Response to the Editors and Reviewers

Report from The BMJ's manuscript committee meeting

* We found the topic compelling and in line with BMJ goals to help reduce research waste. We note that not much has been published about research waste in China. We were somewhat concerned about whether this is a problem that is limited to statins (perhaps because of intense commercial interest in expanding markets) or whether this is a signal of much broader research waste across multiple therapeutic areas. Perhaps you could comment on this in the discussion.

Based on our own experience, this challenge is looming over many aspects of biomedical research in China, much beyond the scope of clinical therapies. However, in this study we only present the evidence on the redundancy of clinical trials evaluating statins. More evidence is needed to claim the existence of broader research waste. In the Discussion section, we have encouraged future studies to dig deeper and wider on this issue as below:

"Fourth, our study was limited to only one drug class, one disease condition, one type of comparator, and only RCTs. Future studies are needed to evaluate the existence of research redundancy over the entire clinical trial community and the general biomedical research in mainland China."

* We do not think the search strategy is adequately reported. In particular, we are not confident that an independent researcher could reproduce the search. We also note that the search strategy seemed to focus on western databases such as pubmed and Cochrane plus one Chinese database. If you are comparing China with the rest of the world we wondered if you need to include databases that would pick up poorer small low quality trials like they have for the Chinese trials. Then there might not be such a difference. We wonder if this is a fair comparison.

We have expanded previous literature search to the four major Chinese bibliographic databases to capture more redundant trials in the revised manuscript. The search details are fully reported in Supplement 1.

* Is there a reason you did not perform some assessment of study quality such as a risk of bias

assessment? (Study quality seems a separate though related question of interest, in addition to redundancy or equipose.

We did not perform risk of bias assessment for two reasons: (1) redundant trials deprived patients in the control group of beneficial treatments regardless of their quality; all redundant trials lead to unnecessary MACEs; (2) we are not conducting a systematic review on a specific research question; a risk of bias assessment does not add to our argument.

* In general we agreed with the reviewer who says that reporting about trials outside China does not really add much given the small number of studies. However, we do wonder whether these findings are likely to be relevant to other countries with more uniform registries and ethical oversight of drug studies? What are your thoughts about India, for example? Again, perhaps something to mention in the discussion.

Per the suggestion, we have removed statin trials conducted outside China from the revised manuscript.

There are many incentives behind the massive redundancy of clinical trials, some of which are unique to mainland China. For example, doctors and nurses from both research hospitals and primary settings are under tremendous and indiscriminate pressure for research publications; more than 99% of redundant trials are published in Chinese and only indexed in Chinese bibliographic databases not accessible to English-speaking researchers. Our study is enlightening for researchers in other countries, but the discussion should be on a nation-specific, case-by-case basis because of the varying incentives. We added a short discussion to the revised manuscript as below:

"Our findings are enlightening for researchers in other countries, especially developing countries that share certain characteristics with mainland China. However, the discussion should be on a nation-specific, case-by-case basis because of the varied incentives behind research redundancy."

* Our statistician notes that "the main finding is quite striking and certainly will raise tremendous debate. "Since 2008, 1,954 redundant clinical trials had been initiated or continued recruiting, in which 87,787 patients received placebo or no treatment (control group) for 20,915 person-years"

-however, all editors agreed with his statement that "the issue is far more nuanced than the researchers make out, at least in general. Many recommendations are made for clinical practice which still need replication and validation in future studies. What if new trials do not agree with previous evidence? Furthermore, IPD meta-analyses are increasingly of interest because they allow investigators to pool IPD from multiple studies in order to examine patient-level variation in finer detail. Thus, even if the overall treatment effect has been found to be clear in previous studies, there may still need to be further data collection (in new trials) to increase sample size for an IPD meta-analysis to examine treatment-covariate interactions. Of course, the tension is that individuals in the control are then not receiving a treatment that is likely to be effective. So this is a major issue, especially if it then leads to unnecessary events, as the authors rightly point out. I'm not sure how to get the balance right, or even when to know to 'stop' new trials. The authors refer to cumulative meta-analysis, which is very useful. But often trials are done in slightly different populations, or have different primary outcomes and estimands than previous trials, which is why they are funded when previous evidence exists." Could you please comment on this and make sure that your discussion and interpretation are balanced? We do agree that patients getting inappropriate control treatment is cause for concern and debate, and a strong BMJ topic area.

This is a wonderful question. Besides the strong recommendation from clinical practice guidelines, there are two other reasons behind our choice of March/April 2008 as the timepoint to define redundancy: (1) our cumulative meta-analyses confirmed the benefits of statins by 2002/2004, years before 2008; (2) about 400 statin trials published before 2008 consistently demonstrated the benefits of statins; there was no clinical uncertainty to justify an equipoise between statins and placebo.

Several timepoints can be adapted to define redundancy, among which we chose the latest one – the release of clinical practice guidelines – rather than the earlier dates based on the cumulative meta-analyses. Moreover, we gave researchers a one-year 'gracious period' to be aware of the guidelines. Therefore, the cutoff timepoint of March/April 2008 is in fact, rather conservative. We added these arguments to the Method section of the revised manuscript as below:

"The rationale behind the choice of March/April 2008 as the cutoff timepoint was further supported by the following assumptions: (1) cumulative meta-analysis based on eligible trials had established the benefits of statins for CAD by March/April 2008; (2) the conclusion of eligible trials published before March/April 2008 were consistent, undermining the treatment uncertainties to justify subsequent clinical trials."

We also agree that the question "when is enough enough?" is very interesting and challenging. This is a question being tackled by the Evidence-Based Research Network which advocates for the explicit consideration of existing evidence when justifying a new trial and when placing new trial results in the context of what is known. In our study, the statin trials share some unique characteristics that facilitate a decision on when to stop initiating new trials. We have added a discussion of this issue to the Discussion section as below:

"Previous studies have suggested that external evidence, including systematic reviews, may be overlooked by researchers before initiating new clinical trials on similar topics. However, even if systematic reviews confirm the benefits of a treatment in the early stages of clinical research, it is challenging to know whether future trials may modify, or even reverse, that early conclusion because early trials tend to exaggerate positive findings while later trials often report reduced effect sizes. Consequently, it may not be appropriate to label some clinical trials as 'redundant' or 'unethical'. In our study, these concerns may be alleviated because the eligible trials consistently reaffirmed the benefits of statins among patients with CAD. This is quite unusual and differs from other studies using cumulative meta-analyses, in which a proportion of subsequent trials were in favor of the control group. The consistency of findings undermines the treatment uncertainties required to support the clinical equipoise to initiate subsequent clinical trials on similar topics."

* We need more information on how the extra events are derived in each group. These are based on the observed differences in risk between the control and treatment group in each trial. Differences may arise due to chance, and are subject to uncertainty. Therefore, we are confused as to how this may (or may not) impact upon the extra events derived. We wonder if additional analyses might be welcome. For example, should differences be derived based on the summary risk ratio from a meta-analysis? Or better still, use the empirical Bayes estimates of the treatment effect for each trial, which can be obtained after fitting a random-effects meta-analysis. These can then be applied to calculate the risk difference in each trial, and then the extra events derived for each trial? Also, could there be publication bias issue, such that the trials included are not a representation of all trials? Similarly, can cumulative meta-analysis be biased by this concern? These are things to consider, as the main analyses may also be sensible starting point.

This is a beautiful question. Unfortunately, a meta-analysis may not be the best tool to address the statistical uncertainty within individual trials.

(1) It is crucial for our statement to be based on evidence, i.e., what has occurred and been reported by the authors. We hesitated to extrapolate the occurrence of unnecessary clinical events to other clinical trials in which clinical events are not reported. Therefore, the unnecessary MACEs were estimated only within the included trials. On the contrary, meta-analysis assumes the included trials are a random sample of a larger pool of trials, which contradicts our assumption.
(2) The included trials in our study are rather heterogeneous. The efficacy of statins depends on many factors. For example, high-dose statins and long-time treatment schedules benefit patients more than low-dose statins and short-term treatment schedules; patients with a more severe type of coronary artery disease tend to take more advantage of statins. Therefore, the most unnecessary MACEs came from a small fraction of clinical trials in which patients with unstable angina pectoris or myocardial infarction in the statins group had been taking high-dose statins for a long time. Conducting a meta-analysis will 'average' the effect of statins over all trials, leading to underestimated unnecessary MACEs.

We applied a bootstrap method to account for the statistical uncertainty within individual trials and updated it in the revised manuscript. We assumed the distribution of risk difference in each individual trial follows a normal distribution and estimated the distribution parameters by the observed values. We ran the bootstrap1000 times to construct a 95% confidence interval of the unnecessary MACEs. The precise method of bootstrap has been added as Supplement 2.

* We agree with the reviewer who recommends removal of the quasi-randomised trials, as they dilute the message. These could be included in supplementary material, perhaps.

We have removed the quasi-randomized trials from the revised manuscript. Since less than 5% of the redundant trials were quasi-randomized, excluding those trials had a very limited impact on the result; therefore, we did not include them in supplementary materials.

* Please also consider other potential nuances when interpreting these findings. For example: Are we that sure that statins will have the same effects in Asian populations in LMIC settings as in Western countries with European ancestry? We aren't sure for drug eluting stents, for example. There is huge industry pressure to increase the use of statins so why wouldn't a

poorer country wish to make sure before prescribing these drugs to hundreds of millions of people? A guideline from the Chinese Medical Association may not settle the matter. What about the need to fully evaluate the harm to benefit balance in a particular subgroup? Might not a trial be justified?

The publication of the Chinese Medicine Association guidelines is only one of the reasons to consider those trials as redundant. About 400 statin trials conducted in China have been published by March/April 2008. Those trials have consistently reiterated the benefits of statins among patients with CAD. We believe those trials are more than enough to break the clinical equipoise. Moreover, our cumulative meta-analyses based on clinical trials conducted in China confirmed the benefits of statins since as early as 2002/2004.

As all the statin trials in the revised manuscript are conducted in mainland China, the redundant trials cannot be justified by different populations or settings. Most patients with CAD are also suffering from other comorbidities, and most statin trials recruit patients regardless of those comorbidities. We don't think restricting the patients to a specific subgroup can adequately justify randomizing patients with CAD to placebo or no treatment.

In the manuscript, we summarized the evidence as below:

"In general, there are five arguments supporting our classification of 2,045 trials as redundant. First, the release of CPGs strongly recommending statins to all patients with CAD based on 'abundant evidence' should disturb the clinical equipoise required to justify starting new trials; second, the results of our cumulative meta-analyses suggested that the cutoff timepoints of March/April 2008 were in fact conservative; third, the consistency of the results from eligible trials undermined the treatment uncertainties, as discussed above; fourth, all eligible trials were conducted in mainland China so the redundancy could not be justified by the unsatisfactory representativeness of Asian populations recruited in clinical trials in Western countries; fifth, it is also noticeable that the landmark clinical trials outside China, such as the 4S trial (Scandinavian Simvastatin Survival Study) published in 1994, were completely ignored by redundant trials."

And: In a context where nobody is receiving good medical care and "standard care" might well not include a statin is it right to say that a trial of stain vs usual care or placebo is always

unethical? Even those in the control arm are likely to receive better care than those outside the trial.

Since evidence has piled up supporting statins' benefits, including statins to treat coronary artery disease should be considered 'usual care' by clinical practitioners by March/April 2008. Many generic types of statins could be produced by domestic pharmaceutical companies at a low price and covered by health insurance. We believe the access to statins is available for most patients in China, at least for those who participated in the redundant trials.

In some underdeveloped areas of mainland China, statins may not be affordable by some patients. But this cannot justify the clinical practitioners taking advantage of those patients for a redundant trial. The wasted resource should be used to improve the access of statins to patients (the cost of statins is likely a small fraction of conducting a trial). The unnecessary MACEs could have been, at least partially, prevented by prescribing statins to vulnerable patients enrolled in the control group.

* We also think it may be unwarranted to suggest that all ongoing trials should stop early because a guideline has been published. This itself would render all those trials underpowered and "wasteful". Also, some guidelines are of poor quality or influenced by commercial entities. The majority of the trials were not focusing on clinical outcomes but presumably biochemical or imaging outcomes. Might not some of that be legitimate enquiry?

As we have addressed above, the publishing of guidelines is only one of the reasons to consider a statin trial as redundant. We may consider the publishing of guidelines as the last call to stop conducting redundant trials to hurt patients. Guidelines can make strong recommendations based on limited evidence, but this is not our case. The Chinese Medical Association guidelines explicitly underlines the abundancy of evidence on statins, which has also been confirmed by cumulative meta-analyses in our study.

As long as statins' benefits are established, it will be unethical to conduct clinical trials comparing statins with placebo, regardless of the outcomes of interest. Patients in the control group are deprived of statins for weeks or even years, so there will be an adverse effect on the wellbeing of patients even if the investigators only measured surrogate outcomes. It is not acceptable to conduct a statin trial knowing the benefits of statins but assuming a short deprivation of statins would not lead to unnecessary MACEs among patients.

On the other hand, we don't know the reasons for those trials not reporting clinical outcomes. For example, some investigators failed to report MACEs because MACEs were not their outcome of interest, or there was no statistical significance (outcome reporting bias). Still, patients in the control groups did experience unnecessary MACEs.

* Although only 10% of the published articles reported ethical approval this probably underestimates the number where approval was obtained. Our recent experience of screening papers on MedRxiv is that all the Chinese studies report ethical oversight and the country that most frequently tries to dodge this step is the UK (albeit for observational studies more than trials). Please consider that failure to report ethical approval doesn't necessarily mean that it wasn't obtained. Did you try to contact authors of trials to verify this? If not, describe this more neutrally as a reporting problem rather than assume a clear violation of ethical standards (since we don't know).

We agree that failure to report ethical approval does not mean that it was not obtained because we did not contact the authors to verify. This may merely be a reporting problem. Our study found that all statin trials conducted in China and published in English reported ethical committee approval, while most statin trials published in Chinese did not. This may explain the different findings regarding the reporting of ethical committee approval because most papers on MedRxiv are in English.

Some small hospitals and primary care settings in China do not have an ethics committee. We believe a proportion of statin trials did fail to obtain ethics committee approval, but it's challenging to estimate the exact number.

* We thought your findings raise all sorts of questions about research ethics and the incentives to publish in China. Might you comment on your thoughts about the reasons for this many studies?

The clinical practitioners in China, including doctors and nurses, are under tremendous pressure to publish research because their performance has been evaluated based on their publications rather than the clinical practice. But many of them did not receive adequate training to conduct innovative research, so what they have been doing is to copy and repeat previous studies. We have discussed this point in the revised manuscript as below:

"First, investigators may not be trained to consider existing evidence before initiating clinical trials. Although we do not know how the authors justified their trials, the fact that very few redundant trials cited systematic reviews or previous trials suggests a lack of appreciation on prior evidence. Second, investigators are under tremendous pressure to produce publications. This may also explain why only 20% of included trials reported clinical events: it is much easier and faster to conduct clinical trials on surrogate laboratory outcomes. Third, where ethics approval is reported, the committees reviewing trial protocols failed in their responsibility to check the scientific foundation and protect participants from enrolling in harmful trials. Currently, the requirement of an ethics committee approval by the China State Food and Drug Administration only covers clinical trials for the marketing license of drugs. Moreover, many redundant trials were conducted in primary care settings where an ethics committee was not feasible. Therefore, some redundant trials might fail to obtain any ethical approval at all. Fourth, some journal editors fail to evaluate the scientific value of the publications adequately. By accepting manuscripts from such trials, those journals provided a means for redundant trials to be published, thereby validated the redundancy as acceptable. It is suspected that those journals may be more interested in pursuing profits rather than scientific merits. Fifth, only a small proportion of trials reported funding source, most of which were either central or local government agencies, who failed to evaluate the scientific value of the redundant trials before providing funding. Last, none of included trials were registered in trial registries, of which a function is to reduce resource waste by declaring and presenting what has been conducted and what is currently being done in the clinical trial community."

** Comments from the external peer reviewers**

Reviewer: 1
Comments:
This is an interesting and well-written manuscript describing the number of MACE owing to not providing statin treatment to the control group of clinical trials on coronary artery disease patients conducted in China after clinical practice guidelines supporting the use of these drugs in this indication were issued. The control group received either placebo or no treatment. It is an important work since it describes the many Chinese clinical investigators that have conducted trials that harmed participants. This is a topic that is seldom address and that needs more attention.
The methodology used in this analysis is correct and the interpretation of the findings are basically correct. However, I believe that since most (90%) of the clinical trials were not approved by the relevant REC, the authors need to provide some more info regarding the Chinese

regulation on clinical trials (do they need REC approval? If so, when this regulation was implemented?...) that is most likely unknown to the vast majority of potential readers.
I think this work deserves publication but need to consider two important modifications. First, it is unclear why quasi RCTs were included in the analysis. Since 97% of all studies were RCTs, data provided by quasi RCTs should, most likely, be negligible. Second, it is also unclear the need to include 78 non-Chinese trials in this analysis. The data provided by these trials is of very limited interest. Furthermore, since readers do not know in which countries these trials were conducted and when the relevant clinical practice guidelines were issued in those countries, they cannot correctly contextualize the findings. Inclusion of these 78 trials in the manuscript raises more questions than answers and, honestly, there is no need to include them in this analysis, which merit lies on describing what happened in China. I strongly suggest to omitting all data from all quasi RCTs and from the 78 non-Chinese trials.
Other suggestions.
There are too many acronyms that make reading anything but user friendly.

Thank you for the wonderful suggestions. In the revised manuscript:

1. We have removed quasi-randomized trials;
2. We have removed randomized trials conducted outside China;
3. We have spelled out all the synonyms except for the disease conditions;
4. We added some background information about the current situation of ethical approval in China to the Discussion section as below:

"Currently, the requirement of an ethics committee approval by the China State Food and Drug Administration only covers clinical trials for the marketing license of drugs. Moreover, many redundant trials were conducted in primary care settings where an ethics committee was not feasible. Therefore, some redundant trials might fail to obtain any ethical approval at all."

One decimal is enough; using 2 decimals is of no interest.

We have kept only one decimal in the revised manuscript.

Page 1/25 Line 49. The authors mentioned that China is the biggest producer of scientific publication. However, it would be more informative to refer to the China production on clinical trials, since this is the subject of the work.

We would love to provide the number of clinical trials conducted in China. However, we did not find a high-quality reference that addresses this question.

Page 2/25. Line 3. I think authors should inform here (to prevent misunderstandings) on the types of treatment (placebo, no treatment) received by patients of the control group.

We have added 'without statins' to prevent misunderstanding.

Page 2/25. Line 25. I do believe that here the authors should be more cautious. I suggest something like the following: "Clinical trials conducted thereafter may be redundant and raising concerns unethical about ethics".

Thank you for the suggestion. As we have reconstructed the Abstract, this sentence was deleted from the revised manuscript.

Page 3/25. Line 26. The authors stated: "The scale of redundancy may be much larger in the entire clinical research community,..." To whom they are referring with 'the entire clinical research community...'? Are the authors referring to all clinical trials assessing all types of medicines and devices? I think the authors should not speculate here —although I agree with their statement.

We have removed this argument from the revised manuscript because we do not have evidence for it, although this argument is very likely true.

Page 3/25. Line 39—56. I agree on how the issue is explained. However, there is something lacking: clinical equipoise is needed at study start —otherwise it is unethical to run it. Yet equipoise refers to the clinical setting in which the trial is going to be conducted. If there are differences (eg, ethnic/genetic, special populations) between previous trials and the one to be conducted, then investigators and RECs could consider that clinical equipoise exists, and the trial can be conducted. I believe that this scenario should be an exception but could happen. I mention this for the authors to consider.

Thank you for the suggestion. It is possible to justify a clinical trial on a different population or subgroup; however, most redundant trials in our study cannot be justified by this argument.

About 400 statin trials conducted in mainland China were published by March/April 2008. Those trials are more than enough to establish the benefits of statins, which is confirmed by cumulative meta-analyses of RCTS conducted in China. On the other hand, most patients with CAD are also suffering from other comorbidities, and most statin trials recruit patients regardless of those comorbidities. Therefore, we don't think the redundant trials can be justified by the population or a subgroup.

I suggest that the fact that only 249 (10.04%) of trials were approved by RECs should be mentioned here. It is a very relevant finding that helps readers to understand the context.

We prefer not to add this to the Abstract owing to the word count limit. Although most redundant trials failed to report ethics committee approval, we don't know if those trials failed to obtain approval, or they did not report it.

Page 4/25. Lines 33—35. I think it is not relevant to refer to 'scientific publication from China'. In this statement papers on physics, chemistry, etc, which are of no interest here. I suggest that the authors should refer only to clinical trials, the subject of their work.

We would like to provide the number of clinical trials conducted in mainland China. However, we did not find a high-quality reference for this number.

Page 5/25. Lines 7—9. This first sentence could be removed since the info is included in lines 14—16.

Thank you for pointing this out. We have removed the duplicate statement.

Line 25. A short definition of 'quasi RCT' would be appreciated by many readers (if the authors maintain them in the revised version. As I mentioned above, I suggest to omitting these studies in the revised version of this manuscript)

We have removed quasi-RCTs from the revised manuscript.

Lines 27—37. The authors should mention whether the mentioned diagnoses were included (eg SAP) or not (ischemic heart failure) on the CPGs.

In the Method section, we have stated that the two clinical practice guidelines cover all types of CAD:

"We conducted a literature review to identify eligible trials, defined as RCTs comparing statins with placebo or no treatment among patients with CAD, including stable angina pectoris (SAP) and acute coronary syndrome (ACS)."

"In March and April 2007, two CPGs developed by the Chinese Society of Cardiology of the Chinese Medical Association were published, which strongly recommended (based on Grade A evidence) statins therapy for patients with SAP and ACS, respectively."

Lines 37—40. Where all the 7 mentioned statins mentioned on the CPGs, and all recommended for all indications?
In addition, were all the 7 statins included in the CPGs tested in Chinese patients for all indications (SAP, ACS, UAP, MI) included in this analysis? In other words, maybe statin X was not tested in a placebo-controlled trial in China when it was included in the CPGs for indication Y…in this case, running a placebo-controlled trial will be ethically correct.

The seven types of statins share the same pharmacological process and biological functions. In the clinical practice guidelines (both in China and Western countries), they are always referred to together as 'statins'. Statins are recommended for patients with CAD regardless of the type, although some new types are preferred due to better safety profiles. For example, atorvastatin and rosuvastatin are preferred over lovastatin.

Because of their similarity, once the benefits of a type of statins is confirmed, the appropriate way to evaluate other types of statins becomes to conduct active-control randomized trials, i.e., to compare a new type of statins with an old type. Remember that all redundant trials in our study used a placebo or no treatment as control, which completely deprived patients of a beneficial treatment.

Page 6/25. Line 8. And Page 7/25 Line 46. Including trials outside of China could be difficult to interpret and misleading. CPGs in other countries could have been issued in different years than the Chinese CPGs and even including different statins. This would meant that perhaps, one or more of these trials were ethically correct (clinical equipoise) since the drug was not tested for a given indication before and were not included in the CPGs. How did authors take this into account?

We have removed the statin trials outside China from the revised manuscript.

Lines 42—44. Why sample size was extracted only from trials outside China?

We have removed the statin trials outside China from the revised manuscript.

Page 8/25. Line 40. I think the flow chart of the 78 non-Chinese trials should be showed in the manuscript. The country of origin (where were these trials run) is relevant. The year when CPGs on the use of statins for CAD of each country were issued should also be provided. (This should be done if authors maintain this info in their manuscript. As mentioned before, I suggest to omitting anything referring to these 78 trials).

We have removed the statin trials conducted outside China from the revised manuscript.

Page 9/25. Line 10. If 96.98% of studies were RCTs, I wonder why quasi RCTs were also included in this analysis. I think the work should be focused on describing only RCTs. What do quasi RCTs data actually add to this work?

We have removed the quasi-RCTs from the revised manuscript.

Line 15. Only 249 (10.04%) of trials were approved by RECs. How many of these 249 were approved before the CPGs were issued? How many of all the rest were run after the CPGs were issued?

This is a great suggestion. We have provided the percentage of trials that reported ethics committee approval among redundant trials and 'non-redundant' trials separately in the revised manuscript as Table 1.

Page 10/25. Line 13. The authors refer to 'mainland' China, and to 'inside' China all along the manuscript. What is the difference between mainland and inside here? I presume mainland refers to China except Hong Kong (or you refer only/also to Hainan?). Am I correct? Authors should consider explaining this to the wide audience of The BMJ.

We have revised the wording to make the terms consistent. Mainland China includes Hanan, but not Hong Kong or Macau. There is a sensitive debate over the status of

Taiwan, so we prefer not to explicitly define mainland China in the manuscript to avoid political issues.

Page 12/25. Lines 40—43. The authors should mention the actual figures instead of mentioning 'thousands' which is not very informative.

We have provided the exact number here in the revised manuscript.

Page 13/25. Line 15. I would suggest that in addition to include references from western countries, the authors should include a refence from China on the need of having a REC approval before the start of any clinical trial. Most readers will not know when this requirement was mandated in China, something that will help contextualize the lack of REC approval for some 90% of trials —a (negative) striking finding indeed!

We have provided a reference for the REC requirement of clinical trials in mainland China and some discussion about the fact that clinical trials in mainland China may be conducted without approval from an ethics committee.

Line 25. Predatory journals. The authors should be more specific on this. The important figure here is not whether there were some (n=5, 15…?) predatory journals publishing these papers, but how many trials (5%, 50%...?) were actually published on predatory journals.

We removed this point from the revised manuscript because we do not have evidence to support this argument. We did not evaluate the specific journals publishing these trials, so we do not know which journals were predatory or how many redundant trials were published in predatory journals. It is beyond the scope of this study.

Line 33. The authors should inform readers if Chinese regulation mandates (and since when) registration of clinical trials. Any comment here on the Chinese clinical trial registry?

Currently, the government or academic organizations in mainland China do not require investigators to register clinical trials in a primary registry, such as ClinicalTrials.gov or the Chinese Clinical Trial Registry. The only incentive is the requirement of English journals.

Page 16. If the authors decide to leave the 78 non-Chinese trials in this analysis, then they should mention as a limitation the fact that they did not take into account when were issued the CPGs of the countries where these trials were conducted.

We have removed the non-Chinese trials from the revised manuscript.

Lines 18—20. Seems REC legislation is lacking in China. Does this mean that currently clinical trials can be conducted in China without prior REC approval? The authors should comment on this.

Based on our experience, clinical trials can be conducted in China without ethics committee; we did find a reference to support this argument. We now mentioned this in the Discussion section as below:

"Currently, the requirement of an ethics committee approval by the China State Food and Drug Administration only covers clinical trials for the marketing license of drugs. Moreover, many redundant trials were conducted in primary care settings where an ethics committee was not feasible. Therefore, some redundant trials might fail to obtain any ethical approval at all."

Lines 33-39 The authors should consider mentioning figures here, maybe not exact figures not to be redundant, but approximate figures.

We have added figures in the revised manuscript as below:

"More than 2,000 redundant clinical trials on statins among patients with CAD were identified from mainland China. Such trials have been harming patients, who have experienced more than 3,000 unnecessary MACEs, including nearly 600 deaths. The scale of redundancy necessitates urgent reform to protect patients."

Lines 40-43. See comments above

We have added figures in the revised manuscript, please see above.

Fig 2 & 3. Why there are non-Chinese trials included since 1993? Maybe some of these trials vs placebo were complying with clinical equipoise on those dates and in those countries. As I mentioned above, I suggest to omitting all the data regarding these non-Chinese trials.

We have removed the non-Chinese trials from the revised manuscript.

Reviewer: 2
Comments:
This is a very important study describing serious flaws in the regulation of clinical trials in China. It is well written. Being neither a cardiologist nor a native English speaker I cannot comment on these issues.
General comments:
The Abstract does not cover the content of the paper, e.g. the CMAs are not mentioned. The figures presented on pages 23-25 are not numbered and not mentioned it the main text (unless I have overlooked it).
For the readers it may be interesting to learn when the statins were authorized by the SFDA for the use in China.

Most of the statin trials conducted in China were not conducted for a marketing license. They could be conducted only after the corresponding statins were approved by the Chinese authority, i.e., the State Food and Drug Administration (SFDA). Unfortunately, we could not find the date when the first type of statins was approved by SFDA through either SFDA's website or published literature.

In the discussion I missed a couple of comments:
1) I assume some underestimation of the adverse outcomes by not considering the potential enduring negative longterm effects after the end of a trial.

This is a good point. Not considering the long-term benefits of statins is likely to underestimate the extra MACEs. We added this point to the Discussion section of the revised manuscript as below:

"Second, clinical trials with limited follow-up may not capture the long-term benefits of statins, leading to underestimated treatment effect and extra MACEs."

2) on the trials done outside China.

The statin trials from outside China have been removed from the manuscript.

3) Why are investigators in the PRC so keen on doing redundant trials? Is there an incentive for doing so?

In mainland China, the performance of clinical practitioners is evaluated based on their scientific publications. Typically, a certain number of publications, either in Chinese or English, are required for their promotion. We believe that the desire for publications is a primary factor leading to the massive scale of redundant trials.

4) an explanation why most trials were done with atorvastatin? Is there a negative impact by commercial sponsors?

This may be because atorvastatin is the most popular type of statins worldwide. We are not sure about the impact of commercial sponsors.

Title: If it is true what the authors describe the word challenging sounds to me a bit inappropriate as being to weak. Think about ignores, neglects, contradicts etc.

We have revised the Title to be more direct and simple as below:

"Redundant Clinical Trials Are Hurting Patients

An Example of Randomized Clinical Trials Conducted in mainland China Evaluating Statins among Patients with Coronary Artery Disease"

p.2, Line 25: may be: to weak, as above.

We have removed this part from the Abstract.

p.3, Line 51: better: no known evidence based treatment option...

We have revised this sentence to make it clearer.

p.5, Line 7-19: can be shortened: no need to write twice that no REC needed to be consulted.

The redundant sentence was removed from the manuscript.

p.5, Line 25: please explain in a few words what quasi randomized trials are.

Per reviewer suggestion, we have removed quasi-randomized trials from the revised analyses and manuscript.

p.6, Line 15-27: It is common to specify the search terms used. How was the search done for the trials done outside China?

We have added the search details in Supplement 1. We have removed the statin trials conducted outside of China from the revised manuscript.

p.9, what did trial not reported clinical events report at all?

Those trials reported surrogate endpoints, such as laboratory test results, or self-defined clinical outcomes, such as 'effective' and 'not effective'.

p.9, Line 18-20 number of days should not be analysed using a chi square test.

We have removed this test, thank you.

p.12, Line 16-30. As I understand the CMAs showed for trials in China that statins work. If my understanding is correct, please add that the CMAs showed the benefit for chinese patients in China.

We have added text to highlight that the cumulative meta-analyses were solely based on randomized trials in mainland China.

I missed a few lines regarding the trials done /identified outside China.
p. 23-25 Figures: Could you please provide the outcome/endpoint used in these three CMAs.

We have provided the outcome used in our cumulative meta-analyses.

The references of all trials mentioned should be provided in an appendix available in the web.

The purpose of our study is to reveal the existence of redundant clinical trials conducted in mainland China, rather than to accuse individual investigators of conducting redundant trials. We defer to the editors but would thus prefer to not include the specific references for trials identified as redundant. Perhaps we could provide list upon request?