Author’s response to reviews

Title: Effectiveness of acupuncture for breast cancer related lymphedema: Protocol for a single-blind, sham-controlled, randomized, multicenter trial

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Author’s response to reviews:

Dear Dr. Tom Rowles and Dr. Yan Zhang:

Thank you very much for valuable and helpful comments in your reply.
We have studied comments carefully and tried our best to revise the manuscript. Revised parts are marked in red in the paper. The point-to-point responses to the reviewers’ comments are listed as following:

Response to Dr. Yan Zhang:

This protocol is of interest of the journal, but it has following shortcomings to be addressed.

Introduction Part:

"background" is the only subheading in introduction, please consider removing it.

Response: Thank you very much for your suggestion. We have removed it.

Question 1. P3, line 9-11: It needs more background information/data in China where the study takes place in. Just citing US data appears insufficient;

Response: Thank you very much for your comment. We have cited the Chinese breast cancer data instead of US data.

Question 2. P3, line 13-15: Health insurance coverage is not the best indicator of economic burden on the society, authors may want to add other indicators such as loss of productivity etc;

Response: Thank you very much for your advice. We have modified this sentence. The sentence now reads “it imposes a big burden on the society with long-term costs, and makes up a significant source of hardship for many families due to health-related productivity loss”.

Question 3. P3, line 16: "there is no way to forecast whether an individual patient will develop lymphedema or not.", I find it difficult to draw the same conclusion as authors stated based on the cited article, there are also other articles indicating risk factors for BCRL. I suggest authors to revisit this statement and make conclusion with caution. In addition, adding background information regarding risk factors of BCRL will help the readers to understand why certain variables are chosen for this study;

Response: Thank you very much for your advice. We have revised this statement, and added background information regarding risk factors of BCRL.
The sentence now reads “According to research, important risk factors for BCRL includes obesity, axillary lymph node dissection, postoperative radiotherapy, infection, history of lymphangitis, and axillary drainage. Moreover, there is no cure for BRCL so far, and the only way is to avoid risk factors, reduce the severity of symptoms and improve the function of the affected arm.” Moreover, we have added a sentence in the “Statistical analysis” part, which reads “In addition, regression analysis will be performed to analyze the effects of co-variances (risk factors) such as BMI, axillary lymph node dissection, postoperative radiotherapy, infection, and history of lymphangitis on the overall outcome of this treatment.”

Question 4. P3, line 44-55. The research aims are too vague to measure, and those actually sound more like the research approaches. I suggest the authors to have more specific questions or hypotheses written so to better lead the statistical analysis later.

Response: Thank you very much for your advice. We have reorganized the research aim.

The sentence now reads “Therefore, with this protocol, we aim to evaluate the safety and the effectiveness of acupuncture for the treatment of BCRL”.

Method Part:

Question 1. Study Setting/Design: I suggest the authors to summarize their study design such as a multi-center two-arm (?) randomized clinical trial before describing the setting.

Response: Thank you very much for your comment. We have modified this sentence.

It now reads “This multi-center two-arm randomized clinical trial study will be performed in the following three medical centers”

Also, please provide average numbers of the breast cancer patients seen annually at each center for readers to understand how representative the sample might be. P4, ling 5-8, the description of intervention is confusing, I suggest the authors to describe the intervention group and control group separately.

Response: Thank you very much for your advice. We have added the average numbers of the breast cancer patients seen annually at each center. As for the description of intervention, we have also described both groups separately. It now reads “For patients assigned to the real acupuncture group, a standard acupuncture procedure using the real will be performed; for patients assigned to the sham acupuncture group, a standard acupuncture procedure using the sham needles will be performed. The acupoints, frequency (3 times a week for 4 weeks), and duration (30 minutes after de qi) of each patient in both groups should be the same. And for
ethical consideration, every participant will receive a standard decongestive therapy following acupuncture (real or sham).”

Question 2. Eligibility criteria: There is a conflicting information regarding BMI. It includes BMI 18-28 and excludes overweight women. However, the general cutoff for overweight is BMI 25-29.9. Please explain the discrepancy.

Response: Thank you very much for your comment. We have corrected it. The BMI inclusion criteria is 18-25.

Question 3. Intervention: are sham-acupuncture performed at the same points as real acupuncture group?

Response: Thank you very much for your comment. We are sorry that we have not make this clear. We have reorganized this part, and there is one sentence added, which reads “The acupoints, frequency (3 times a week for 4 weeks), and duration (30 minutes after de qi) of each patient in both groups should be the same.”

Please describe the main characters of Steinberger needle and why is it considered to be ideal for sham acupuncture instead of just citing it.

Response: Thank you very much for your advice. We have moved some sentences from the discussion part here. And it now reads “Streitberger needles have the appearance of the real needles, however, they will not penetrate the skin. They can be placed at the same acupoints as the real acupuncture group, and held in position by adhesive plaster with a plastic ring, which is conducive to the blinding purpose.38 When the needle is pushed against the skin, a pricking sensation just like the real insertion will be generated. However, as the pressure increases, the needle shaft will bounce back into the handle, which guarantees the skin unbroken and makes an artificial impression of needle insertion (Fig. 2).”

Is a decongestive therapy standard treatment for BCRL? Please describe why it is chosen for both intervention and control groups.

Response: Thank you very much for your comment. Yes, the decongestive therapy is a standard treatment for BCRL. For ethical consideration, we included it in both groups, otherwise, the interest of participants in the sham group might be undermined in this trial.

Question 4. Outcome, Measures, and data collection: The method section lacks appropriate description of measures of the outcomes. For instance, for the primary outcome-ARLVR: how
limb volume is measured? It states "to take assessments of both limbs by perometer (p6-7)", what is a perometer? How is that measured?

Response: Thank you very much for your comment. We have revised the data collection part. It now reads “Before the first treatment session, every participant will get an assessment of both limbs by perometer, which is an automated infrared light digital scanner equipped with a microcomputer. When the limb is placed inside, the infrared light transmitters located on two sides of the perometer will be activated, and the blockage of the transmission of infrared light from both sides caused by the limb will be recorded and calculated. As the transmitters move along the limb, a series of images will be recorded. Hence a highly accurate measurement of the limb size and volume will be created. And these results will serve as the baseline data. Following the treatment of each session, participants in both groups will be asked to take assessments to get the interim data. Upon the last session, the assessments of both limbs will be adopted as the end-point data. For each arm, the measurement will repeat three times to ensure the reliability. Table 1 illustrates all the time points when measurements are taken during the whole procedure.”

I suggest the authors to add proper measurement description for each outcome, particularly for lymphedema, then describe the data collection accordingly, such as when are baseline, pre-intervention, mid-point, and end-point data collected etc.

Response: Thank you very much for your suggestion. We have added measurement description for the outcomes, including the baseline, mid-point and end-point data in the revised “data collection” part. Please refer to the response to the question above.

Question 5. Sample size estimation: although there were not identical studies done, there are similar trials conducted before. For instance, Cassileth's study published in 2013 used the a ratio outcome to assess acupuncture for lymphedema (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3738927/). Consult with a biostatistician to obtain more accurate estimated effect size.

Response: Thanks for your kind advice. We have read up this paper you mentioned, and calculated the effect size based on this study and the preliminary data we have collected. Please refer to the updated additional file A2.

Question 6. Data management: There is no adequate description of data management; most of that paragraph is about loss to follow-up. P. 13-22 should be moved to other section describing potential risks in data collection procedure.
Response: Thank you very much for your comment and suggestion. We have moved those lines describing potential risks in data collection procedure to “Data collection” part. And we have also expanded the data management part. Please refer to the revised paragraph on Page 8-9.

Question 7. Statistical analysis: I am concerned about the test proposed. As there are only two groups (real vs sham acupuncture) to compare, ANOVA will NOT be the proper test. If the authors tried to compare three sites, then you can use ANOVA, but that is not research questions of this study. Overall the statistical analysis section is inadequate; please consult a statistician to rewrite. If the test changes, you will need to perform sample estimation again to get new adequate number.

Response: Thank you very much for your comment. We have consulted with a statistician. As pointed out by you, the research aim of this trial is to compare the difference between the two groups (real vs. sham acupuncture), and the proper statistical analysis method is t test or non-parameter test based on the normality test of the whole data. Moreover, before the use of t test, we should employ one-way ANOVA to see whether there is significant difference between three centers. Analysis of covariance adjusted for clinical center and baseline will be applied on the condition that significant difference exists between three centers. As suggested by you, we have expanded the statistical analysis section. And we recalculated the sample size (Additional file A2).

Discussion Part:

Information about Steinberger needle (p9, line 9-28) should be moved into methods. Information about perometer (p9. Line 28-39) should be moved into methods.

Response: Thank you very much for your kind advice. As shown in the response above, we have move the information parts of Steinberger needle into “methods” part.

And there are some other minor changes in the manuscript, which are marked red in the “Revised manuscript with tracked changes”.

All the authors are very grateful for your careful and hard work on our manuscript. We hope our responses will meet your requirements. If you have any queries, please feel free to contact us.

Best regards.

Sincerely,

Shengming Dai