Subject: BMJ - Decision on Manuscript ID BMJ.2015.030236

Body: 04-Jan-2016

Dear Dr. Azoulay

Manuscript ID BMJ.2015.030236 entitled "Pioglitazone use and bladder cancer risk: a population-based cohort study"

Thank you for sending us your paper, manuscript # XXX entitled "YYY" We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Jessamy Bagenal
jbagenal@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=0e3de3dd553648919c130ecc51d2bca1

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.

Members of the committee were: Chair: Wim Weber, Statistician: Tobias Kurth, Jose Merino, Elizabeth Loader, Tiago Vialleneuva, Mihnas Rubin, Roeggla George

Decision: Put points
Comments from the virtual meeting:

In general comments were supportive and editors felt this was a live topic and a well performed study, this was based on fairly supportive reviews.

Many of the reviewers had concerns about the novelty of this submission, and this was discussed again at our meeting. However, it was an editorial decision that this paper did add sufficiently and was still a very important issue given the different results out there. But it would be good if the authors could address some the issues raised about novelty by the reviewers.

There was also a discussion following the reviewers comments about the lack of information about how important confounders were handled, and several of the editors had similar concerns. However, it was felt that many of the reviewers comments were addressable.

It was an editorial decision that the concerns raised about ethics was not a priority given there is mention a statement from the Clinical Practice Research Datalink committee in the UK and a vote from Canada
First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

* Please clarify what is meant by misclassification being possible because of CPRD recording prescriptions written by GP's and not those filled or taken by patients. The GPs on the editorial board felt that pioglitazone is not something they would start the patient on since it is a niche drug (but rather an Endocrinologist would do), but they are likely to prescribe the refills.

*We would particularly like you to respond and address the points made by the reviewer Bell

* There were mixed reviews about confounders and we'd like some more clarification about how they were handled. Specifically our statistician's main concern is the use of time varying Cox models. In this model only the main exposure was updated but not the covariates. This may have been done because of concerns of inappropriate control of "time varying" confounders, which is a relevant concern. However, here, it remains the question whether confounding is adequately addressed.

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

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
Pioglitazone use and bladder cancer risk: a population-based cohort study by Tuccori et al.
The authors look to clarify uncertainty about the relationship and strength of association between pioglitazone use and bladder cancer. This follows several large reports (n=193,099 [20]) of conflicting data regarding this issue. In this work, the authors do find a link between the drug and subsequent bladder cancer (HR: 1.63, 95% CI: 1.22 to 2.19). They compare the findings with those for rosiglitazone. The large size/follow up allows a relevant sensitivity analysis that further supports the direct association.

The strengths of this report are the design (large cohort, clear inclusion criteria (newly treated), homogenous population and follow up rates). Weaknesses include the lack of granularity of the CPRD dataset and lack of novelty of the topic. For example, the authors adjust for many confounders in their model, but miss many that are relevant for bladder cancer aetiology. Specific missing data include occupation (page 8 lines 6-25; as the second commonest cause of bladder cancer), and pelvic radiotherapy.

Overall this work is a welcome addition to this field, but i wonder if it is enough to overturn the pre-exsiting conflicts. Certainly the sensitivity analysis are very convincing.

Comments:
1. How was smoking data handled? A binary Yes/No will be insufficient in this analysis
2. Please explain "Pioglitazone users were …more likely to have prior bladder conditions" (page 11 and table 1). This is a concern (to my mind), as many patients with bladder cancer (esp. CIS) are misdiagnosed in the community with benign bladder conditions. To explore this, please look at the time from entry to bladder cancer diagnosis in patients with & without prior bladder conditions. Is there a difference? If the cancer diagnosis occurs within 3 years of entry – then I suspect these patients had occult malignancy at entry. Would the 2.9% difference in the rate of prior symptoms explain your findings? I do note no difference between the pioglitazone and rosiglitazone population, in this respect (sup table 5), but this is a smaller sample size.

3. With concerns to misclassification of cancer (page 15, lines 8-15) – could you cross the CPRD with relevant UK cancer registries?
4. Please detail the time between starting an anti-diabetic agent and the bladder cancer diagnosis in all cohorts. This is not clear from your data

Jim Catto

Additional Questions:
Please enter your name: James Catto

Job Title: Professor of Urological Surgery

Institution: University of Sheffield

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
Originality

Although the authors cite previous work suggesting a risk of bladder cancer in patients taking a certain anti-diabetic drug, this is a major study which adds value to what was previously known.

Importance

Since diabetes is a widespread and potentially fatal disease, this study is important since it investigates a cancer risk associated with the diabetes treatment.

Scientific reliability

The study appears to be very reliable since it uses standard methodology, with a very large number of patients and a large number of cancer cases, and has obtained statistically significant results.

Overall design

Excellent - see comments in the previous paragraph.

Participants studied

The participants are appropriate to the research question.

Methods - including ethics

I think the methods are absolutely fine, but I have some concerns about the ethics. If the patients studied are UK residents there needs to be ethical approval from a UK research ethics committee (REC) approved by the Health Research Authority (HRA) - approval by the ethics committee of a Montreal hospital is not sufficient, nor is one by an advisory committee for the database used (CPRD).

Were any identifiable data sent to Canada? The HRA requires that REC approval be given for any export of identifiable data outside the European Union.

I don't see any mention of how many patients were excluded because they did not consent to inclusion, which prompts the question of whether they were asked for consent. Under UK law the use of patient data without consent may be not just unethical but actually illegal if it is in breach of a legal duty of confidentiality. There is a way round this if a regulatory body (Confidentiality Advisory Group or Health and Social Care Information Centre) gives permission for research to be carried out without participants' consent, so we need to know whether such consent was obtained.

It may be that the custodians of the database have obtained a general ethical approval covering not only the present study but also any others using the database. If this is the case then the manuscript should say so, and give the name of the approving REC. It may be that the database only includes patients who have consented (on either an opt-in or opt-out basis) so that no legal exemption for patient consent is necessary. Again the MS should say if this is the case.

In short, the paper needs to give enough information to provide assurance of ethical approval and legality for the present study, which will also remind readers, if they need reminding, of the need to careful of such matters in their own research.

Results

The results of the study are clearly set out.

Interpretation and conclusions

The conclusion that one of the drugs studied has a causative link to bladder cancer appears to be well justified.

Abstract

This is a fair summary of the study and its conclusions.

Additional Questions:
Please enter your name: Trevor Benn

Job Title: Retired Statistician

Institution: Retired

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: None - I don't know the authors, nor do I have any connection with their institution or any drug company

Reviewer: 3

Recommendation:

Comments:
Review of "Pioglitazone use and bladder cancer risk: a population based cohort study"

Dr Ian Clements 19th November, 2015
This paper is of immense importance to patients who have diabetes type 2 and are presented with the option of being treated with either pioglitazone or rosiglitazone to control this co-morbidity. Earlier studies have found conflicting outcomes regarding the former increasing the risk of bladder cancer; this has caused concern amongst both doctors and the patients (some of whom I believe have sued on the basis of their bladder cancer). These disparate results may have been because of smaller numbers, shorter time-spans, no comparison drug, or poor research design. This paper notes this, and addresses the issues by having many more patients than those earlier studies, and covering a longer time-span – over 15 years.
As well as determining whether pioglitazone increased the risk of bladder cancer, they were also able to make a meaningful comparison with the similar (of the same class) aforementioned alternative – to the latter's advantage.
The authors seem to have addressed most, if not all, of the significant confounding factors and explained why some missed would probably be an insignificant influence on their conclusions: that pioglitazone use increases the risk of bladder cancer. This effectively resolves the uncertainty that resulted from the conflicting results of the earlier studies and will be a welcome piece of information for all type 2 diabetic patients who may be offered this drug.
On the issue of areas relevant to patients that are missing seems to be the researchers purposefully excluding patients from all stages of the design and, most oddly to me, "There are no plans to involve patients in the dissemination of results." There is no explanation for this, other than the implicit one that none in the intended audience would find it odd. The implication is that only doctors would know of these results, and then only if they chance to read about this research and then may tell their patients – this appears contrary to patients being able to give fully informed consent to the usage of pioglitazone. Whilst I appreciate that this research may well need to be filtered via the regulatory regimes such as NICE in the UK, and, if the results are accepted by them, perhaps made mandatory (that this drug not be used); but until then, patients are put at unnecessary risk and may successfully sue. I suggest that given the wide applicability of the conclusions – that use of pioglitazone increases the risk of bladder cancer and that this is a drug that may be offered to any diabetic patient – then perhaps the authors ought to have advocated wide publicity.
The challenge that patients face as a result of this, and all too much medical research, is knowing about it before they are called upon to make a fully informed decision. Given that there is at least one alternative drug which appears as

efficacious, this is a pity.
The only reference omissions I found were two meta-analyses
"Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting" and
"Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies"
Both of which supported this study's conclusion.

Additional Questions:
Please enter your name: Dr Ian Clements

Job Title: Patient reviewer

Institution: Consumer for NCIN Urology SSCRG

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 4

Recommendation:

Comments:
The article from Tuccori et al. contributes to address an important issue concerning the risk of bladder cancer following pioglitazone use. This is a very important topic since many observational studies have been conducted during last few years, however with controversial results on the risk estimates for bladder cancer (as also acknowledged by the authors), both for methodological limitations or for residual confounding.
The present study run in the UK setting is conducted also with the attempt to overcome methodological limitations such as the "disease latency" and the drug exposure as time-varying variable. However, some subgroup analyses remain to be performed to further challenge the robustness of results and to increase the data reliability.
Specific issues are following:
Firstly, risk estimates of bladder cancer should be presented through a specific analysis by the three subgroup populations: i) incident users of antidiabetics; ii) switchers; iii) add-on therapy.
In addition, a description of the ascertainment of use for each antidiabetics during the follow up (in the two periods, i.e. in the 1-year latency period and in the post latency period) should be provided in full (also as an adherence measure e.g. MPR if possible). Details on definition of exposure over time should be provided. To be clear: for example, an incident user of pioglitazone should have filled how many prescriptions per month (or per quarter or per year) to be considered on treatment? Similarly a definition of switchers should be included in the methods.

Secondly, a subgroup analysis between the two groups (pioglitazone and no-TZD users) to show how risk estimates varies according to a series of variables, also considered as confounders, should be included. Specifically, the effect of age, BMI, smoking, HbA1C, duration of treated diabetes, Charlson index, previous antidiabetic drugs, should be evaluated.
Moreover, the difference between the groups in the "duration of diabetes treated" and previous use in metformin should be further elaborated, since for metformin has been postulated a protective role for cancer and diabetes itself is a risk factor for cancer.
Table 2: please provide the full adj HR including also the previous use of antidiabetics in the model.
Finally, given the etiology of cancer is complex please try to extend the latency period from 1 to 2 years in a sensitivity analysis.

Additional Questions:
Please enter your name: Francesco Trotta

Job Title: Dr

Institution: Department of Epidemiology, Regional Health Service, Lazio

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I consider the first authors as a good friend and selected researcher, which may influence my judgment, even though this is a nice study.

Reviewer: 5

Recommendation:

Comments:
Thank you for submitting this paper to the BMJ. This is an interesting topic and a well written paper.

I have three areas of concern.

1) There have been a number of studies looking at the association of pioglitazone and bladder Cancer. The paper does not really explain why this paper is important and worthy of publication in the BMJ. Is pioglizatone still being used in the UK - what were the regulatory actions? Do we want to use this drug more because it is a more useful drug? Should urologists be screening patients that have been exposed to the drug? Is this still a relevant story???

2) Given the number of studies and their conflicting studies is this paper definitive in its findings or is it adding to the noise? The statistical analyses appear to be very

credible and probably represent the best that can be achieved retrospectively. Why were patients younger than 40 excluded from the study? Patients younger than 40 still get UCC albeit rarely?

3) Currently there is very little biological data to support the findings cited by the authors. Have there been any animal studies using the drug? What about genotyping the tumours or patients (like aristolochic acid)?

Suggestions for improvement:

Please can the manuscript explain what happened to pioglitazone after the controversy of the risk of UCC broke? Was the product withdrawn from the UK or other parts of the world? Is it still being prescribed in the UK? More detail here would improve the appeal of the paper to the journal's general readership.

How beneficial is pioglitazone to diabetics? For example is this drug very beneficial and therefore it is important to establish its safety so it can be used. If there are other drugs that are equally beneficial - why still study the possible carcinogenic effect of this drug?

Possible biological explanation for the observed affect of pioglitazone:

It is difficult to imagine that Urothelial cell carcinoma is being induced after such a short exposure time. Can this be supported by citing other carcinogens in UCC or other cancers? UCC is known after exposure to other drugs e.g. aristolochic acid et al. What are their exposure times???

Additional Questions:
Please enter your name: Aidan Noon

Job Title: Consultant Urological Surgeon

Institution: The Royal Hallamshire Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 6

Recommendation:

Comments:
The authors report the results of a population-based cohort study with the aim of identifying an association between the use of pioglitazone and bladder cancer. They

find an association that exists for pioglitazone but not for rosiglitazone, demonstrating that the association is specific to pioglitazone and not consistent across the drug class.

This study is designed to address some of the shortcomings of existing studies in the area – in particular a set of methodological issues that may have contributed to different results in previous studies.
I was particularly interested in two aspects of the study, where I thought there may be some issues in the methods. The first was the presence of a sensitivity analysis, which is necessary where there are a series of potentially arbitrary choices about how to decide on the inclusion and exclusion criteria, and the definitions for exposure and outcome. I could not find any specific fault in the sensitivity analysis, and I note that the results were relatively consistent when those decisions were relaxed or modified.

The second aspect was unmeasured confounders, which could invalidate the results. The method used to address unmeasured confounders appears reasonable and I did not find any faults or issues.
It may be asking too much to include further analysis in the text, and it does not appear to present a particular risk to the study, but I did note that rosiglitazone use in the cohort dropped off rapidly by about 2007/8 while pioglitazone faced a steadier decline. Is there any chance that further differences in practice between 2007 and 2010 might have contributed to the differences in the outcome measure? Was there a specific reason not to use pairwise comparison?

The comparison with other studies is clear and identifying the biases and methodological differences across the set of existing studies appears reasonable. While I don't think it is necessary to report, there appears to be a reasonably clear association between the conclusions made in the studies reporting on bladder cancer and pioglitazone (refs 4 to 14) and the sources of funding and competing interests in those studies. Beyond the biases that have been reported, it is possible that conflicts of interest are an underlying source of bias that predisposed authors to (a) particular study designs; and (b) conclusion statements that include obvious "spin".

As hard as I looked, I was unable to find anything specifically problematic with the manuscript, and I felt that any places where problems may have been introduced were more than adequately covered and described by the authors. I wonder if the BMJ policy on access to patient data is relevant here. Overall, I felt the study was excellent, addressed an important topic, and I could find no faults in the work.

Additional Questions:
Please enter your name: Adam Dunn

Job Title: Senior Research Fellow

Institution: Macquarie University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: None

Reviewer: 7

Recommendation:

Comments:
General Comments
This well written and interesting paper reports on the apparent association between pioglitazone use and incident bladder cancer in a large population based cohort of adults resident in the U.K. The authors could address the following comments to make the paper more convincing.

Major Comments
1. From the results presented for year of cohort entry, it appears that the length of follow-up of patients may differ between the categories of TZD users. It is possible that pioglitazone users may have been followed up for longer than non-pioglitazone users, and that this might contribute to a higher rate of incident bladder cancer diagnosis. The multivariate models currently adjust for year of cohort entry, but that may not entirely capture differences in length of follow-up. It would be helpful to have information on the duration of follow-up available for pioglitazone users, rioglitazone users and non TZD users (added to Table 1 and Supplementary Table 5). Are you also able to adjust for potential differences in length of follow-up in the models?
2. I am also uncertain whether the dose response relationships found with the cumulative duration and cumulative dose variables might be confounded by duration of follow-up – are patients with a lower cumulative duration or dose of pioglitazone also followed up for a shorter period of time, with less chance to develop bladder cancer? Please explain how you have allowed for this in your analysis.
3. I think that the pioglitazone versus rioglitazone head to head comparison theoretically would provide the most compelling evidence for a causal association between pioglitazone and bladder cancer, as there should be a lower risk of imbalance in potential confounders between these two groups of patients. For this comparison I note that the statistical evidence for a difference in association is much less strong (lower confidence limit 1.01 for main model and 0.94 for sub-cohort model). I note from Supplementary Figure 4 that more pioglitazone new users were trimmed due to non-overlapping propensity score distributions than rioglitazone new users. Did you also do analysis without including propensity scores? Were the sensitivity analyses also done for the head to head comparison?
4. Did you consider sensitivity analyses examining associations with a different cancer (or other outcome) you would not expect to be associated with pioglitazone use? If such an analysis demonstrated no association this would add support to your findings that there is a real association with incident bladder cancer.

Minor Comments
1. Please comment on whether all assumptions for the models were tested and whether they were found to hold.
2. Why were the data for year of cohort entry suppressed for new pioglitazone users for 2000 and 2001? Why were there no patients started on rosiglitazone after 2010?
3. Please make it clearer that pioglitazone and rosiglitazone users in Table 1 and Supplementary Table 1 respectively refer to new users at cohort entry, whereas Table 3, and Supplementary Table 5 refer to new users at any time from cohort entry until end of follow-up.
4. In the Methods, Based cohort, please provide justification for why you excluded patients with more advanced form of type 2 DM (as indicated by prescription of insulin). You mention this in the Discussion in relation to other studies' short comings, but it would also be helpful to explain this here.

5. Please define immortal time bias
6. For the dose-response relationship for pioglitazone, was the risk of bladder cancer with cumulative doses below 10,500 mg, as well as above 28,000 mg higher than for doses in between? If so, do you have an explanation for this?
7. Figures need titles as well as legends.

Additional Questions:
Please enter your name: Katy Bell

Job Title: NHMRC Early Career Research Fellow

Institution: University of Sydney

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 8

Recommendation:

Comments:
Dear authors and editors

Thank you for the opportunity to review this manuscript. In general I think this is a very well written and still relevant issue to address. As the authors mention there has been published contradiction reports on the subject and additional, well-designed studies are needed. This is a observational registry study, based on a large population which yields a number of cases of the rare adverse event but is also limited by its design of a registry study.

1.) The authors mention they have controlled for a number of confounders such as smoking and HbA1c. However, this Hba1c was one value, measured before inclusion. I can't see how one arbitrary HbA1c value could say much about the general control over years of the individual patient. Also, if I understand the design correctly, patients were included in the cohort if they were to switch between therapies / initiating new drug class - then I would expect all patients to be not in control/ high in Hba1c at that point of time?
2.) I suggest occupational history also to be a relevant confounder for BC that is not commented on tin the text.
3.) The authors mention that the pioglitazone users were more likely to have prior bladder conditions a baseline - could you maybe comment on this, what kind of conditions, what do you think is the reason and if it may affect the results?
4) In the beginning of the discussion it is stated that there was up to 15 yrs of follow-up - I don't understand how, if follow up started the year after cohort entry

(i.e. 2001) and until 31 July 2014 as is stated in the methods section?

5) In the results section you mention the incidence rates for BC for pioglitazone users vs other British T2 diabetics. For the readers reference I think it could be nice to shortly mention in the discussion if the incidence matches for other T2DM populations and the general population, to put it into perspective.

Additional Questions:
Please enter your name: Frida Emanuelsson

Job Title: MD

Institution: Copenhagen University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Employee of Novo Nordisk AS.

Information for submitting a revision

Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests

statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

5. Contributorship statement+ guarantor (see http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship)

6. Transparency statement: (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/transparency-policy)

7. Copyright statement/licence for publication (see http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)

8. Data sharing statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research)

9. Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ's style, as detailed below:

a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own

practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

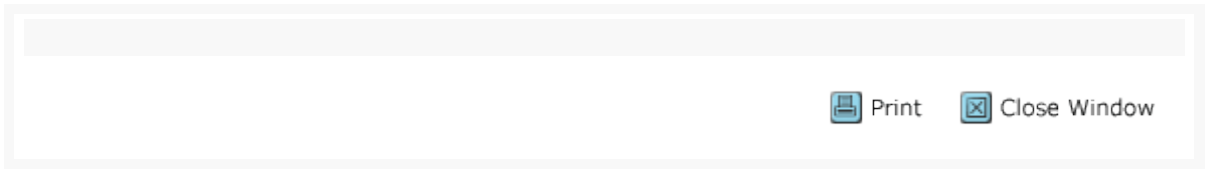
i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

Online and print publication: All original research in The BMJ is published with open access. Our open access policy is detailed here: http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model). The print and iPad BMJ will carry an abridged version of your article. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using the template downloadable at http://resources.bmj.com/bmj/authors/bmj-pico. Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper’s BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

Date Sent: 04-Jan-2016



| All Rights Reserved.