03-Jul-2023
BMJ-2023-076336 entitled "Evaluating the effects of Risk Mitigation Guidance opioid and stimulant dispensations on mortality and acute care visits during dual public health emergencies"

Dear Dr. Slaunwhite,

Thank you for sending us your paper. 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.

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.

Di Wang
Clinical Editor, the BMJ

T: 010 6410 0685
E: dwang@bmj.com
W:bmj.com/company
dwang@bmj.com

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

https://mc.manuscriptcentral.com/bmj?URL_MASK=dc2d04e65df740be9a3dcbb2a83ee5a1

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: Kamran Abbasi (chair), Tim Cole (statistical editor), Tim Feeney, Nazrul Islam, Navjoyt Ladher, Tiago Villanueva, Di Wang, Wim Weber, Megan Barling (transfer editor), Sophie Cook (BMJ Medicine editor in chief), Megan McGill (editorial production assistant)

Decision: Put points

Detailed comments from the meeting:

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:
The editors acknowledge the importance of the topic, but need to be convinced the methods are valid, the results are reliable and the interpretation is appropriate, before reaching a decision.

Specific points:

From stats editor:

1) Please refrain from using causal language, e.g. "RMG reduced the hazard", for the observational design.
2) More context information about the program and its uptake, etc. should be clarified more upfront in the paper. Presumably withdrawal symptoms were the driver to seek an RMG prescription? Only in the Discussion does it emerge that "the vast majority" of those at risk of overdose did not receive RMG. If causality is claimed, it needs to be justified in the Discussion – e.g. close matching etc. One wonders that maybe the Pandemic provides the most unusual and potentially unique situation that the RMG dispensations received by the tiny proportion of individuals made a big difference whereas those who could not access them were getting much worse, thus the benefit were exaggerated.
3) In Abstract and Results, aHR of overdose mortality for dispensations of RMG stimulants was 0.39 [95% CI 0.13-0.17]).The point estimate does not fall into the 95% CI?
4) Results compare ≥1 and ≥4 days per week RMG – why not 1-3 vs ≥4 days?
5) Why give results for multiple matching methods – e.g. Figures 4 and 5? This is over-complicated.
6) Please include only one significant digit for p values in table 1.
7) Please clarify the direction of SMD in figure 1.
8) Figure 3a. Matching makes no difference to all-cause mortality (A), and little to overdose mortality (B)?
9) Figure 3 and Figure 4D are not cited in text. The figures are hard to work out.
10) Please omit Figure 2, or put it in Supplement.

From other editors:

1) I feel like the overarching theme, harm reduction, is largely missing from the Intro. Many pivotal studies, including some from BCCDC, and guidelines are missing too.
2) "The RMG was the first known clinical guidance issued by a provincial or state government in North America to encourage physicians and nurse practitioners to prescribe alternatives to the illicit drug supply" - interesting! But presumably alternatives such as methadone maintenance treatment exist, even if guidance not issued by provincial or state governments. It'll be helpful to more adequately contextualize the study.
3) exposure [mis]classification: the authors spoke about case finding algorithm with varying sensitivity and specificity. However, this requires the knowledge and objective definition of the gold standard. There were no details on those. How did the authors ensure the gold standard definition. If they knew the gold standard, why did they use an algorithmic definition? The more detailed description about the 2 case definitions in table S5 doesn't shed much light on how complete/reliable the capture was.
4) It is confusing that hdPS was used for matching and then also IPTW. Further clarifications are needed.
5) It all hinges on the matching, and this is not very clearly explained. How many people had a use disorder and did not get any RMG medication? It would help to have a table with raw data on both cohorts.
6) The authors don't mention accounting for missing data prior just using (presumably) inverse probability of censoring weights combined with inverse probability of treatment weights. It seems reasonable to adjust for censoring, but neither more details in depth, nor references were provided.
7) Table 1: RMG Case/Control: these are not cases and controls; rather exposed and non-exposed.
8) Fig 4 & 5 show heterogeneous findings. Which one should we trust?

9) What proportion of people eligible for RMG treatment took it up. "In 2021, overdose deaths in BC increased by 130% compared to 2019, and the monthly number of paramedic-attended overdose events increased by 31% with a high of 2647 events in July 2021" in the Intro suggests the program is not yet making a difference at population level?
10) Is it assumed that this might carry over into non-pandemic scenarios? that isn't clear to me.
11) I'm puzzled by the difference in results related to mortality vs. care visits. One would expect these results to be in the same direction.
12) Dissemination statement is needed and can go in the end Matter. This tells readers how you plan to share your work, conferences, Social Media, blogs, policy, grand rounds etc. Please include this.

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 Reviewers

Reviewer: 1

Recommendation:

Comments:
Using the administrative health data in British Columbia, Canada, the investigators conducted a propensity score-matched cohort study to evaluate the effect of opioid and stimulant RMG (Risk Mitigation Guidance) dispensations on mortality and acute care visits during the dual public health emergencies of unregulated drug poisoning and COVID-19. The study showed that RMG opioid dispensations of ≥ 1 day significantly reduced the risk of all-cause and overdose mortality in the subsequent week but not the risk of all-cause or overdose-related acute care visits compared with the control group. Dispensations of RMG stimulants significantly decreased the risk of acute care visits for any causes but had no significant effect on overdose-related acute care visits. The research question has important clinical and public health implications. The sample size is large, and the manuscript is well-written. Some details of the study design and data analysis need to be clarified to evaluate the validity of the findings.
1. Each individual without the RMG prescription (non-exposed) was matched to an individual with the RMG prescription (exposed) using a high-dimensional propensity score (HdPS) in each pre-defined monthly block (i.e., the exposed person received the RMG medication). Within each monthly block, the time zero (i.e., starting date of the follow-up) for the exposed individuals is the date of the RMG prescription. However, it is unclear what the time zero is for non-exposed individuals. The time zero must be defined when calculating HdPS because the value of the time-varying predictors for HdPS, such as all-cause or overdose-related acute care visits before time zero, may vary depending on how it was defined within that time block.
2. How was the time zero defined for an individual with ≥4 days of opioid or stimulant RMG/week?
3. If an unexposed individual was selected into a non-exposure cohort in an early time block, could that person be chosen again in the non-exposed cohort in the later time blocks if s/he did not receive the RMG prescription?
4. Please specify when the follow-up time ends for each individual.
5. "Weighted estimation of the parameters of MSMs requires fitting several models: the structural (i.e., weighted) model, the exposure model, and the censoring model (Page 7, the 1st paragraph). However, the censoring was not defined in the statistical analysis section.
6. It is unclear what the time-varying analysis meant in this paper. For example, if an individual changed his/her RMG medication from 1 day/week during the early follow-up to not-receiving RMG medication later, would that individual's follow-up time be censored when s/he stopped receiving RMG medication, or was that considered the time-varying exposure? Please clarify.
7. Several potential confounders, such as education, smoking, alcohol consumption (except ever-diagnosis of alcohol disorder), marital status, and body mass index, were not listed in Table 1. Were these variables available in the dataset or not included when HdPS was calculated?

8. Age is a strong risk factor for all outcomes in this study and is likely to be associated with RMG prescription; thus, using age instead of age categories may be better to minimize the confounding effect by age.
9. If an individual experienced multiple outcome events, such as all-cause or overdose-related acute care visits during the follow-up, was only the first visit considered in the data analysis?
10. "A total of 5,882 persons were dispensed opioid (91.1% [n=5356]) or stimulant (18.0% [n=1061]) RMG prescriptions between March 27, 2020, and August 31, 2021." (Page 7, last paragraph). However, in Table 1, the total number of recipients at the first time of opioid RMG dispensation was 5371, and the number of recipients at the first time of stimulant RMG dispensation was 1059. Please clarify why the number of subjects in the text differed from Table 1.
11. In Table 1, the P value, instead of the standardized mean difference, was used to compare the difference in baseline characteristics between the two comparison cohorts. The investigators may consider using the standardized mean difference in Table 1. Thus, Figures 1 and 2 can be deleted.
12. The investigators may consider using a table to present the number of subjects, the number of each outcome event, the rate of the event for the exposed and non-exposed cohort, and the hazard ratio and confidence intervals when comparing two cohorts. Doing so would make it easier for the readers to capture the study's main findings.
13. What were the results presented in Figures 3a and 3b? The findings in these two tables were not commented on in the manuscript.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Yuqing Zhang

Job Title: Professor of Medicine in Residence

Institution: Massachusetts General Hospital, Harvard Medical School

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:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: No

Reviewer: 2

Recommendation:

Comments:
The study examines the effect of COVID-19 pandemic policy to provide risk mitigation guidance (RMG) prescribing of opioids and stimulants to patients with opioid use disorder (OUD) and stimulant use disorder (StUD). The study compares the group prescribed to RMG to a control group identified using propensity score matching and then compare differences in four outcomes: all cause mortality, overdose mortality, acute care visits, and overdose acute care visits. The study finds RMG is associated with significantly lower rates of all-cause and overdose mortality.

I will say the project is ambitious and on an important topic. The authors have clearly undertaken a painstaking and careful analysis. However, I have some major concerns outlined in the comments below.
More major comments

1. I think the biggest quantitative limitation is that propensity score matching can help to match individuals prescribed RMG opioids or stimulants to controls based on observable characteristics. But differences on unobservables are an important limitation to acknowledge. In this case, I think the issues is particularly acute for a few reasons (more below). Broadly, the concern is that there are unobservable characteristics of those prescribed RMG that both drive their prescription but are also correlated with the outcomes. For example, patients with OUD or StUD who are able to connect with the health care system, or have resources to connect with the health care system (transportation, etc.), or those whose

providers think they may be better able to handle RMG, etc. Unfortunately, I think this is a case where the bias of the estimates is in the direction of finding a large impact of the RMG program. A few items that are concerning to support this.
a. Figure 1 A/B first highlights the issue. Those not prescribed are more likely to have income assistance, unstable housing, OAT dispensation. While these specific characteristics are likely handled by the matching process, it is an indication that there may be important differences between the two groups.
b. If I am reading Figure 3a and 3b correctly there are huge mortality differences between the two groups. In the opioid group, 60% (3205/5371) of the control group dies compared to just 0.4% of the RMG group (23/5371). This is concerning as it suggests these are really very different groups. I don't see how RMG could be responsible for this large of a difference. In particular, because most of the deaths in the RMG group are overdose deaths but only about 40% of those in the control group are (1308/3205). The concern is that these differences are so large (and the differences are present in non-overdose deaths which are less directly tied to RMG) they suggest issues with selection making it difficult to interpret the findings.
c. Finally, Figure 4 Panel B shows a big issue in the opioid group. When restricting to those not on OAT (which might be the fairest comparison to ensure that not conflating RMG with OAT effects) we actually see the results reverse—now hazard ratio is above 1 for RMG. At some level I think this model is the most accurate by (a) focusing on overdose mortality, which is the outcome most clearly causally tied to RMG; and (b) omits the OAT group that might be confounding the results. So, worry that the sign reversal is a big issue.

2. One analysis that might further help to elucidate the selection issue is a survival curve. If the curves start to separate before there is a plausible period time for RMG to work then this might be indicative of selection (there was actually a paper about this in this week's JAMA Internal Medicine titled "Detecting selection bias in observation studies – when interventions work too fast".).

3. Would help to better understand what RMG prescribing looked like – specifically what do individual-level trajectories look like. Do individuals tend to continue taking or drop off? Does dosage change? Right now, the >1 day or >4 day doesn't seem sensitive enough to explain such huge drops in mortality (adjusted hazard rates of 0.1 for overdose mortality is enormous and hard to see how just 1 day or 4 days of RMG would be enough to have this effect). Again, worry that some of this is further demonstrating selection.

4. For the main results in Figure 4, are these multivariate analyses? Table S12 suggests maybe multivariate. But would make that clear in Figure 4.

More minor comments
1. All-cause acute events seems like the outcome that fits the study least well. Particularly, because not clear what the correct sign should be (there are reasons that RMG might increase or decrease) whereas the other variables have a clearer hypothesized sign.
2. Figure 2 not clear which axis goes with set of bars or lines.
3. Figures S1-S3 not clear how to read these – are these average prescriptions among those prescribed? Something different? Would help to add a footnote explaining the figures a bit more.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal,

depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Joel Segel

Job Title: Associate Professor of Health Policy and Administration

Institution: Penn State 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:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

Reviewer: 3

Recommendation:

Comments:
This peer review was done under the Peer Review and Biomedical Editing Training Initiative (Peerspectives), which has been developed in cooperation with the BMJ. In total, three trainee reviewers - PhD students from the Charité - Universitätsmedizin Berlin and one experienced mentor reviewed this paper. All participants have agreed to the BMJ reviewer policies.

Trainee reviewers/PhD Students:
Lukas Mödl
Lena Schneider
María Ana González

Mentor (takes responsibility for the review):
Mariska Leeflang

Summary:
This study investigates the causal effect of Risk Mitigation Guidance (RMG) opioid and stimulant dispensations on mortality and use of acute care. Opioid and stimulant RMG dispensations were introduced at the onset of the COVID-19 pandemic in British Columbia, Canada. The study uses a matched retrospective cohort study design and finds that, compared to the matched control group, reduced overdose and all-cause mortality in people receiving RMG prescriptions. No significant reduction of overdose-related acute care visits was identified.

Importance and originality:
Overdose related deaths have increased substantially in North America over the past year. RMG prescribing by physicians and nurse practitioners was introduced to reduce overdose incidents among people from illicit drug supply. The RMG dispensation policy was introduced during the COVID-19 pandemic to reduce the risk COVID-19 infections during isolation and quarantine measures among people using opioids and stimulants. Since then, the program has been prolonged. The authors present that to date there is limited evidence on the effectiveness of prescribing pharmaceutical alternatives on reducing mortality. This makes this study a necessary and needed addition to inform drug policy to address the opioid overdose crisis.

Major Comments:
1. While the need to assess the effect of the exposure on the outcome of all cause and overdose-related mortality is clear, the introduction does not detail the relevance of looking into acute care visits. This context would be helpful to understand the relevance of this outcome (page 4).
2. Using and linking several population-level administrative databases is a comprehensive method to define the study cohort. Please add a short statement on how the data was linked and how the validity of the data linkage was ensured (pg 5, line 26 - 38).
3. Understanding the matching technique is essential to assess the validity of the findings. It would therefore be important to describe the matching approach step by step for a broader audience (p 6, line 30 - 49). Further as both investigator-selected and high-density propensity scores approaches are used to identify covariates for propensity score matching, it remains unclear how these approaches were used together. Please add one or two sentences clarifying the choice of covariates in the main text (pg 6, line 38 - 40). It should also be clear at what scale covariates were used, as Figure 1 seems to suggest that age was discretized (pg 20).

4. Authors report both adjusted hazard ratios as well as adjusted odds ratios (pg 8 line 56 - pg 9 line 4). However, the methodology section only mentions a logistic regression, which estimates odds ratios. It should be specified if another model was used to perform the analysis.
5. Please briefly explain further the implications of the missing subgroup analysis on the generalizability of the results (pg 10, lines 30 - 33 and pg 10, lines 49 - 51).
6. We would suggest simplifying Table 1 by removing the total rows and removing the p-values as they are not indicative of a successful matching (pg 17). The reporting of the standardized mean difference should suffice to demonstrate this (pg 20 and 21).

Minor Comments:
7. As this study has a matched retrospective cohort design we suggest to use the STROBE template for cohorts and not for case-control studies.
8. The title could be more explicit referring to the alluded crises by detailing “COVID-19 and opioid overdose”, for example.
9. Please clearly state the study design in the abstract's methods section (pg 2, line 2). We would also suggest adding the study design to the title.
10. In the abstract the total number of people receiving RMG opioids or stimulants is not clear, see “5,882 persons were dispensed opioid (91.1% [n=5356]) or stimulant (18.0% [n=1061])” (page 2, line 20 - 21). The percentage adds up to more than 100 percent. Likely this is due to people who can receive both (see page 7, line 56), so this should be clarified in the abstract.
11. In the abstract “Findings” section (pg 2, line 25) aHR is reported as 0.39 [95% CI 0.13 - 0.17] which appears to be an error as the aHR is outside the confidence interval.
12. The last paragraph of the introduction (page 5, line 7 - 13) might be better placed as the first paragraph of the methodology section.
13. The investigator selected as well as inclusion of time as a confounder variable are based on current knowledge through the systematic review. While this is helpful, the covariate selection should ideally be based on and accompanied by a directed acyclic graph (DAG) (page 6, line 31 - 33).
14. The published protocol suggests a 5:1 matching ratio. Could you clarify why a matching ratio of 1:1 was chosen despite specifying differently in the protocol (page 6, line 41).
15. Please specify the SAS macro version used for the analysis (pg 6, line 35).
16. Lack of clarity on the categorization of dispensation frequency: Please specify a rationale for choosing a sub-analysis of minimum 1 day and more or equal to 4 days of dispensations in the analysis (page 7, lines 17 - 26).
17. The methodology for analysing the number of days of dispensation is listed under the section sensitivity analysis (page 7, line 17- 26). However, the results of this analysis are reported as main results of the analysis in the abstract and in the main text. It would be recommended to move the description of the methodological approach to the Statistical Analysis section.
18. Please cite the protocol when you refer to it consistently throughout the manuscript (pg 10, line 25).

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Mariska Leeflang

Job Title: Associate professor

Institution: Amsterdam UMC

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: This peer review was done under the Peer Review and Biomedical Editing Training Initiative (Peerspectives), which has been developed in cooperation with the BMJ. In total, three trainee reviewers - PhD students from the Charité - Universitätsmedizin Berlin and one experienced mentor reviewed this paper. All participants have agreed to the BMJ reviewer policies.

Participants' competing interests: María Ana González (German Academic Exchange Service DAAD scholarship holder: 2017 - 2018; 2022 - 2026)

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

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 and public involvement statement

https://docs.google.com/document/d/1djgVLEUFtPQzLpf5HyuiFcMgrNJ_o7Yb8z73zgXxXYM/e

11. Dissemination plans: At the end of the paper please state how the results of your study have been (or will be) sent to patients and the public under the heading "Dissemination plans". If you have prepared a lay summary eg for your funders, please include it in a supplementary file.

If you have not disseminated and have no plans to do so, please state why.

12. Patient confidentiality forms when appropriate

13. 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.

Please report all outcomes that were listed in the trial registry, or explain that you will publish them elsewhere. Please clearly identify each outcome as primary, secondary, or post-hoc in the text, abstract, and any tables or figures. We expect authors to report prespecified outcomes. If outcomes in the trial registry have later been changed, please explain the reasons for the change and the dates of the change in the paper. You may report the changed outcomes, but we will expect you to also report on the originally specified outcomes unless otherwise agreed with the handling editor for your paper.

Occasionally the outcomes that are prespecified in a trial registry do not match up with those included in the trial protocol. When there are discrepancies between protocol and registry specified outcomes, we expect the paper to report and interpret the registry specified outcomes. You may also report any protocol specified outcomes, but if you do please be sure to include the date of the protocol and the point at which each outcome was added to the protocol, and explain why the registry entry differed from the protocol and why the registry was not updated to reflect any protocol changes.

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.

Please report all outcomes that were listed in the trial registry, or explain that you will publish them elsewhere. Please clearly identify each outcome as primary, secondary, or post-hoc in the text, abstract, and any tables or figures. We expect authors to report prespecified outcomes. If outcomes in the trial registry have later been changed, please explain the reasons for the change and the dates of the change in the paper. You may report the changed outcomes, but we will expect you to also report on the originally specified outcomes unless otherwise agreed with the handling editor for your paper.

Occasionally the outcomes that are prespecified in a trial registry do not match up with those included in the trial protocol. When there are discrepancies between protocol and registry specified outcomes, we expect the paper to report and interpret the registry specified outcomes. You may also report any protocol specified outcomes, but if you do please be sure to include the date of the protocol and the point at which each outcome was added to the protocol, and explain why the registry entry differed from the protocol and why the registry was not updated to reflect any protocol changes.

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).

END