SUMMARY STATEMENT

Primary Finding of Paper Unchallenged:

The primary finding reported in our paper is that – based on recalculation of data included in the 2012 CTT meta-analysis –statins do not provide significant reduction in overall mortality for people with less than 20% risk of CVD over the next 10 years. The lack of proven mortality benefit for this population is a new finding that has relevance for tens of millions of low-risk people globally who are currently or soon may be treated with statins based on recommendations that rely on CTT's 2012 meta-analysis published in the Lancet. Dr. Collins has not challenged this conclusion, and his request for retraction of the article is not based on this finding.

Statements About Statin-Related Events Withdrawn:

Two statements about potential adverse events related to statins in our article were withdrawn. First, we erroneously interpreted the rate of discontinuations of statins due to statin-related events in the paper by Zhang et al. Rather than the 18% discontinuation rate due to statin-related events stated in our paper, the correct figure from the paper by Zhang et al. is "up to 9%." Second, statements that statin-related adverse events occur in 18-20% of patients treated with statins were withdrawn. This is the correct figure for the number of people in uncontrolled observational studies who believe or whose physicians believe that a statin-related event occurred. But our article did not include these necessary caveats and did not make clear that the data came from uncontrolled observational studies.

Basis of Dr. Collins' Request for Retraction:

Dr. Collins requests withdrawal of the paper because "these exaggerated claims about the size of the harms of statin therapy changes this balance [of benefits and harms of statins in low-risk patients] materially and invalidates the overall conclusions."

Our Response:

The primary conclusion of our article is rigorous, remains uncontested and is not changed by the correction: CTT data do not show significant reduction in overall mortality and there is no evidence of reduction in serious adverse events associated with statin therapy for people at less than 20% 10-year risk of CVD. Neither the primary conclusion nor balance of benefits and harms of statin therapy presented in our paper for this population would change if future research shows the true incidence of statin-related adverse events turns out to be 3%, 5%, 10%, 20%, or more.

Request for retraction of our article is not substantiated because our withdrawn statements on statin-related events do not invalidate our overall conclusions. Retraction would not only censor clinically important and timely public health information, but also constrain legitimate scientific discourse.

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INTRODUCTION

The BMJ analysis article "Should people at low risk of cardiovascular disease take a statin?" provides important information about the real world benefits and harms associated with statin therapy for people at less than 20% risk of cardiovascular disease over the next 10 years. It criticizes the view of the CTT group and the 2013 Cochrane review promoting use of statins for this low-risk population and argues that the evidence (relying necessarily upon CTT data) shows that people with a 10-year risk of less than 20% derive no significant reduction in overall mortality or serious adverse events, that the risk of harm is not known precisely but is certainly greater than 0, and therefore that prescribing guidelines should not be broadened to include people with < 20% 10-year risk of ASCVD.

Placement of our article in the rapidly unfolding context of expert opinion on the benefits of statin therapy in the low-risk population is critical in understanding the importance of this message. At the time our BMJ article was written and published (prior to release of the updated US guidelines in November 2013 and NICE draft guidance in February 2014), the 2013 Cochrane Review had radically reversed its position (of just two years earlier) on the benefits of statins in low-risk people based upon CTT data, stating:

> Our previous conclusion urging caution in the use of statins in people with low risk of cardiovascular events is no longer tenable in light of the CTT Collaboration findings.[1]

Relying upon the same CTT data presented in the 2012 meta-analysis published in the Lancet, we reconstructed denominators for patients in the two strata of low-risk patients (< 5% 5-year risk and ≥ 5% to < 10% 5-year risk), which allowed us to perform statistical analyses on the combined low-risk groups.

Our primary findings

The primary finding of our article is that, according to our reanalysis of the CTT data, the benefits of statins for low-risk people are likely exaggerated and that there is no overall benefit to statin therapy in this low-risk population: no reduction in overall mortality or total serious adverse events.

Although Dr. Collins takes issue with our reliance on Figure 3 of the 2012 CTT meta-analysis, he does not dispute our finding that CTT data do not show a reduction in overall mortality associated with statin therapy in the population with less than 20% 10-year risk of cardiovascular disease. In fact, Webfigure 8 – to which he refers in his request for retraction –confirms our results based on Figure 3 in the 2012 Lancet meta-analysis. Further, Dr. Collins refutes our reliance on all-cause mortality, pointing out that "effects of treatment on cause-specific mortality are more readily generalizable to different circumstances…where proportions of deaths from different causes may differ." Although this contention is debatable, Dr. Collins is correct that CHD and stroke mortality constitute a lower proportion of overall mortality in the population with lower CVD risk. However, Webfigure 8 of the 2012 CTT meta-analysis shows that statin

[1] Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;1:CD004816. p. 14

therapy does not reduce cause-specific mortality related to either CHD or stroke mortality. Thus, the primary finding of our paper—that statin therapy does not reduce the risk of death is confirmed in people with less than 20% 10-year risk of CVD. [Note: The category of "Non-vascular death" in Figure 3 of the 2012 CTT meta-analysis is mislabeled, it should be titled "Non-vascular death of known cause."]

In making the decision about whether or not low-risk people should be treated with statins, physicians and their low-risk patients should have the opportunity to understand a) there is no proven overall benefit to statin therapy; and b) that the limited cardiovascular benefit of statin therapy in this low-risk population is of such a low magnitude (NNT=140 over five years to prevent one stroke or heart attack) that it is not enough to provide a reduction in death from coronary heart disease or stroke, or provide a reduction in total serious adverse events. And thus, the small chance of benefit (in decreased risk of non-fatal heart attack or stroke) would be offset by other serious adverse events, making statin therapy in the low-risk population without a net benefit. (For reasons explained in our BMJ article, we did not include the "softer" outcomes such as coronary revascularization procedures.)

Our secondary findings

The purpose of the rest of our article was to show that statins are not risk free and they can cause harm. It was not possible in the space allotted to be comprehensive in terms of all of what is known about statin harms. We agree that it is difficult to assess the magnitude of the harms from both RCTs and observational studies and that the magnitude of harms with statins is uncertain and debatable at this time. We think that the correction that is published on the BMJ website is sufficient to correct our inaccurate interpretation of the article by Zhang et al. about the percentage of people who discontinued statin therapy due to statin-related events.

Dr. Collins' communication to BMJ states that our paper as well as the paper by Malhotra "need to be prominently retracted in order to avoid repeated reference to these misleading claims [about adverse events related to statins] and to mitigate the damage caused." The article by Zhang et al. stated "Statin-related events were documented for 18,778 (17.4%) of patients." We agree with the correction of our article published by BMJ May 15 2014, stating a) that our reference to the "nearly 18%" rate of statin-related events reported by Zhang et al. needed to be qualified with a statement that the data came from an uncontrolled observational study; and b) our statement that 18% of the patients in the study by Zhang et al. discontinued statin therapy "because of statin-related adverse events" was not correct, and should have stated that "up to 9% of the study population having possibly discontinued statin therapy as a consequence of statin-related events."

In the introduction of his Note to the panel, Dr. Collins writes:

> 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.

We disagree with Dr. Collins. The primary message in our BMJ Analysis piece is that for people with a 10-year risk of < 20%, statin therapy does not produce a net health benefit, and therefore

any risk of adverse events greater than zero tips the benefit/harm equation towards harm. Confusion about interpretation of the paper by Zhang et al. should not be used to suppress these important and, prior to publication of our paper, unreported findings.

This issue clearly has important consequences for low-risk patients, especially because the magnitude of the harms from long-term statin use will probably not be known for many years. At this time, an open debate of the scientific issues is the only approach that is in the best interests of the public. We welcome such an open debate.

We do not believe the inflammatory statements in Dr. Collins' Note to the Panel, listed below, contribute substantively or constructively to such debate:

- **"Deliberate repeated misrepresentation of the evidence about the rate of side-effects"**
- "deliberate intent to mislead the medical profession and the public despite the potential for harm to patients"
- **"**This is an entirely specious argument. "
- **"**although the principal reason for retracting it is the deliberate and repeated misrepresentation of the magnitude of the harms of statins"
- **"**decided to confuse readers deliberately"
- **"**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)."
- **"**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"

We disagree with some of the conclusions of the 2012 CTT meta-analysis, and we are concerned about the effect of these conclusions on expert guidelines, physicians, and many millions of patients. We do not, however, believe that personal attacks, attribution of ill motives, and trial by media will best serve patients' interests or advance this important scientific debate.

REBUTTAL TO DR. COLLINS' STATEMENTS

What follows is a response to the specific issues raised by Dr. Collins in his request for retraction. The headings in quotes are from his communication.

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

We agree with Dr. Collins that the findings by Zhang et al. with regard to the frequency with which the people in their observational study reported the discontinuation of statin therapy

due to statin-related events was interpreted erroneously in our paper. Zhang et al. reported that 17.4% of people (in unstructured routine follow-up visits) reported statin-related events. And further, that up to 9% of patients treated with statins discontinued their statin therapy because of statin-related events (the authors noted that lack of greater precision was due to potential inaccuracies of default categorization in electronic medical records). We agreed to a correction as soon as this error was brought to our attention.

Dr. Collins also includes as an example of a "serious misrepresentation" our statement that "the side-effects of statins…occur in about 20% of people treated with statins." The article by Zhang et al. stated:

> **The rate of reported statin-related events to statins was nearly 18%,** substantially higher than the 5% to 10% usually described in randomized, placebo-controlled, clinical trials. This finding is consistent with previously published observational studies. [Emphasis added]

The statement in the box of our article would have been more accurate had we stated that statin-related events were reported in about 20% of people who participated in an **uncontrolled observational study**. We agreed to completely withdraw the bullet point in a box; however, simply adding the words "in an uncontrolled observational study" would have brought the statement into alignment with the article by Zhang et al. While we regret not including this language in our manuscript and have agreed with retraction of the bulleted statement, we disagree that this is a "serious misrepresentation of evidence."

Given the constraints of space, we did not address in our BMJ article (but in retrospect probably should have) that of 107,835 statin-treated patients followed in routine care settings over 8 years in the study by Zhang et al., more than half, 57,292 discontinued their statin therapy at least temporarily. Zhang et al. stated that only 30% of patients who discontinued statins in their study had "reasons for statin discontinuation documented in unstructured electronic medical record fields" and that the natural language processing tools used to compensate for this "are not perfectly accurate." Because the routine follow-up visits were unstructured—without specific query about muscle symptoms, cognitive changes, sexual difficulties, fatigue, etc.—the true rate of ascertainment of such symptoms and capture in electronic medical records is unknown. The true rate of statin-related side effects among the 57,292 people who discontinued statin therapy is not known.

Response to "Deliberate repeated misrepresentation of the evidence about the rate of side-effects"

We categorically deny deliberate misrepresentation of the side effects of statins. Dr. Collins' personal attacks and impugning of motives do not advance constructive scientific debate about the benefits and risks of statins in low-risk people. We have not responded with accusations that CTT deliberately misrepresented the mortality effect of statin therapy in low-risk people. We believe this is a matter best resolved by scientific debate, as in our BMJ article, the primary point of which remains unrefuted.

Dr. Collins wrote, "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…"

Dr.Takhar's letter made three points. First, our article "is a useful counterbalance to the Cochrane review on use of statins in primary prevention and useful to me as a practicing GP discussing the pros and cons of statins on an almost daily basis." This would argue against retraction of the entire paper. Second, the box bullet point in our article stating that side effects occur in about 20% of people treated with statins "is not conclusively backed up by the detailed evidence in reference presented." In our response to Dr. Takhar we quoted Zhang et al: "'The rate of statin-related events to statins was nearly 18%' in this retrospective cohort study." Later in the response we stated: "the incidence of statin-related side effects reported by Zhang et al. was, in fact 'approximately one fifth.'" Perhaps Dr. Collins would be less critical if we had added "in an uncontrolled observational study" to the second statement. But the fact that the study by Zhang et al. was a retrospective cohort study had already been established, and only through the most negative of lenses could the juxtaposition of these two statements be considered "deliberate misrepresentation."

And third, Dr.Takhar correctly pointed out that "35% of those who discontinued [statin therapy] due to statin adverse effects were rechallenged and the majority of these (92%) were still taking statins 12 months [sic]." His concern was that the predominance of successful re-challenge "would imply the true figure for statin-related adverse events is much lower than the 20% quoted in the key message." If statin therapy were providing an overall benefit to the low-risk population analyzed in our paper, the point raised by Dr. Takhar would have greater impact on our article: that people who experience statin-related events should be rechallenged because many would be able to tolerate this (presumably beneficial) therapy. However, given the uncontested lack of net health benefit we reported in our paper, the fact that statin rechallenge had a high success rate in the paper by Zhang et al. is not the point, rather it is that a significant number of people treated with statins experience statin-related events, and when there is no benefit as in the low-risk population, these events are not offset by therapeutic advantage.

Dr. Collins is correct that Prof. Jewell and John Abramson serve as experts in litigation. Nonetheless, we believe the difference between "statin-related events" and "statin-related side effects" is a distinction without a practical or material difference in the context of an uncontrolled observational study—both terms obviously include events that are believed by patients or their physicians to have been related to statin therapy.

Dr. Rita Redberg and Dr. Abramson stand by their statement made in a New York Times op-ed piece: "18 percent or more of this group will experience side effects…" We did not say that all of these side effects were **caused** by statins, but rather reflected the language of Zhang et al., which noted that the rate of statin-related events "was nearly 18% this retrospective cohort study."

We were not aware of Dr. Collins' communication about this in March 2014. As noted in Dr. Godlee's editorial, Dr. Collins "declined several requests to send a rapid response or letter for publication." Thus, we did not have the opportunity to respond to Dr. Collins' concerns at all.

We respect Dr. Collins' right to question and debate our findings. This process would, however, be far more productive and constructive without buttressing the scientific debate with attribution

of less than honorable motives.

Response to "Summary of the paper by Zhang et al. (Ann Intern Med 2013)"

Dr. Collins states in his note to the panel that the authors of Zhang et al. concluded that "*many of the statin-related event may have other causes*…" The rest of the sentence reads: "many of the statin-related events may have other causes, **are tolerable, or may be specific to individual statins rather than the entire drug class**."[Emphasis added]

As noted in our comments on the letter by Dr. Takhar, we understand that the primary point of the paper by Zhang et al. is that rechallenge of people who discontinued statins because of statin-related events is often successful. This is an important point for people who stand to benefit from statin therapy. However, having shown no overall mortality benefit, Webfigure 8 of the 2012 CTT meta-analysis showing no benefit for CHD and/or stroke mortality, and no evidence of reduction in Serious Adverse Events, the experience of perceived problem related to statins stands as a negative given no net benefit in the low-risk population. This distinction is highlighted by the rest of the quotation for Zhang et al. noted above.

Dr. Collins' note cites the article by Buettner et al. to show that reported rates of musculoskeletal pain occurs in both statin users and non-users, and that observational studies are therefore prevented from determining a causal association between statins and myalgia. We also cited Buettner et al. in our paper, and Dr. Collins' description of the findings of the article is not accurate—5.3% (statistically significant) more statin users than non-users experienced musculoskeletal pain:[2]

> **MEASUREMENTS AND MAIN RESULTS**: …Among statin users (n=402), 22.0% (95% CI 18.0–26.7%) reported musculoskeletal pain in at least 1 anatomical region during the last 30 days, compared with 16.7% (95%CI 15.1–18.4%) of those who did not use a statin. Compared to persons who did not use statins, those who used statins had multivariable-adjusted odds ratios (95%CI; p value) of 1.50 (1.07–2.11; p=.01) for any musculoskeletal pain, 1.59 (1.04–2.44, p=.03) for lower back pain, and 1.50 (1.02–2.22, p=.03) for lower extremity pain.
>
> **CONCLUSION**: Musculoskeletal pain is common in adults ≥40 years without arthritis. In this nationally representative sample, **statin users were significantly more likely to report musculoskeletal pain**. [Emphasis added]

Dr. Collins' statement that the investigators "have concluded that pain occurring during statin use may be unrelated to statin use" is true but ignores the statistically significant increase in musculoskeletal pain reported by statin users, as documented by Buettner et al. above.

Similarly, Dr. Collins cites a paper by Mansi et al. to show that high rates of musculoskeletal pain occur in both statin users and non-users, and therefore pain may be inaccurately attributed to statin therapy. True for any individual patient, but like Buettner et al. above, Mansi et al. (cited

[2] Buettner CA, Davis RB, Leveille SG, Mittleman MA, Mukamal KJ. Prevalence of musculoskeletal pain and statin use. *J Gen Intern Med* 2008;23:1182-6.

in our paper) reached the following conclusion:[3]

> **Conclusions and Relevance**: Musculoskeletal conditions, arthropathies, injuries, and **pain are more common among statin users than among similar nonusers**. The full spectrum of statins' musculoskeletal adverse events may not be fully explored, and further studies are warranted, especially in physically active individuals. [Emphasis added]

Dr. Collins describes the correction to our article published in BMJ May 15, 2014 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 precise language used in the article by Zhang et al. was:

> The rate of reported statin-related events to statins was nearly 18%... This finding is consistent with previously published observational studies.

The correction in BMJ states:

> The conclusion and summary box of this Analysis article by Abramson and colleagues stated that side effects of statins occur in about 18-20% of patients. **The authors withdraw this statement**. [Emphasis added]
>
> …the article did not reflect necessary caveats and did not take sufficient account of the uncontrolled nature of the study.
>
> As Zhang et al. point out, the rate of statin-related events attributed to statins in their study was uncontrolled and therefore may be inflated because events attributed to statins might have occurred in a placebo group as well.

The correction in BMJ is consistent with the letter recently written to BMJ by Zhang, Plutzky, and Turchin that defined "statin-related events" as "clinical events or symptoms BELIEVED to have been caused by statins." In our opinion, the BMJ correction rectifies our oversight in not stating the necessary caveats and the uncontrolled nature of the study.

Dr. Collins expresses concern about language in an email by the BMJ Editor that was later included in the correction, which he states misrepresent Zhang et al.'s statement:

> *"…as many as 87% of statin discontinuations among patients with documented statin-related events could have been due to these events"*

The language included in the May 14 correction of our article is virtually identical to that of Zhang et al:

> "…'as many as 87%' of these discontinuations could have been due to statin-related events.' "

[3] Mansi I, Frei CR, Pugh MJ, Makris U, Mortensen EM. Statins and musculoskeletal conditions, arthropathies, and injuries. *JAMA Intern Med* 2013;73:1-10.

Given that we used virtually the same language as Zhang et al., including the statement "could have been due to these events," we do not understand Dr. Collins' argument that the correction misrepresented the statement by Zhang et al.

Dr. Collins writes that the evidence in the paper by Zhang et al. does not support the claim "that statins cause side effects in 18-20% of patients." In fact, Zhang et al. do not use the word "cause" but do report such occurrence:

> **The rate of reported statin-related events to statins was nearly 18%**, substantially higher than the 5% to 10% rate usually described in randomized, placebo-controlled, clinical trials (24). **This finding is consistent with previously published observational studies** (28-31). Similar to both clinical trials and observational studies (23, 32), musculoskeletal symptoms were predominant, accounting for 40% of statin-related events. Overt rhabdomyolysis was found in only 0.006% of the study patients, also consistent with previous reports that statin-induced myopathy is rare (33). [Emphasis added]

Had we aligned our language more precisely with that of Zhang et al. above by adding the bold language below, the retracted bullet would have been substantiated:

> **In published uncontrolled observational studies, statin-related events**—including muscle symptoms, increased risk of diabetes (especially in women), liver inflammation, cataracts, decreased energy, sexual dysfunction, and exertional fatigue—occur in about 20% of people treated with statins.

Dr. Collins discussed with the Editor on May 8 2014 the fact that rates of statin-related side effects are equal in statin and placebo groups of RCTs. This claim does not take into account that, for example, the largest of all studies included in the CTT meta-analysis—the Heart Protection Study with 20,536 patients (of which Dr. Collins is the lead author)—included a screening phase that excluded more than half of the volunteers, then carried out a run-in phase that involved 4 weeks of placebo followed by 4-6 weeks of fixed dose simvastatin 40 mg daily. More than one third of those who passed the initial screening were later either deemed not eligible or withdrew in the process of the run-in period. Thus, patients with early perceived side effects were removed from the randomized study population, potentially minimizing the rate of adverse events during the study period and potentially compromising the external validity of the results with regard to adverse event experiences.

In their recent letter to the BMJ editor, Drs. Zhang, Plutzky and Turchin weighed in on the fact that the "actual etiological relationship" of statin-related events could not be established by their research. Their letter cited a recent article by Mampuya et al., which, in turn, stated:

> [Statins] are generally safe, but in some patients, statin therapy is stopped because of intolerance to the drug that may result in muscle aches and weakness, gastrointestinal symptoms, liver enzyme abnormalities, or other nonspecific discomforts. The rate of reported statin-related events is about 5% to 10% in randomized, placebo-controlled clinical trials. **This rate has been reported as high as 20% in observational studies [6 citations noted]. The discrepancy between clinical trials and observational studies**

> **can be explained by patient selection in randomized trials, which often exclude old patients and those with many comorbidities and enroll fewer women**.[4] [Emphasis added]

That the rate of statin-related events in observational studies is as high as 20% cannot be disputed. As stated elsewhere in this memo, if we had the opportunity, we would add clarifying language to the fourth bullet point in the box of our article stating that that 20% number was derived from uncontrolled observational studies. Nonetheless, 20% of people experiencing or believing they are experiencing side effects from a therapy that provides no net benefit is an important fact that should be known by people at low risk of cardiovascular disease and the physicians who care for them.

Finally, Dr. Collins states that it is "not appropriate for the BMJ to publish" our statement that "determination of harms cannot be left to industry alone." Dr. Collins ignores the evidence presented in the 2012 Cochrane Review titled "Industry sponsorship and research outcome" showing that industry sponsored studies had more favorable harm results RR: 1.87 (95% CI: 1.54 to 2.27) and:

> **Authors' conclusions**
>
> Sponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions than sponsorship by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.[5]

Note that these findings relate to sponsorship of the trials and not, as Dr. Collins suggests, whether or not trials were conducted independent of the sponsor.

The debate about the necessity of full transparency of clinical trial data is beyond the scope of the issues being discussed here. However, acceding to Dr. Collins' effort to suppress discussion about potential bias in harm data from commercially sponsored clinical trials of statins from taking place in a respected scientific forum would do serious harm to the goals of a) ensuring that clinical trial data are used optimally to ensure patient safety; and b) promoting responsible scientific debate in general.

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

Dr. Collins argues that adverse event data from RCTs "provide robust assessments of the effects of statins on adverse events." This claim is at odds with the article by Mampuya et al. (cited

[4] Mampuya WM, Frid D, Roccoco, et al. Treatment strategies in patients with statin intolerance: The Cleveland Clinic experience, *American Heart Journal*, 2013; 166:597-603.

[5] Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev 2012;12:MR000033.

above and in Zhang et al.'s recent letter to BMJ) providing a partial explanation for the disparity between statin-related events reported in RCTs and observational studies. Further, this claim is at odds with a recent Cochrane Review titled "Industry sponsorship and research outcome (Review), which found that industry sponsored studies had more favorable harm results (RR: 1.87 (95% CI: 1.54 2.27)) compared to non-industry sponsored studies.[6] All of the statin trials included in the 2012 CTT meta-analysis were at least partially funded by industry. As we noted above, the exclusion of statin-intolerant patients during the run-in period of the largest of the statin clinical trials, the Heart Protection Study, as well as patient selection certainly play a role in the discrepancy as well. The bottom line on this point is that the comparative robustness of adverse event data from RCTs vs. observational studies, with commercial versus noncommercial sponsorship thrown into the mix, is debatable, but certainly not cause for retraction of our article.

Serious adverse events

Simply because the CTT protocol of 1994 did not include serious adverse events in toto does not negate the central importance of this standard indicator of the rate of serious illness/serious adverse events (SAEs) that occur during the course of a study. Because SAE recording and reporting are standard in Clinical Study Reports, and because of their comprehensive overview of study events, it is reasonable to expect that the manufacturers would report SAEs to CTT, which in turn would report SAEs in total rather than limiting their reporting of SAEs to the subset of non-vascular death and site-specific cancer. Dr. Collins notes that the 2012 CTT meta-analysis reported no evidence of adverse effect on non-vascular death or on any site –specific cause of cancer. We ask a different question of the data: given the lack of mortality benefit of statins in low-risk patients, determination of net benefit would rely on a reduction of overall SAEs. Such information was not presented. Perhaps Dr. Collins is not currently in possession of data about Serious Adverse Events from the studies included in the 2012 CTT meta-analysis. If not, he could make this known and request such information from the trial sponsors and researchers to include this important variable in the CTT meta-analyses.

Cause-specific mortality

With regard to cause-specific mortality, data reported in Webfigure 8 that accompanied the 2012 CTT meta-analysis published in Lancet show that statin therapy did not reduce CHD or stroke deaths for those with < 5% or those with ≥ 5%, < 10% 5-year risk. Further, Mantel-Haenszel adjusted RR does not show significant reduction in CHD or stroke mortality for the two groups combined. Neither is there a significant reduction in CHD and stroke mortality combined associated with statin therapy for people with < 10% 5-year risk (equivalent to < 20% 10-year risk).

It would not be consistent to restrict SAE reporting to "treatment specific" problems, without reporting treatments specific (i.e. CHD and stroke) death rates associated with statin treatment in low-risk patients.

Selective presentation of lack of adverse event results from specific clinical trials is not helpful in this discussion. Dr. Collins notes that repeated measurement of cognitive function in the

[6] Op.cit. Lundh et al.

PROSPER trial shows no adverse effect on that outcome. However, Dr. Collins does not mention that in the same study, PROSPER, elderly people treated with statin therapy developed significantly more cancer (8.5% pravastatin group compared to 6.8% in the placebo group, p=0.02).[7]

The article by Macedo et al. (BMC Medicine 2014) is cited by Dr. Collins as evidence that "carefully conducted randomized trials in meta-analyses of trials… find only small excesses of myopathy (about one per 10,000 per annum)."[8] The problem with Dr. Collins' additional information is that the citation is to the 2012 CTT meta-analysis, i.e. it simply echoes the CTT's definition of myopathy (see below for more complete discussion of the myopathy/myalgia issue).

Long-term follow up has been published for a small number of trials. Given the incompleteness of this manufacturer-volunteered data, data from those few studies may have been "cherry-picked" and do not stand as definitive evidence of long-term benefit. (But this is going beyond the realm of our paper and issues that should be considered in Dr. Collins' request for retraction.)

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

Dr. Collins disagrees that our correction of the incidence of statin-related events associated with discontinuation of statins in the article by Zhang et al. does not impact the primary finding of our article. He writes, "This is an entirely specious argument." Without elevating to his level of rhetoric, the primary focus of our article was clearly to show that there is no overall mortality benefit nor evidence to support a reduction in serious adverse events associated with statin therapy for people with less than 20% 10-year risk of CVD. It makes absolutely no difference whether the calculation about mortality is based on Figure 3 or Webfigure 8 from the 2012 CTT meta-analysis, see below. In fact, the latter shows no cause-specific mortality benefit associated with statin therapy in this low-risk population for CHD and/or stroke. Further, no evidence is provided that statin therapy in this low-risk population is associated with a reduction in serious adverse events. Thus, the statistically significant but small reduction in the risk of stroke and MI is not enough to demonstrate an overall health benefit gleaned by treating people with low risk with statins. Contrary to Dr. Collins' position, when there is no overall benefit to statin therapy in the low-risk population, any degree of harm tips the risk/benefit equation in the negative direction. Thus, Dr. Collins is not correct when he states:

> Withdrawal of these exaggerated claims about the size of the harms of statin therapy changes this balance materially and invalidates the overall conclusions. [Emphasis in original]

This is the crux of the matter: our BMJ Analysis piece shows that for the low-risk population (less than 20% 10-year risk of CVD) there is no overall benefit to statin therapy, therefore any

[7] Shepherd J, Blauw GJ, Murphy MB, et al. on behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360: 1623-1630.

[8] Macedo AF, Taylor FC, Casas JP, et al. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis, *BMC Medicine*, 2014; 12:51-66.

incidence greater than zero on the harms side of the equation is determinative of the benefits/harm balance.

Dr. Collins is unequivocally incorrect when he says that correction of the reported frequency of statin-related adverse events invalidates the conclusion of the paper, which – he claims – supports retraction. He is also incorrect when he denies that recalculation of the mortality benefit for low-risk people is the primary focus of the paper.

Dr. Collins points our attention to Webfigure 8 rather than Figure 3 of the Lancet publication for all-cause mortality data. Like the calculation we presented in our BMJ Analysis piece, data from Webfigure 8 show no significant reduction in all-cause mortality for those with < 5%, those with ≥ 5%, < 10% 5-year risk, or both groups combined. Prof. Jewell has recalculated the Mantel-Haenszel calculation for the two groups combined and found, as in our BMJ article, there is not a significant reduction of all-cause mortality associated with statin therapy for the two groups combined, RR 0.92, 95% CI 0.84-1.01).

 All-cause mortality is not the best way to assess effects of treatment on survival

Again, the results of the impact on statin therapy for people at less than 20% 10-year risk of CVD is unchanged whether the data from Figure 3 or Webfigure 8 are used. Further, if one takes the position that overall mortality is too broad an endpoint to evaluate the effect of statins on cardiovascular deaths, then deaths from CHD and deaths from stroke should be considered. Based on the data in Webfigure 8 and the concerns raised by Dr. Collins, in retrospect we should have included cause-specific mortality (CHD and stroke) in our BMJ article.

 All SAEs combined is not a good way to assess efficacy or safety

We do not disagree with Dr. Collins that important information can be derived from looking at comparative rates of specific serious adverse events. However, in considering the overall effect of statins (especially in the low-risk population), the totality of serious adverse events is most relevant. Dr. Collins misrepresents our argument: that the evidence shows a greater than zero risk of adverse events associated with statins does not translate to claiming an increase in SAEs. We don't know, because the data have not been made available by the studies' commercial sponsors, what the net effect of statin therapy on serious adverse events in the low-risk population is. However, assuming that there was not a statistically significant difference in the incidence of SAEs between statin/more statin and placebo/less statin in low-risk patients, this does not prove that statin-related adverse events do not occur. Nor does it show that statins provide an overall health benefit (combined with the mortality data discussed above) in low-risk patients.

Dr. Collins posits that our contention that the overall rate of serious adverse events is important "equally mean[s] that there is no serious harm associated with statin therapy." His suggestion that lack of evidence of increase in serious adverse events justifies putting tens of millions of low-risk people on a therapy for which benefit has not been established gets to the core of why our paper should not be retracted.

 Misleading comparisons of myopathy and myalgia rates

Dr. Collins' statement that we "decided to confuse readers deliberately" is false. As shown below, when Dr. Collins took his case to the media, it is he who confused the issue.

As a result of Dr. Smeeth's suggestion in the peer review process (that muscle pain is common in the general population with or without exposure to statins), we clarified the findings from the NHANES data to show that current statin-users have a 50% greater likelihood of reporting muscle pain than comparable non-users of statins :

> The excess risk of myopathy associated with statins reported in the CTT meta-analysis is 0.5 per 1000 patients over five years—number needed to harm (NNH) is 2000. However, a cross sectional analysis from the National Health and Nutrition Examination Survey database shows that the **prevalence of muscle pain** in statin users is 50% greater than in non-users. In absolute terms, this increase in **muscle pain** is 100 times greater than that reported in clinical trials—53/1000 patients, NNH=19.13. [Emphasis added]

The point we were making was that although myopathy (as defined by CTT) is rare, one out of about twenty real people at low risk of CV disease will experience muscle pain as a result of taking a statin, from which they will derive no overall benefit.

In response to Dr. Smeeth's peer review comments, we clarified the endpoint in the NHANES data set as "muscle pain" in contradistinction to the definition of myopathy used in the CTT meta-analysis (muscle symptoms plus blood creatine kinase levels > 10 x upper limit of normal).

The confusion here is understandable. Dr. Collins uses "myopathy" to mean muscle symptoms plus significant enzyme elevations, whereas a paper titled "Statin myopathy: A common dilemma not reflected in clinical trials"[9] (a paper we considered but did not cite) included a range of symptoms under the umbrella of myopathy: myalgia, myositis, and rhabdomyolysis. This, too, is a valid definition of myopathy. The concern addressed in our BMJ paper was not limited to the incidence of serious and rare muscle disorders, but rather included muscle symptoms far more likely to affect people treated with statins. In our citation of Buettner et al. we made clear a) that the outcome measure was muscle pain; b) that these symptoms occurred in non-users of statins as well; c) that the prevalence of these symptoms was 50% greater in statin users than in non-statin users; and d) that the frequency of statin-related muscle pain in real people is greater than the frequency of myopathy (as defined by CTT) in people included in clinical trials.

Fernandez et al. address the very issue that Dr. Collins and we have raised about the incidence of myopathy in clinical trials versus the real world. In the section titled "Why is statin-induced myopathy so uncommon in clinical trials?", the authors discuss the exclusion of vulnerable patients in clinical trials, the exclusion of up to 30% of participants in active pre-randomization phases of clinical trials, and that the statins trials were designed to test efficacy:

[9] Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: A common dilemma not reflected in clinical trials, *Cleveland Clinic Journal of Medicine*, 2011; 78:393-403.

> …and were not sensitive to adverse effects like muscle pain. When they looked at myopathy they focused on rhabdomyolysis – the most severe form – rather than on myalgia, fatigue, or other minor muscle complaints.

Dr. Collins certainly has a right to choose a more limited and severe definition of myopathy, but he doesn't have the right to impose that choice on us. We are addressing the more common problems that affect low-risk people who will derive no net benefit from statin therapy and changed the language in our article in response to Dr. Smeeth's comments in an attempt to avoid this confusion. Dr. Collins asserts that the difference between definitions of myopathy is "a further misrepresentation of the evidence on statin side effects" on our part, whereas we assert that the broader definition of myopathy (as used in the article published in the Cleveland Clinic Journal of Medicine) is more relevant to the consideration of recommendation of statins for people at low risk of CV disease. This can be a good faith disagreement resolvable by further clarification, but certainly is not evidence, as claimed by Dr. Collins that we "decided to confuse readers deliberately," nor does it constitute cause for retraction of the article. Further, we considered three studies that reported histopathological findings of muscle abnormalities in statin-treated patients with or without muscle symptoms and **normal creatine kinase levels**,[10] [11] [12] but did not have space to include them in our paper.

Dr. Collins cites our BMJ letter of December 20, 2013 as evidence that we "decided to confuse readers deliberately." Dr. Huffman et al. commented to BMJ on November 27, 2013:

> The authors also conflate muscle pain (myalgias), an important side effect of statins, with myopathy, a rare and more serious problem, both of which warrant ongoing study.

Dr. Huffman et al.'s comments are consistent with the CTT's definition of myopathy used in analysis of clinical trials. By this definition, "myopathy" represents a rare and serious consequence of statin therapy. The definition of myopathy that we used (as used by Fernandez et al.) is also valid. It differs from the CTT's definition, in being broader, and – we feel – more germane to the question of whether low-risk patients should be treated with a statin. For the reasons stated above, we disagree with and find no support for Dr. Collins' assessment that the difference between these two approaches was intended to "confuse readers deliberately."

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[10] Draeger A, Monastyrskaya K, Mohaupt M, Hoppeler H, Savolainen H, Allemann C, et al. Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia. J Pathol 2006;210:94-102.

[11] Mohaupt MG, Karas RH, Babiychuk EB, Sanchez-Freire V, Monastyrskaya K, Iyer L, et al. Association between statin-associated myopathy and skeletal muscle damage. CMAJ 2009;181:E11-8.

[12] Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 2002;137:581-5.

In fact, it is Dr. Collins who appears to have conflated serious myopathy and muscle symptoms overall on BBC:

> There have been over 100,000 patients in trials where they get either placebo or active therapy. There is a **very, very low risk of muscle problems**, there is a small increase in diabetes, but these are far outweighed in the high-risk patients, and indeed, even in the patients at lower risk – they are being considered by NICE by the reductions in the risks of heart attacks and strokes. [BBC News audio, Today Programme, May 15, 2014] [Emphasis added]

Dr. Collins repeated his conflation of serious myopathy with more common muscle symptoms in the following article that appeared in The Guardian on March 21, 2014:

> "We have really good data from over 100,000 people that show that the statins are very well tolerated. There are only one or two well-documented [problematic] side effects." **Myopathy, or muscle weakness**, occurred in one in 10,000 people, he said, and there was a small increase in diabetes. [Emphasis added]

Here Dr. Collins' equates the frequency of myopathy due to statins – defined as muscle symptoms plus blood creatine kinase levels > 10 x upper limit of normal – with "muscle weakness," a much less serious and more frequent statin-related event.

Without opining on his motives, we believe that Dr. Collins is misleading the public by underestimating the frequency of less serious and more common muscle symptoms associated with statin therapy. And we also believe that this misrepresentation will be particularly important to people at low risk of cardiovascular disease for whom statins provide no overall benefit. Thus, as a result of this review, we request that Dr. Collins correct this conflation of myopathy (by the CTT definition) and muscle symptoms related to statins in each of the media outlets in which it was made.

 Other claims of hazards are not reliable

Dr. Collins cites the 2014 article by Macedo et al. as providing evidence against a causal association of statin therapy with increased incidence of cataracts. Dr. Collins quotes the RR for cataracts at 1.01 with a 95% confidence interval of (0.86, 1.19) as appears in Macedo's supplemental Figure S10, based on 6 studies in their meta-analysis. The three "high-quality" studies give a much different perspective with what appears to be a *significant* increase in Relative Risk of approximately 1.25 (even using random effects for these three studies). The three lower quality, and generally smaller, studies are the only three which show an estimated reduction of risk although their results are necessarily variable. The three higher quality studies *incorporate 99% of the data*. It is statistically improper to turn an estimated Relative Risk of 1.25 into 1.01 on the basis of 1% of the data. The reason this happens is the use of the random effects meta-analytic approach here (and random effects only looks appealing because the three lower quality studies yield such different Relative Risks in the first place—the three higher quality studies are somewhat more consistent) which gives *22% of the weight* to the inaccurate smaller studies that contain 1% of the data.

As it happens, there is one large study here that dominates the total sample, which yields a highly statistically significant Relative Risk of 1.30 with a 95% confidence interval of (1.26, 1.35). The two cohort studies both yield significant increases in risk. There is clearly a possible association between statins and cataracts, that remains unproven at the present time, but cannot simply be made to disappear by statistical machinations.

We go into the above detail rebutting Dr. Collins' claim that "in the meta-analysis of observational studies including the hypothesis-generating study, the relative risk for cataracts is 1.01 with a 95% confidence interval of 0.86-1.1" for two reasons. First, to show that evidence from the meta-analysis cited by Dr. Collins actually supports the statement in our BMJ paper that statin therapy is associated with an increased incidence of cataracts. And second, to show that interpretation of complex papers can, without bad faith, be imprecise.

 Comments about minimizing adverse effects in trials are ill-informed

Dr. Collins notes that exclusion of patients with co-morbidities creates populations within clinical trials "that are directly relevant to normal practice." This argument loses credibility when 36% of the people who were deemed eligible to participate in the Heart Protection Study were not subsequently randomized after participating in the dual-phase pre-randomization run-in process. Furthermore, the fact that as many people were screened out during the placebo phase of the run-in period as were screened out during the statin treatment phase of the run-in period provides no reassurance that the population that ultimately participated in the Heart Protection Study is generalizable to the population of patients treated with statins in the real world.

Dr. Collins notes, "…the randomised trials typically sought and recorded all SAEs." We don't doubt that, but do note the omission of the comparative incidence of serious adverse events that occurred in the totality of studies included in the CTT meta-analysis.

 Limitations of cost-effectiveness comments

We introduced statin prices derived from the USA because US guidelines were about to be updated (although we had no inside information about either the recommendations or the timing of the update, the impending update was public knowledge). Dr. Collins suggests that we referred to PCSK9 inhibitors to "mislead readers further.' In fact, our reference to more expensive cholesterol-lowering drugs in the pipeline was included because this is directly related to the primary point of our article: that according to CTT data there is no benefit to broadening the population of people for whom statin therapy is recommended to include those with less than 20% 10-year risk of CV disease. If this undisputed finding is suppressed by retraction of our paper, surely the number of people who become potential candidates for the new classes of cholesterol-lowering drugs will increase. Because the primary finding in our article, that low-risk people do not derive an overall health benefit from statin therapy, the potential cost of new cholesterol-lowering drugs in the pipeline is highly relevant to the discussion about who should be treated with statins.

Response to "Reasons for recommending retraction of articles containing such misleading claims"

The primary reason Dr. Collins states for recommending retraction of our article is "…these claims of the side-effect rate of 18 to 20% with statin therapy are not supported by the evidence that is cited." As noted above, Zhang et al. wrote: "The rate of reported statin-related events to statins was nearly 18%...consistent with previously published observational studies." An article cited in the May 28, 2014 letter to the BMJ by Zhang, Plutzky, and Turchin by Mampuya et al. states the rate of statin-related events "has been reported as high as 20% in observational studies" (without the qualifier "uncontrolled"). This statement was supported by 6 citations. In other words, Dr. Collins recommends retraction of the article because of the distinction between "statin-related events" and "statin side effects." We agreed to retraction of the latter statement because it "did not reflect necessary caveats and did not take sufficient account of the uncontrolled nature of the study." Dr. Collins calls our statement of the side effect rate of 18 to 20% with statin therapy a "clear misrepresentation of the evidence" that supports retraction, but no such charges were made against Zhang et al. or Mampuya et al.

Patient safety is the ultimate goal. Our paper makes a significant contribution to the discourse about the benefits (or lack thereof) of statin therapy in the low-risk population. The exact frequency of statin-related adverse events is not known, but is clearly greater than zero, and observational studies show that up to 20% of people treated with statins believe that they experience a statin-related event. NHANES data show that muscle symptoms occur significantly more frequently in patients taking statins than in those not taking statins, NNH=19.1. Evidence of other side effects also exists. Low-risk patients and their physicians have the right to understand what the most complete scientific evidence shows about the balance between benefits and risks of statins. Retraction of our article would be detrimental to this goal specifically, and detrimental to scientific discourse more generally.

Response to "Potential conflicts of interest"

John Abramson has received no royalties from his book. The publisher's advance was more than consumed by pre-publication legal and editing fees. To the best of his knowledge he has not contracted with curtisbrown.co.uk, nor can he remember ever doing a speaking engagement through any such agency (the link found by Dr. Collins is probably an automatic link to Dr. Abramson's literary agent's company, ICM).

Dr. Collins concludes his note with reference to Dr. Abramson's participation as an expert in litigation:

> …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.

This is a rather unbecoming ad hominem attack, to which Dr. Abramson responds personally:

> I derive no financial benefit from this paper. I wrote in my book (first published in 2004) that the 2001 U.S. guidelines were not evidence based with regard to the efficacy of statins in women (finally admitted in the 2013 U.S. guidelines) and elderly who did not have heart disease. Dr. James Wright and I published in the Lancet in 2007 stating the same.[13] I helped organize a letter to the U.S. National Institutes of Health that led to their issuing a statement showing that 7 out of 8 members of the expert panel responsible for the 2004 update of U.S. guidelines for cholesterol-lowering had financial ties to statin-makers. I co-authored an article in 2010 pointing out the epidemiological inconsistencies in the JUPITER trial.[14] I co-authored a paper published in JAMA in 2012 titled "Clinical Trial Data Should be a Public Good."[15] I was retained as an expert in statin litigation in early 2013. Dr. Collins' accusation that I could benefit from making misleading claims about statins is without foundation.

Dr. Collins has long-standing relationships with industry, including the CTT's ongoing exclusive access to patient-level data upon which they rely for their publications. One could certainly raise questions about his motivation for remaining uncritical of industry's influence on research, arguing so strongly for retraction of our paper, and specifically wanting to discredit Dr. Abramson and Prof. Jewell.

The scientific evidence should stand for itself, without being embellished by slant attacks on personal integrity.

CONCLUDING STATEMENT

Determination of whether or not our BMJ paper should be retracted should be made based on the best interests of patient care and support of unfettered legitimate scientific debate. The primary finding of our BMJ Analysis piece is that CTT data show that statins provide no proven overall mortality benefit, and that no evidence of reduction in overall serious adverse events associated with statin therapy in the low-risk population has been presented by the CTT group or the manufacturer-sponsors of the clinical trials. This has not been challenged.

The frequency of statin-related events or adverse events associated with statin therapy is impossible to determine accurately at present, but is clearly greater than zero. We have corrected

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[13] Abramson J, Wright JM. Are Lipid-lowering guidelines evidence-based? *Lancet*, 2007: 369:168-169.

[14] de Lorgeril M, Salen P, Abramson J, et al. Cholesterol Lowering, Cardiovascular Diseases, and the Rosuvastatin-JUPITER Controversy, *Archives of Internal Medicine*, 2010; 170: 1032-1036

[15] Rodwin M, Abramson J, Clinical Trial Data is a Public Good*, Journal of the American Medical Association*, 2012;308:871-2

a miscalculation from the study by Zhang et al. and withdrawn statements about the frequency of statin-related events that lacked proper qualifying description.
Contrary to Dr. Collins' assertion, these corrections do not invalidate the primary finding of our paper, nor do they materially change the balance of benefit and harm associated with statin therapy for people with <20% 10-year risk of CVD.

We understand that the finding of no mortality benefit in the low-risk population goes against the current intellectual grain, but given the scientific rigor of our primary finding, our paper stands as an important contribution to medical knowledge and should remain in the public domain.

Potential Conflicts of Interest: John Abramson and Nicholas Jewell serve as experts in litigation, including a case involving the association between Lipitor and new onset diabetes in women. John Abramson also delivers lectures to non-profit (primarily educational) institutions for which he sometimes receives payment.

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