolute

**Comment [A1]:** The rates of adverse events depend on what is being reported for each trial. So, for example, adverse events that are given as the reason for discontinuation (which are not necessarily causal "effects", as is indicated by the similar rates in the active versus placebo groups within each trial) should not be compared with rates of all adverse events or with all serious adverse events (as has been incorrectly done below in this letter). In addition, definitions used in different trials may differ in ways that complicate any comparisons between trials.

**Comment [A2]:** INCORRECT. The rates for the reported outcome of "myalgia" in WOSCOPS were actually 0.6% versus 0.6% (not 0.06% vs 0.06%; a 10-fold error). However, in addition, "muscle ache' ... [1]

**Comment [A3]:** Error: see note 3

**Comment [A4]:** INCORRECT: If a more similar definition of myalgia (including all cases of muscle aching) is used for b ... [2]

**Comment [A5]:** POINT OF CLARIFICATION: It is not made clear what is meant here by the word "effects" (b ... [3]

**Comment [A6]:** It is not appropriate (as has been done in this letter) to compare rates of events that are defined very ... [4]

**Comment [A7]:** These percentages are for "AEs leading to discontinuation" ... [5]

**Comment [A8]:** INCORRECT: Lovastatin was tested (not losartan, which is a blood-pressure lowering drug)

**Comment [A9]:** These percentages are for "AEs leading to discontinuation" (with some rounding): 5.7% vs 5.8% (see L ... [6]

**Comment [A10]:** By contrast with the events quoted for the two trials above, these appear to be the percentages ... [7]

**Comment [A11]:** These are not the overall discontinuation rates in HPS, but instead are rates for "Discontinuatio ... [8]

**Comment [A12]:** SERIOUSLY MISLEADING: The rates quoted for METEOR are the basis of the claim b ... [9]

**Comment [A13]:** These percentages are for "AEs attributed to study treatment" (see N Engl J Med 1998; 339: 1349 ... [10]

**Comment [A14]:** Neither of these rates is comparable to the rates given for the other trials. The discontinuation ra ... [11]

**Comment [A15]:** This outcome would appear to be "AEs leading to discontinuation", although the cor ... [12]

**Comment [A16]:** As discussed above, the similarity of rates in the statin versus placebo groups within each of thes ... [13]

**Comment [A17]:** INCORRECT: Not comparing like-with-like. When the placebo group rates for similar (alt ... [14]

rates can vary thirtyfold (almost three thousand per cent).[Error: Actually 7-fold, not 30-fold difference: see note] These data most certainly require analysis by a third party with appropriate expertise.

A further serious concern is that the data driving NICE guidance on statins comes almost entirely from pharmaceutical company funded studies. Furthermore, these data are not available for review by independent researchers, only those who work for the Oxford Cholesterol Treatment Trialists Collaboration (CTT).

The CTT has commercial agreements with pharmaceutical companies which apparently means that they cannot release data to any other researchers who request to see it. Which, in turn, means that the latest reviews of the data by NICE and also by the Cochrane group are totally reliant on the CTT 2012[1] meta-analysis analysis of this concealed data?

4. **Industry bias**

The overdependence on industry data raises concerns about possible biases. Extensive evidence shows that industry funded trials systematically produce more favourable outcomes than non- industry sponsored ones.[5,6]

Notably, only one major non-industry funded study on statins has been done. ALLHAT-LLP. The main findings were summarised: *'Although pravastatin has been shown in multiple large clinical trials to reduce CHD morbidity and mortality,* ***NO*** *benefit was demonstrated in ALLHAT-LLT, the largest clinical event trial of pravastatin published to date.*' (6b)

*True levels of adverse events*

We are also concerned that the rate of adverse effects in post-marketing studies is, in most cases, far higher than that found in the pre-marketing studies. In part this is due to the fact that the clinical trial populations studied in premarketing trials are highly selected. Furthermore, industry sponsored trials include pre-randomisation run-in periods where those who fail to tolerate statins are excluded. RCT patients may therefore not represent the population that will actually take the drugs in the real world. RCTs may thus grossly underestimate adverse effects such as myopathy or cognitive impairment,[7] and fail to detect drug interactions e.g. amlodipine and statins.

***Important findings from some other non-industry sponsored studies***

A double blind randomised controlled trial that compared 1016 low risk patients receiving simvastatin 20 mg or pravastatin 40 mg with placebo showed that both drugs had a significant adverse effect on energy/fatigue exercise score with 40% of women reporting reduced energy or fatigue with exertion.[9] Reducing exercise capacity in a healthy group when physical inactivity is a major contributor to the development of cardiovascular disease is extremely counterproductive.

**Comment [A18]:** See above: about 7-fold not 30-fold (i.e. a 4-fold error)

**Comment [A19]:** INCORRECT: This section relates to adverse events. However, the published protocol for the CTT collaboration (see Am J Cardiol 199575:1130-4 in Supporting Material) makes it clear that only major vascular events, cause-specific mortality and site-specific cancer were sought for these meta-analyses, and not all other serious or non-serious adverse events (which are, therefore, not held by CTT/CTSU). In addition it is not correct that the CTT database is only held in Oxford since it also held, and analysed separately, at the University of Sydney.

**Comment [A20]:** INCORRECT: The CTT collaboration involves agreements with the academic investigators who did the trials and/or the companies who funded them that their data will not be given to a third party without their permission. When asked by NICE if the CTT collaboration could help with its analyses, CTSU offered in writing to contact all of the investigators seeking such permission (but, given their timelines, NICE did its own analyses of all of the data available to it).

**Comment [A21]:** As above, the adverse event data from the different trials are not held by, and so not "concealed" by, CTT/CTSU.

**Comment [A22]:** Not demonstrated to be true and not referenced. If similar types of events are considered then, typically, the rates are similar. For example, the rate of musculoskeletal pain recorded in the observational study reported by Buettner et al (referenced in the BMJ paper by Abramson) was about 20%. Similarly, in the Heart Protection Study, muscle pain or weakness was recorded on at least one occasion in 33% of the patients randomly allocated simvastatin vs 33% of those randomly allocated placebo during the 5-year study period (see Lancet 2002; 360: 7–22 in Supporting Material). That is, many of the patients allocated placebo rep... [15]

**Comment [A23]:** INCORRECT: It was actually CTSU's SEARCH trial that found interactions for myopathy between simvastatin 80mg daily and amiodarone, confirmed interactions with amlodipine and with diltiazem, and identified an association with a variant in the SLCO1B1 gene. Subsequently, CTSU's THRIVE trial identified an interaction of statin w... [16]

**Comment [A24]:** It is of note that this was not one of the pre-specified analyses of that trial, but was instead one of a large number of exploratory analyses, involving data-derived emphasis on a subgroup (i.e. women rather than all of the patients) for a non-prespecified outcome, which has not been independently confirmed. Perhaps of relevance, given the concerns expr... [17]

A large observational study involving 153,840 postmenopausal women aged between 50 and 80 years enrolled in the Women's Health Initiative study found that statins were associated with a 48% increased risk of developing diabetes.[8]

Potential psychiatric symptoms including depression, memory loss, confusion, and aggressive reactions have also been associated with statin use.[10]

Erectile dysfunction, to take another significant adverse effect, is not mentioned in the statin trials. Yet, when it was specifically looked for, around 20% of men appeared to be affected. [11]

**5. Loss of professional confidence**

We are also concerned that GPs feel that this guidance is a 'step too far. It is instructive to note that a survey of 511GPs carried out by Pulse magazine revealed that '….*almost six out of ten (57%) oppose the plan to lower the current 10-year risk threshold for primary prevention, while only 25% support it. Furthermore, 55% would not personally take a statin or recommend a family member does so based on a 10% 10-year risk score*.' (11b)

More recently the General Practitioners Committee (GPC), which negotiates on behalf of GPs in the UK passed the following resolution: '*In light of the Cochrane review of the effectiveness of antiviral influenza treatments, the GPC will request that NICE refrain from recommending a reduction to the current treatment threshold for primary prevention of cardiovascular disease with statin therapy unless this is supported by evidence derived from complete public disclosure of all clinical trials' data'* **(11c)**

Asking GPs to meet targets that they feel uncomfortable with risks a damaging split within the profession, and a loss of confidence among the public, who are likely to recognise increasingly that GPs are being asked to prescribe statins despite feeling it is inappropriate.

**6. Conflicts of Interest (real and perceived)**

We are also seriously concerned that 8 members of NICE's panel of 12 experts for its latest guidance have direct financial ties to the pharmaceutical companies that manufacture statins.[12] Furthermore, some members of the guideline panel are also involved in next generation, more expensive, cholesterol lowering drugs, which are not yet on the market.[12] If cholesterol lowering becomes established in low risk people, the indications for these new cholesterol lowering drugs such as the ApoB Antisence drugs and PCSK9 inhibitors will probably expand as well. We feel that parties with industry conflicts should not be participants in generating recommendations regarding drug use that will influence medical care across the population.

We fear that the CTSU could be perceived as having a major conflict of interest in the area of cardiovascular disease prevention/lipid modification, which has an impact on the Unit's perceived objectivity. We strongly urge that other researchers, for example, the Cochrane Stroke Group and Cochrane Heart Group, should be able to scrutinize and assess all the data that the CTT has utilised over the years to produce their extremely influential studies.

CTT is a part of the Clinical Trials Service Unit (CTSU) in Oxford, which has carried out many very large studies on statins, and other lipid modification agents with pharmaceutical company support, and has received hundreds of millions in funding over the years. To consider just one such study (REVEAL). REVEAL is being funded by Merck Sharp &

**Comment [A25]:** By contrast, a carefully conducted meta-analysis of the evidence from the randomised-controlled trials found that there was a proportional increase of diabetes of only about 10% (see Lancet 2010; 375: 735-42 in Supporting Material)

**Comment [A26]:** By contrast with such "associations" which may not be causal, large-scale randomised placebo-controlled trials (e.g. HPS and PROSPER) have shown no effect on cognition or memory (see Lancet 2002; 360: 7–22 and 1623-30; J Neurol 2010; 257: 85-90).

**Comment [A27]:** MISLEADING CLAIM: This error is similar in nature to the way in which the results in the paper by Zhang et al were misrepresented in the BMJ papers by Abramson et al and by Malhotra; those misleading claims have been withdrawn. However, the same type of error is being repeated here: an "adverse event", which does not imply causation (since the referenced study in only 82 individuals with follow-up was not randomised, controlled or blinded), has been described in this letter as an "adverse effect", which – falsely – does indicate causation. There is no good evidence to support this claim that statin therapy causes erectile dysfunction in 20% of men who receive it. (The repetition of this type of error does illustrate the inadequacy of the partial, and confused, correction and related editorial in the BMJ for the papers by Malhotra and Abramson et al.)

**Comment [A28]:** See CTSU statement on measures taken to ensure that its research is conducted independently (https://www.ctsu.ox.ac.uk/about-ctsu/documents/independent-research)

**Comment [A29]:** As above, see CTSU statement: the CTT collaboration is not funded by industry, but instead is funded by government and charity

Dohme, which developed anacetrapib. A grant of £96 million towards the cost of this multi-million dollar study has been provided to the University of Oxford.(13)

We are concerned that financial conflicts of interest and major commercial bias may have corrupted the database on statins, resulting in an underestimate of the incidence of statin side-effects. Unless all of the data are made available it is impossible to establish a cost per QALY, as there may be DALYs [disability adjusted life years] not accurately accounted for.

We call for all of the data from the clinical trials to be made available to credible researchers, for example, the Cochrane Stroke and Heart Groups. We believe that there is a need for a more robust post-marketing analysis of suspected adverse effects from statins prescribed in a community setting.

To conclude we urge you to withdraw the current guidance on statins for people at low risk of cardiovascular disease until all the data are made available. The potential consequences of not doing so are worrying: harm to many patients over many years, and the loss of public and professional faith in NICE as an independent assessor. Public interests need always to be put before other interests, particularly Pharma.

Yours Sincerely

Sir Richard Thompson, President of the Royal College of Physicians

Professor Clare Gerada, Past Chair of the Royal College of General Practitioners and Chair of NHS Clinical Transformation Board

Professor David Haslam, General Practitioner and Chair of the National Obesity Forum

Dr J S Bamrah, Consultant Psychiatrist and Medical Director of Manchester Mental Health and Social Care Trust

Dr Malcolm Kendrick, General Practitioner and Member of the British Medical Association's General Practitioners sub- Committee

Dr Aseem Malhotra, London Cardiologist.

Dr Simon Poole, General Practitioner

David Newman, Assistant Professor of Emergency Medicine and Director of Clinical Research, Mount Sinai School of Medicine, New York

Professor Simon Capewell, Professor of Clinical Epidemiology, University of Liverpool

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(3b) http://www.health-heart.org/Pfizer's49LipitorStudies.PDF

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(13) http://www.ctsu.ox.ac.uk/reveal/REVEAL_news_release.pdf

**Page 2: [1] Comment [A2]** **Author**

INCORRECT. The rates for the reported outcome of "myalgia" in WOSCOPS were actually 0.6% versus 0.6% (not 0.06% vs 0.06%; a 10-fold error). However, in addition, "muscle ache" was reported in the same part of the WOSCOPS paper for 2.9% vs 3.1% of patients, yielding total rates of 3.5% vs 3.7% (see highlighted section in N Engl J Med 1995; 333: 1301-7 in the Supporting Material).

Note: In the METEOR trial, MedDRA was used to classify adverse events, and that coding system includes muscle aching in the definition of myalgia. Consequently, for the comparison of WOSCOPS versus METEOR, the definition of myalgia should include all cases of muscle ache.

**Page 2: [2] Comment [A4]** **Author**

INCORRECT: If a more similar definition of myalgia (including all cases of muscle aching) is used for both trials, comparison of the rates in METEOR of 12.1% and in WOSCOPS of 3.7% yields a difference that is not 200-fold but is only about 3-fold (i.e. more than a 60-fold error in this open letter to NICE which was widely disseminated to the media and public).

**Page 2: [3] Comment [A5]** **Author**

POINT OF CLARIFICATION: It is not made clear what is meant here by the word “effects” (by contrast with “events”, as used earlier in the letter). Based on the rates quoted for some of the trials listed below, it would appear that what was intended by "effects" was something like "adverse events that lead to the discontinuation of the active or placebo study treatment". However, when the rates quoted in this letter are compared with the published results for these trials, it is apparent that a variety of different outcomes have been selected for the different trials and that the results given for some of the stated outcomes are not correct.

[For comparison with the published results for these trials, see the highlighted sections in the papers in the Supporting Material.]

Note: Strictly speaking, adverse events that lead to discontinuation of study treatment should not be described as "effects" since this implies that they are caused by the treatment which is not necessarily the case (and, indeed, a causal relationship is not supported by the similarity of the rates in the unbiased comparisons between the blinded active statin and placebo groups within each trial).

**Page 2: [4] Comment [A6]** **Author**

It is not appropriate (as has been done in this letter) to compare rates of events that are defined very differently in different trials: in particular, "Total adverse events" in METEOR (not "effects" as is mistakenly stated in the letter: see below) versus the smaller subset of adverse events that led to discontinuation of the study (active or placebo) treatment in the other trials. The rates in the METEOR trial of adverse events leading to discontinuation (i.e. "effects") have been reported (11% vs 8%: see JAMA 2007; 297: 1344-53 in the Supporting Material) and they are, in fact, comparable with the rates in the other trials.

Whereas it is not scientifically appropriate to make non-randomised comparisons of such event rates between trials, it is entirely appropriate to make randomised controlled comparisons within each trial of the rates of particular events since these are based on unbiased blinded assessments of events defined in the same way for both the patients allocated the active statin treatment and those allocated the placebo treatment within any particular trial.

**Page 2: [5] Comment [A7]** **Author**

These percentages are for "AEs leading to discontinuation” (see JAMA 1998; 279: 1615-22 in the Supporting Material).

**Page 2: [6] Comment [A9]** **Author**

These percentages are for "AEs leading to discontinuation” (with some rounding): 5.7% vs 5.8% (see Lancet 1994; 344: 1383-9 in the Supporting Material)

**Page 2: [7] Comment [A10]** **Author**

By contrast with the events quoted for the two trials above, these appear to be the percentages for “All treatment-associated AEs” (with some numerical discrepancies: 23.0% atorvastatin vs 25.4% placebo: see Diabetes Vasc Dis Res 2008; **5**: 177–83 in Supporting Material). For similarity of comparison, the reported rates for "All discontinuations due to AEs" were 8.5% vs 10.3% or, alternatively, discontinuations due to adverse events thought to be treatment related were 2.9% vs 3.4%. (Note: The difference in the rates of these two "effect" outcomes illustrates how the precise definition used could impact substantially on the rates in different trials.)

**Page 2: [8] Comment [A11]** **Author**

These are not the overall discontinuation rates in HPS, but instead are rates for "Discontinuations attributed to AEs" (with a small numerical error: 4.8% simvastatin vs 5.1% placebo; see Lancet 2002; 360: 7–22 in Supporting Material)

**Page 2: [9] Comment [A12]** **Author**

SERIOUSLY MISLEADING: The rates quoted for METEOR are the basis of the claim below that there is a thirty fold difference in rates between the trials. However, as is explained in note 7, the percentages given here for METEOR are not comparable with the rates cited for many of the other trials since they relate to "All adverse events“, whereas the rates cited for the other trials are subsets of all adverse events. The published rates for the comparable outcome of "adverse events leading to discontinuation” in METEOR are 11% rosuvastatin vs 8% placebo (see JAMA 2007; 297: 1344-53 in Supporting Material).

Note: If, on the other hand, it was intended that rates of all adverse events in the other trials be compared with METEOR then the rates quoted for all of the other trials are incorrect.

**Page 2: [10] Comment [A13]** **Author**

These percentages are for “AEs attributed to study treatment” (see N Engl J Med 1998; 339: 1349-57 in Supporting Material), which is different from the outcome of AEs leading to discontinuations with which it has been compared in most of the other trials

**Page 2: [11] Comment [A14]** **Author**

Neither of these rates is comparable to the rates given for the other trials. The discontinuation rates of 25% vs 25% in JUPITER seem to refer to the number of participants not taking their study medication at the time of study termination, and therefore include all reasons for treatment discontinuation (i.e. not just adverse events leading to treatment discontinuation), whereas the rates of 15.2% vs 15.5% refer to serious adverse events (a subset of all adverse events: see N Engl J Med 2008; 359: 2195-207 in Supporting Material).

For comparability with the rates given for the other trials, publicly available results for adverse events leading to discontinuation of 143 (1.6%) vs 158 (1.8%) are available on the ClinicalTrials.Gov website: http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_6111&studyid=317&filename=CSR-D3560L00030.pdf

**Page 2: [12] Comment [A15]** **Author**

This outcome would appear to be “AEs leading to discontinuation”, although the correct result for that outcome is 305 (9.2%) pravastatin patients vs 300 (9.1%) placebo patients (see Eur Heart J 1997; 18: 1718-24 in Supporting Material)

**Page 2: [13] Comment [A16]** **Author**

As discussed above, the similarity of rates in the statin versus placebo groups within each of these trials is “curious” only if it is not accepted that such randomised blinded controlled comparisons provide robust unbiased evidence of a lack of an adverse effect on these different measures.

**Page 2: [14] Comment [A17]** **Author**

INCORRECT: Not comparing like-with-like. When the placebo group rates for similar (although not identical) outcomes in these trials are considered (including, in particular, for METEOR) then they range from only about 2% to about 14% (based on adverse events leading to discontinuation), which is about a 7-fold (not 30-fold) difference. However, as noted above, the definitions used in the different trials differ, and so too do the types of patient and follow-up duration, which may lead to differences in rates between trials.

**Page 3: [15] Comment [A22]** **Author**

Not demonstrated to be true and not referenced. If similar types of events are considered then, typically, the rates are similar. For example, the rate of musculoskeletal pain recorded in the observational study reported by Buettner et al (referenced in the BMJ paper by Abramson) was about 20%. Similarly, in the Heart Protection Study, muscle pain or weakness was recorded on at least one occasion in 33% of the patients randomly allocated simvastatin vs 33% of those randomly allocated placebo during the 5-year study period (see Lancet 2002; 360: 7–22 in Supporting Material). That is, many of the patients allocated placebo reported aches and pains, as did a similar proportion of those allocated simvastatin 40 mg daily, but there was no excess associated with statin therapy.

**Page 3: [16] Comment [A23]** **Author**

INCORRECT: It was actually CTSU's SEARCH trial that found interactions for myopathy between simvastatin 80mg daily and amiodarone, confirmed interactions with amlodipine and with diltiazem, and identified an association with a variant in the SLCO1B1 gene. Subsequently, CTSU's THRIVE trial identified an interaction of statin with niacin and an increased risk of myopathy in Asians. All of these findings were brought to the attention of the regulators and published prominently.

**Page 3: [17] Comment [A24]** **Author**

It is of note that this was not one of the pre-specified analyses of that trial, but was instead one of a large number of exploratory analyses, involving data-derived emphasis on a subgroup (i.e. women rather than all of the patients) for a non-prespecified outcome, which has not been independently confirmed. Perhaps of relevance, given the concerns expressed in this letter about making data available publicly, results for the pre-specified outcomes in that trial of “cognition, serotonin biochemistry and aggression” or of the secondary outcomes “mood, and other cognitive, behavioural and biochemical measures” (see Controlled Clinical Trials 2004; 25: 178-202 in Supporting Material) ) do not appear to have been published (apart from a Circulation Abstract 2006 on cognition, which indicated no adverse effect of the statins tested: see Supporting Material).