Author’s response to reviews

Title: Self-declared stock ownership and association with positive trial outcome in RCTs with binary outcomes published in general medical journals - a cross-sectional study

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The authors would like to thank the reviewers for their remarks and the time and effort spent assessing the current manuscript. The suggested alterations strengthened the manuscript considerably. Point to point comments are found below.

Reviewer #1: It is stated that conflicts of interest are being investigated, and yet it appears that instead you are investigating only declarations of conflicts of interest, which are not the same thing. Are you familiar, for example, with the JAMA debacle with Dr. Jonathan Leo? http://www.policymed.com/2009/03/jama-editor-calls-critic-a-nobody-and-a-nothing.html

So did you do any investigating into undeclared conflicts of interest, or did you just take the authors are their word, blindly trusting them to always tell the truth?

Authors: Thank you for pointing this out, we are aware of the work by Dr Leo, which strengthen our belief that this type of work needs to be conducted. We did only consider self-declared conflict of interest, which probably underreports the actual conflicts of interests. We believe that this is a limitation to our study and have now added the following sentence in the discussion. “As we only considered self-declared conflict of interest, there is a potential of underreporting of the actual conflict of interest that might exist.”

Reviewer 1: The reality is that in general there are far too many positive outcomes that are not rooted in fact. This is true whether there are obvious conflicts of interest or not, since even the ones that are not obvious, or are not even financial, still cause investigators to cheat so as to skew
the results. You are comparing bad trials to bad trials. What, then, can you conclude if you find no difference?

Authors: Thank you for commenting on this important aspect. We agree with the reviewer and have now added the following sentence in the discussion and the references. "Several mechanisms on how positive outcomes can be achieved have been proposed, for example by statistical analysis such as randomization procedures, parametric analyses, run-in enrichments technique, and dichotomizing of ordered data [17]."


Reviewer 1: Also, it says that you accepted as randomized and trial that made the claim. This is far too lenient an approach, as many trials claim to have randomized yet in fact did not:

Authors: Thank you for correctly pointing this out. We fully agree with the reviewer and have added the following sentence to the discussion as a further limitation of our study and added the reference below. “Furthermore, we included all randomized studies that mentioned the term random in the methods section. Since this can include studies with vague description of their randomization procedure, this is a further limitation of our study [18].


Reviewer #2: General Comments. This manuscript addresses an important issue and it appears to be carefully designed, performed and interpreted.
Specific Comments.

Abstract. Conclusion. Consider inserting between the first and second sentence, an additional sentence that like "Because the factors related to conflict of interest are not independent, a multivariable analysis should be cautiously interpreted. However, after multivariable adjustment....." A similar kind of qualification could be added to the conclusions at the end of the manuscript.

Authors: Thank you. We agree with the reviewer and have now added the additional sentence in the conclusion of the abstract and at the end of the manuscript. “...because the factors related to conflict of interest are not fully independent, a multivariable analysis should be cautiously interpreted. However...”

Reviewer #2: Methods, 6th line of text. Is there an error in stating "... Med, randomized OR randomized and..."?

Authors: Thank you for acknowledging this. We have now added the following text ”...N Engl J Med and randomized OR randomized...”

Reviewer #2: The exact meaning of the term "blinded for review" used at different points in the text is a bit ambiguous.

Authors: We have now substituted the term "blinded for review" with the authors initials throughout the text.

Reviewer #2: Statistical Analyses. With the differences between the studies with different COI types with respect to the proportion of positive studies and the greater ease in interpreting and comparing relative risk than odds, I would suggest the authors consider using relative risk (estimated using a Poisson regression analysis) than odds ratios.

Authors: Thank you for pointing this out. In agreement with the reviewer we have considered using RR instead of OR. Both OR and RR are common measures to assess the strength of
association in epidemiology. OR and RR are often used in clinical studies where both are in general recommended for cross-sectional studies, and as we consider our study to be a cross-sectional study and since OR is the most commonly used, we found the use of OR to be the most appropriate alternative. RR is most suitable in prospective cohort studies. Since OR can be used in both case control, prospective cohort studies and cross-sectional studies we chose to report the OR. However, in order to add clarity to the analysis we included the sample size, number of observations in each group, but also the degree of precision with confidence intervals and statistical significance in order for the reader to make its own judgment on the degree of association.

Reviewer #2: However, statistical significance is of course related to both sample size and the effect size. At least for trials with predetermined sample size or stopping rules, sample size is more related to imprecision than bias while effect size is more likely to be influenced by bias. The investigators might augment their paper by a supplementary analysis relating the type of COI to the effect size identified (whether or not the difference was significant).

Authors: Thank you for this comment. We interpret your suggestion of improvement as being explained in table 2. The unadjusted OR for a favourable outcome relates the particular COI to the effect size with a corresponding estimation of the precision. We have therefore also added the following sentence: “Table 2 shows the association between a favourable outcome and a specific type of COI with the related effect size.”