**Author’s response to reviews**

**Title:** Study on efficacy and safety of Tong-luo Qu-tong plaster treatment for knee osteoarthritis: study protocol for a randomised, double-blind, parallel positive control, multi-center clinical trial

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**Version:** 1  **Date:** 05 May 2019

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Reviewer reports:

Thank you for this protocol which is well written. I would however like more detail as to why you choose an inferiority trial design and also explain the difference in sample size ie 1500 Versus 500. You need to justify both. Also explain more what the differences are in the two applications, one has a herbal base, is the other group only a plaster?

Comment 1: “why you choose an inferiority trial design”

Response: We are grateful for your careful reading of our manuscript. We have revised the text as follows:
A non-inferiority trial design was adopted, with the unceasing development of medical technology, there are increasing number of positive drugs with the exact curative effect in clinical treatments. Once an existing effective positive therapy has been established, it would be unethical to undertake placebo controlled trials [17], which made the application of non-inferiority trial more and more widely used in clinical studies within the last decades [18, 19]. A non-inferiority trial design could be a better alternative to indirectly show the efficacy of the new treatment [20].

Reference:


Comment 2: “also explain the difference in sample size ie 1500 Versus 500”

Response: Thank a lot for your critical reading, we had added the information in the revision:

A number of previous clinical studies also had adopted unequal allocations ratio designs, it was possible to minimize the potentially unethical exposure of patients to placebo [30-32]. However, our study lacked a placebo group, which is different from previous studies. Based on the above, we drew up an appropriate unequal allocation ratio. All eligible patients were assigned in a 3:1 ratio (Tong-luo Qu-tong plaster group:Qi-zheng Xiao-tong plaster group) by a stratified-block randomized method, the study design was ensured to increase the number of patients required to undergo a Tong-luo Qu-tong plaster exposure by employing an unequal allocations ratio, it provided a greater safety assessment and more experiences of efficacy for Tong-luo Qu-tong plaster in this randomised controlled clinical trials to ensure that the trial offer good evidence to answer the trial's research question.

Reference:


“Also explain more what the differences are in the two applications, one has a herbal base, is the other group only a plaster”

Response: We are grateful for your careful reading of our manuscript, we had added the information of two applications in the revision:

Tong-luo Qu-tong plaster is a tape-type Chinese herbal patch, composed of Syzygium aromaticum, Zanthoxylum bungeanum, cinnamon, Rhizoma zingiberis, borneol, camphor, menthol crystal and a hydrophilic adhesive vehicle. It is made by Henan Lingrui Pharmaceutical Ltd (State Food and Drug Administration approval number: Z20000065), the validity period of Tong-luo Qu-tong plaster is 24 months. Qi-zheng Xiao-tong plaster is a medicated plaster made by Tibet Qizheng Tibetan Medicine Ltd (State Food and Drug Administration approval number: Z54020113), it is valid for 36 months. The main components of the Qi-zheng Xiao-tong plaster are Lamiophlomis rotata, Curcuma Longa and a hydrophilic adhesive vehicle. The components of two applications in this trial were different, two kinds of plasters are identical to the tested formulation in terms of texture, size, color, and odor.

General comments:

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English.

Response: Thank you for your careful reading of our manuscript. The manuscript had been revised by a PhD who is fluent in English before the original submission. We checked the manuscript carefully again to improve the English language before resubmission.

Besides, we modified the drug name of the experimental group in this study caused by our error. The original name was Tong-luo Qu-yu plaster, now the correct name is Tong-luo Qu-tong plaster.