Author’s response to reviews

Title: A survey on beliefs and attitudes of trainee surgeons towards placebo

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Author’s response to reviews:

Dear BMC Editorial Team,

We wish to thank the Editorial Team and reviews for their constructive feedback. Please find below a point-by-point response to the Reviewers comments.

Review 1:

1. As the authors have pointed out, difficulties were faced with determining the size of the target population. The response rate cannot be calculated. But even optimistically, the response rate was low. Is it possible to somehow clarify the accuracy of the email list? (Please see more detailed comments below). Given the low response rate, is there any further information (apart from gender) that allows a comparison between respondents and non-respondents? (I note other data was collected about the characteristics of the sample).

- BOTA is a voluntary organisation of orthopaedic trainees. It has an extensive membership and, currently, out of 1,111 orthopaedic trainees registered nationally, 987 are members of BOTA [personal communication with Joint Committee On Surgical Training]. The following sentence has been added to this paragraph as clarification, ‘Although not all of the 1,111 nationally registered UK orthopaedic trainees will be BOTA members this email database was identified as the most complete contact list available to the authors’ (page 4).
We had no direct access to the email list. Instead, a prepared letter of invitation and details of the survey weblink were sent on our behalf by the database controllers. As such, we do not have evidence of “bounced” emails that would act as a measure of the databases completeness. This separation acted as an important step in ensuring participation remained anonymous. Direct access to email addresses, many of which will contain elements of or indeed complete names, would have compromised anonymity, privacy and study validity.

We have contacted BOTA regarding the accuracy of their email lists. This requires contacting multiple data controllers (one for each training region). Most have now responded and inform us that the lists do have some inaccuracies (i.e. bounced emails) but the frequency of this is low (<5%). Please, see also the response to comment no.16.

2. There is some lack of detail about the statistical analyses presented
- The details of the statistical analysis used are now provided (page 6).

3. Abstract Para 3. It may be appropriate, given that this is the main methodological drawback of this study, to include the response rate (or the total number contacted) here.
- We agree that this is an important point. The total number of BOTA members and the estimated response rate have now been included in the abstract.

4. Abstract Para 3. "The majority of trainees thinks that" should be "The majority of trainees think that"
- Typographical error corrected.

5. Abstract Para 4. "show willingness to recruit into placebo controlled trial however" should be "show willingness to recruit into placebo controlled trials however"
- Typographical error corrected.

6. Background Para. I agree with your statement regarding "soft" outcomes being more prone to bias than "hard" outcomes, but can you please provide a reference for the statement
- A meta-analysis of placebo effect in clinical trials, estimated as the difference between the effect in a placebo arm and a no-treatment control arm, demonstrated a significant placebo effect for subjective outcomes, most importantly pain, but not for objective outcomes (reference no. 4).

7 Background Para 2. "clinical symptoms or patient's well-being" should be either "clinical symptoms or a patient's well-being" OR "...clinical symptoms or patients' well-being".

- Grammatical error corrected.

8. Background Para 2. "consequence of patient's expectations" see the previous point.

- Grammatical error corrected.

9. Background Para 2. Can you please very briefly elaborate what you mean by "conditioning".

- We have clarified that we meant “classical conditioning”. However, to elaborate further would be beyond the scope of the article and an adequate explanation can be found in references no. 5 and 6.

10. Background Para 3. There is empirical evidence that can guide the first few statements of this paragraph which I suggest the authors cite. See [HRÓBJARTSSON and GÖTZSCHE. Is the Placebo Powerless? N Engl J Med, Vol. 344, No. 21, May 24, 2001].

- We thank the reviewer for the comment and we have added this reference (reference 4). However, this meta-analysis is more relevant to paragraph 1 on a placebo effect rather than to paragraph 3 describing attitudes toward using placebos.

11. Background Para 5. "about their opinions about placebo" may be better phrased as "about their opinions towards placebo".

- We are grateful for the comment. The sentence has been rephrased and it now reads: “investigate the attitudes and beliefs of British orthopaedic trainee surgeons towards placebo”(page 4).
12. Methods Para 1. Thank you for providing details of ethics approval. This is often neglected in survey research.

- No response required.

13. Methods Para 1. Can the authors please clarify whether all British Orthopaedic Trainees are contained in the list of emails supplied by BOTA. Can the authors also please clarify whether the emails kept by BOTA are accurate, and whether BOTA is in regular contact with trainees with regards to other issues (which would make the accuracy of the contact details more likely).

- Please, see response to comment no. 1.

14. Methods Para 2 to 4. These provide a good overview of the survey used and when placed next to the provided appendix makes everything quite clear.

- No response required.

15. Methods Para 6. Can the authors please provide details on which trainee characteristics were included in the regression model? Can the authors also provide any evidence for why these characteristics were hypothesized to be associated with willingness to recruit. If not, then I would suggest the authors use the term "exploratory" to describe their analysis. Also, I note that the authors planned to compare trainees’ results with those of a previous study done on consultant surgeons. Can the authors please specify which results were compared and what analyses were planned?

- The variables included in the regression model are now listed with, as suggested, the term “exploratory”. Additionally, details of the results that were compared and the statistical analysis used are now provided (page 6).

16. Results Para 1. There are a few concerns here. The response rate is unclear. I appreciate that the BOTA database may not be entirely accurate, but since the authors have chosen it, it should be assumed to be the best representation of orthopaedic trainees available. Therefore is it fair to say that there were 1000 potential respondents and only 189 responded? Was there any evidence of invalid "bounced" emails? My experience with these online survey tools is that invalid emails may be detected when they bounce back to the sender. Also, it would make it much easier to appreciate the response rate if a flow diagram is presented, including how many responded after the first / second reminder.
- The response rate is now clearly reported. Please, see also responses to comments 1 and 3. We had originally qualified this statement to allow the reader to understand that, since the true denominator was difficult to calculate, this represented a ‘worst case scenario’. To avoid confusion, this comment has now been moved to the Discussion section.

- Finally, since we have no reason to suspect that respondents’ answers would differ based on whether a response was received after the first or second reminder email; therefore, we do not feel that a flow diagram is required.

17. Result Para 1. Given there is a low response rate, did the authors make any effort to determine how respondents differed from respondents? For example, does the BOTA database also contain information on the age, gender, and year of training of each of their trainees? Can this information be used to determine the similarity between respondents and non-respondents? This is important to determine whether your respondent sample was representative of BOTA trainees.

- To help ensure honest responses to what is a sensitive topic, the authors agreed that we should not be able to identify individual respondents. Indeed, a promise of confidentiality and anonymity was made in our letter of invitation send to BOTA members. This anonymity was guaranteed by having only proxy access to email addresses. Since, we did not directly email each trainee we cannot know who responded and who did not. It follows that we cannot determine if respondents’ characteristics differed.

18. Results Para 3 to 5. These results are really interesting and I appreciate how the authors have summarized the additional comments made by respondents, which are impossible to summarise numerically but nonetheless shed light on trainees’ attitudes. My only concern is the way these questions on placebo definition were phrased in the survey. I appreciate the authors wanted a concise survey, but is it possible the questions were suggestive of the answer? This is particularly important given the disparity of respondents' answers here, and the answers provided on the effectiveness of placebo and their use in clinical practice. Can the authors please comment?

- Prior to distribution, the survey questions were independently assessed by 11 orthopaedic trainees with an interest in research. No concerns were raised over potentially leading questions. Further, these definitions are found within the existing literature and have been utilised in a similar format in previous published works. Finally, we do not fully understand what disparity the reviewer is referring too. In fact, there was an association
between those respondents that recognised the ubiquity of placebo (i.e. agreed with definition 3) and those that would consider utilising placebo in a greater range of clinical scenarios [data not presented in paper].

19. Results Para 6. I would suggest removing "not significantly different" and changing to "not substantially different". While the meaning is correct, "significant" in the context of a research paper implies inferential statistical analysis was performed.

- Statistical analysis comparing trainee with consultant answers was performed and the details are now included in the methods section (Please, see response no.15). Without this amendment to the methods we agree that this statement was confusing. However, given that an analysis was undertaken the phase ‘not significantly different’ has not been amended.

20. Results Para 6 to 9: Again, the results here are fascinating. As the authors have previously mentioned, there seems to be a misunderstanding of what placebo is and the ethics of their use in clinical practice. It is interesting to see that 60% of respondents would consider using placebo in clinical practice, and that only 13% would not use it because it is ineffective (although by definition a placebo is ineffective).

- No changes required. However, we would disagree with the Reviewer that a placebo is by definition ‘ineffective’. On the contrary, the positive change in response to a placebo intervention underpins the need for placebo controlled trials.

21. Result tables 3 to 5: Although the presentation of the results in these tables is efficient, it is not visually stimulating. Will the authors consider using a graphic instead? For example, a bar graph for each question with the green part of the bar being "yes" and the red part of the bar being "no". (Similar to what the authors have presented in Figure 1).

- The choice of tables was due to the large amount of text required to clearly explain the results. Including this text into the axis of a figure would, we believe, create confusing and visually unappealing figures. However, for Table 3, we are able to reference text in the main body of the manuscript. This has enabled us to create a new figure. The remaining tables have not been replaced.
22. Discussion Para 9. "In our study, the perceived mechanism of the placebo effect were most commonly been attributed to psychological factors, which is in line with other studies." Can the authors please correct this sentence.

- This section has been changed to: “Orthopaedic trainees commonly attribute the mechanism of the placebo effect to psychological factors. Our findings are similar to the previously reported beliefs among orthopaedic consultants as well as physicians” (page 13).

23. Discussion Para 9. "and the fact that placebo response involves actual physiological changes." Should be "and the fact that the placebo response involves actual physiological changes."

- Typographical error corrected.

24. Discussion Para 9. "differs from a natural history of the disease" should be "differs from the natural history of a disease".

- Grammatical error corrected.

25. Discussion Para 9. "None of the respondents suggested adding an observational, non-interventional group to control for the natural history of the disease". Of all the authors' findings, I think this one is of greatest concern. Can the authors please emphasise this finding a bit more, by including a discussion on the implications for trial research. The authors can also cite a couple of trials that have NOT included a non-intervention group (there are plenty of those), and have therefore represented a missed opportunity.

- We are grateful to the Reviewer for this comment. We have added a sentence highlighting the importance of an observational group for interpretation of trial’s results. We have also referred to the earlier systematic review of placebo-controlled surgical RCTs, in which only one identified study included a non-interventional control group as well as a placebo group. As the implications of lack of a control group were discussed in the review, we have provided a reference but we have not repeated the argument.

26. Discussion Para 9. "This may be related to an element of agency" I am not sure what this means? Did the authors mean "an element of urgency"?
- We did mean “agency” in the sense that a surgeon has a direct effect on treatment by performing the actual surgical procedure and being personally responsible for its outcome. This differs from pharmacological treatment during which a physician administers a drug which is manufactured by someone else. Although a physician is still responsible for the choice of the drug, the involvement in treatment is less direct and less personal. However, we agree that this phrase may be confusing and it has been removed. (page 13)

27. Discussion Para 10. "Interestingly, fewer trainees reported that they have never observed an operation with a placebo component than surgeons answering that they have never performed a procedure with a significant placebo component. " This sentence may better be phrased as: "It is interesting that, compared to surgeons, fewer trainees reported that they have never observed an operation with a placebo component".

- Sentence rephrased as suggested.

28. Discussion Para 11. Is there any way the authors can elucidate the response rate? It seems that the reader of the article will assume a response rate of 18.9%. Having used Survey Monkey before, I know there are methods for determining bounced emails, but this depends on the method used to send the survey out. Does BOTA perhaps have a record of the invalid emails? Presumably these emails are used for bulk messages sent out by BOTA, will they be able to tell the authors how many messages bounce?

- Please, see responses to point no. 1 above. Due to the way in which the survey was sent out, we cannot determine the number of bounced emails. Based on communications with BOTA, we know that database is not 100% accurate but can only estimate its accuracy as approximately 95%. However, there are also other reasons why a participant may not have received the invitation e.g. the email went into the spam box, it was sent to a defunct email address etc. We feel that these possibilities are well reflected by the sentence, “The main limitation of this survey is that the response rate cannot be accurately calculated as it is not known how many trainees in the BOTA database actually received the invitation to participate” (page 14).

29. Discussion Para 11. Can the authors discuss potential reasons for the lower response rate? Are trainees / junior doctors less likely to participate in survey research? Could the survey itself have been better? Was the survey addressed personally or generic? Were the reminders sufficient?
A discussion on potential reasons for the lower response rate has now been added: “It may be that trainees are less likely to participate in survey research, perhaps owing to time pressures or survey fatigue. Additionally, it should be noted that the survey of senior surgeons[15] was distributed during a research conference. This might have primed participants to the importance of research and inflated response rates.”(page 14)

30. Discussion: I am not sure about the current orthopaedic training environment in the UK, but in my country the orthopaedic training program is currently undergoing a major review. The authors have identified a number of issues that have been poorly understood amongst trainees (and surgeons). Given that surgical RCTs are only feasible with the general support of the orthopaedic community, can the authors please add a brief discussion about the training implications of their findings? Is there a problem with the teaching of clinical epidemiology and evidence based medicine on the training program? How can this be improved?

- We agree with the reviewer that the education of trainees as a means of facilitating placebo RCTs is an important point to highlight. Therefore, the following sentences have been added to the Conclusions: “High quality research that changes practice and improves care can only be successfully undertaken with the general support of the orthopaedic community. Providing trainees with better training in research methodology, so that they understand the strengths and limitations of different trial design, may facilitate this process.” (page 15)

Reviewer 2

31. Background Para 1. Second sentence starting technological advances contains two separate sentences

- This sentence has now been split as suggested

32. Background Para 1. Reference for the statement made in the last sentence needed, the issue of true efficacy

- Reference provided. Please, see also response no. 6 above.

33. Background Para 3. Explain more clearly why it is important to understand the clinical implications of why surgeon's attitude towards placebo effect is important.
A section “it is not known whether these attitudes represent the beliefs of the whole orthopaedic community or are a generational phenomenon. Understanding the attitudes of surgeons towards placebo may help to answer the question why there have been so few placebo-controlled trials of interventional procedures.[15]” have been added at the end of the Background section. This survey was a consequence of discussions prompted by the ongoing CSAW trial (ClinicalTrials.gov NCT01623011) and our earlier review on harms and benefits of placebo-controlled surgical RCTs. A negative attitude of surgeons towards placebo has often been suggested as a reason why, unlike pharmacological treatment, interventional procedure tend not to be validated in placebo-controlled trials.

34. Background Para 3. Are the surgeons being surveyed orthopaedics consultants?
- Yes, the section refers to a survey of consultant orthopaedic surgeons. This has now been clarified.

35. Background Para 3. Explain why in the context of this study a survey of trainee surgeons is important before stating the aim
- Following sentence added to paragraph: “Additionally, it is not known whether these attitudes represent the beliefs of the whole orthopaedic community or are a generational phenomenon.” (page 4)

36. Methods. Missing statistical methods authors used to compare the differences (chi-squared test)
- Now included. Please, see also response no. 15.

37. Methods. Views of ‘consultants' were referred to repeatedly - clarify what this means. Are these the same as cited in the introduction? Also include statistical method to test whether there is a significant difference
- This has been addressed in previous responses. Please, see comments no. 15 and 34

38. Results. Regression analysis was used to test whether willingness to recruit depended on other factors - these were not reported in page 9
- The full list of variables tested in now listed (page 6). Only positive associations have been presented in the results section, factors that did not influence willingness to recruit can be made by inference.

39. Overall it is an interesting study although at times I found difficult to follow. For instance, findings cited in the abstract were not directly quoted in the Results. Would help if authors could organise the manuscript such that the sections in the Methods matched the sections in the Results.

- For clarity, the Methods section has been structured so as to match the structure of the survey (please, see also comment 14). As suggested, the Results section has now been reordered so as to also reflect this structure.

40. The main drawback of this study was the high percentage of trainees who did not respond to the survey (>80%). This casts doubt on the external validity of the survey, especially as the authors argued the previous survey was biased. It is not reasonable to assume, as the authors had argued, that the respondents were representative based on the male/female split alone. There are clues indicating otherwise, e.g. a percentage with post-graduate degrees, high concentration of trainees in later years of training, etc.

- We acknowledge that the response rate is low and that this might introduce an element of bias into the results. We have therefore been careful to alert the readership to this limitation (Please, see also response no. 1).

- We would like to clarify that we did not suggest that the sample was representative based on the gender split alone but that the gender split was comparable to the gender ratio at the national levels. As for the high number of respondents who hold another post-graduate degrees, to the best of our knowledge, there is no data available on what degrees are held among surgical trainees in the UK. Finally, in the UK, Orthopaedic training begins at the 3rd year of a surgical training pathway. Thus, the 3rd to 5th year of specialty training is actually the start of Orthopaedic training. Respondents listed as locums appointed for Training (LATS) also represent junior trainees within the first few years of Orthopaedic training. Thus, there is in fact a reasonably even split between junior and senior trainees.