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Redundant Clinical Trials Challenging Research Ethics and Hurting Patients: An Example of Clinical Trials Conducted in China Evaluating Statins among Patients with Coronary Artery Disease

Dear Mr. Jia,

I write with some good news! Thank you for sending us your appeal on this paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with it, provided you are willing and able to revise it as explained below in the report from the manuscript meeting. We will make a final decision about publication once we see the revised paper.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Yours sincerely,

Dr Elizabeth Loder

Start the revision process: *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Wim Weber (chair); Richard Riley (statistician); Tiago Villanueva; David Ludwig; Joseph Ross; Elizabeth Loder

Decision: Request revisions before final decision. Revision to be seen and approved by several senior editors.

* 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.

* 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.

* 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.

* 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.

* 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.

* 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.

* 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.

* 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?

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.

* 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?

* 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 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?

In your response, please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

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

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.

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.

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.

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

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)

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

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.

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?

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

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).

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?

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?

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.

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

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!

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.

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?

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.

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.

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

Lines 40-43. See comments 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.

Additional Questions:
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Please enter your name: Rafael Dal Re

Job Title: Senior investigator

Institution: Health Research Institute-Fundacion Jimenez Diaz University Hospital, Universidad Autónoma de Madrid, Madrid, Spain

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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.
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.
2) on the trials done outside China.
3) Why are investigators in the PRC so keen on doing redundant trials? Is there an incentive for doing so?
4) an explanation why most trials were done with atorvastatin? Is there a negative impact by 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.
p.2, Line 25: may be: to weak, as above.
p.3, Line 51: better: no known evidence based treatment option...
p.5, Line 7-19: can be shortened: no need to write twice that no REC needed to be consulted.
p.5, Line 25: please explain in a few words what quasi randomized trials are.
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?
p.9, what did trial not reported clinical events report at all?
p.9, Line 18-20 number of days should not be analysed using a chi square test.
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.
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.

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

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If you have any competing interests (please see BMJ policy) please declare them here: I am president of the Association of Medical Ethics Committees in Germany and I have a strong interest that waste in clinical research gets reduced.