Author's response to reviews

Title: Comparison of heat-sensitive moxibustion versus fluticasone/salmeterol (seretide) combination in the treatment of chronic persistent asthma: design of a multicenter randomized controlled trial

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Author's response to reviews:

Dear Editor:

Thank you for reviewing our submission of MS:1921179967433384. According to your require, we downloaded the paper and read the reviewers comment carefully. Then, we revised the original manuscript and made the reply to the reviewers as follows.

Question1: The manuscript needs editing by a native English speaker. I started to edit it, but the number of changes became quite large, so we should ask the investigators to find someone to do that.

Answer1: Thanks for the advice. We have asked help from a native English speaker.

Question2: It is unclear what the primary outcome is, and at which time point it will be assessed. The paper lists several outcomes measured at several times, but the primary one should be clearly specified.

Answer2: At present, the goal of asthma care is to achieve and maintain control of clinical manifestation of the disease. Hence, we use Asthma Control Test (ACT). ACT will be assessed over a 3-month period before each clinic visit at days 15, 30, 60, and 90. Follow-up visit will be in 3, 6 months after the last treatment session. More detailed have been described in revised paper.

Question3: The analysis will include adjustment for baseline imbalances, but it is not clear if this is the primary or a secondary analysis.

Answer3: Under normal circumstances, baseline characteristics will be tested in regularly statistical method, such as t-test, Wilcoxon rank sum test, Chi-square test. If any imbalances in baseline characteristics between groups are encountered, we should use secondary analysis which was described in paper.

Question4: 20% lost to follow-up is assumed for the sample size calculation, but how missing data will be handled is not clear. It is stated that an intention-to-treat
analysis will be used, but given a 20% loss, how this will be done should be clarified.

Answer4: We will conduct analysis on an intention-to-treat basis, including all randomized participants with at least one measurable outcome report. Missing data will be replaced according to the principle of the last observation carried forward. Of course, we will try our best to avoid lost to follow-up in both groups. We have clarified the below issue. More detailed have been described in revised paper.

Question5: It is stated that this will be a non-inferiority trial, but how the delta was selected should be stated.

Answer5: The determination of the margin # in a non-inferiority trial is based on both statistical reasoning and clinical judgement, and should reject uncertainties in the evidence on which the choice is based, and should be suitably conservative. Therefore, the choice of # is not very easy. To determine #, we carried out a small sample pilot study previously. The primary endpoint chosen was ACT. The result of outcome showed difference in means between the two groups approximately was 0.5. The choice of #= 0.15 (30% of #) appeared to be reasonable based on clinical relevance and statistical judgment.

Question6: Patients will be divided into three categories of asthma, but will they be stratified during randomization on those categories?

Answer6: The aim of this study is to investigate the effectiveness of heat-sensitive moxibustion compared with fluticasone/salmeterol (seretide) in patients with chronic moderate persistent asthma in China. Only one tape patients will be included in trial. The purpose of listing table of three categories of asthma was to contribute to the understanding of readers.

Question7: Rather than list the twelve clinical sites in the text, a table would be simpler.

Answer7: Thanks for the advice. We have done it.

Question8: The Abstract appears to assume the outcome (“… will provide evidence for the effectiveness …”) rather than express uncertainty.

Answer8: Thanks for the advice. We have done it.