Author’s response to reviews

Title: Binafuxi Granules in the treatment of common cold with heat syndrome based on traditional Uighur medicine: study protocol for a multicenter randomized controlled trial

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Version: 1 Date: 06 Jan 2019

Author’s response to reviews:

Dear Editor,

Thank you very much for your letter and the reviews about our manuscript submitted to Binafuxi Granules in the treatment of common cold with heat syndrome based on traditional Uighur medicine: study protocol for a multicenter randomized controlled trial (TRLS-D-18-00957). We sincerely appreciate the professional comments from editor and reviewers. We have revised the manuscript with all the changes highlighted by using the track changes mode. Our responses to the comments are provided in a point-to-point manner. We hope the revised manuscript will be accepted for publication in Trials.

We look forward to your reply soon.

Best wishes,

Sincerely yours,

Prof. Bing Mao
Response to editor as follows:

A. SPIRIT items:

1. Item 5d. Beijing QiHuang Clinical Drug Research Center is the coordinating center, which is in charge of monitoring implementation of trial protocol, data of CRFs and safety of participants, as well as contacting and coordinating the various units. We have added that in the revised manuscript (Page 14).

2. Item 6b. The minimum effective dose of Binafuxi Granules is 2.75 g. We chose the double dose and minimum dose to detect the optimal therapeutic dosage and safety. We have added the details in the revised manuscript (Page 8).

3. Item 16b. The randomization sequence and the randomization list of each unit were generated by the independent statistician, who is not involved in outcome assessment, using the PRCO PLAN function of the analysis system of SAS software (SAS, Cary, NC, USA). The independent drug administrator at each unit assigned numbered packs of study drugs to eligible patients in order by randomization list. The independent drug administrator is the only person who has access to the randomization list while the trial in ongoing. We have added the details in the revised manuscript (Page 10).

4. Item 16c. The independent statistician generates the allocation sequence (Page 10). The investigators enrolled participants and the principal investigator is responsible for subject recruitment in each unit (Page 6). The independent drug administrator assigned numbered packs of study drugs to eligible patients in order by randomization list (Page 10).

5. Item 18b. We don’t have a particular plan to follow up all subjects, because the course of common cold is short and the intervention is just 3 days. But we will follow up any adverse event to completion. We have added it on Page 9.

6. Item 19. All CRFs will be securely stored in a locked location. We have added the details on Page 16.
7. Item 21a. Beijing QiHuang Clinical Drug Research Center is the Data and Safety Monitoring center, which is responsible for monitoring implementation of trial protocol, data of CRFs and safety of participants, as well as contacting and coordinating the various units. We have added it on Page 14.

8. Item 25. The CRA will monitor the process of trial to make sure it complies with the protocol and contact the various units. Any protocol modification should be documented with appropriate justification and approved by the sponsor, primary investigator in each unit and statisticians. Then the final version should be presented to the Ethics Committee, and the SFDA if required. We have added the details on Page 15.

9. Item 26a. The investigators will talk with eligible patients about the study and obtain informed consent from them. The principal investigator is responsible for subject recruitment in each unit. We have added the details on Page 6.

10. Item 27. For protecting the privacy, the personal information of all eligible participants will be concealed by identification codes and all records will be stored in a locked location. We have added the details on Page 6.

11. Item 29. The principal investigator, the sponsor, data administrators and statisticians will perform a blind review to confirm the dataset (Page 16).

12. Item 31a, b. The trial results will be disseminated through scientific journals or presentation at scientific conference (Page 20). The authorship remains undetermined.

13. Item 31c. The data will be available to other investigators. We have added it on Page 19.

We have uploaded the revised SPIRIT checklist and the revised Flow chart.
B. The last few comments:

1. Thank you for pointing out that. The wrong words have been corrected in the revised manuscript.

2. We are sorry for the mistake. The randomization sequence will be kept by the leader and the sponsor. We have corrected that in the revised manuscript (Page 10).

3. The statistical analysis plan has been pre-specified. We have corrected that mistake in the revised manuscript (Page 15).

4. The total score of TUM symptoms (including primary and secondary symptoms) will be summed on baseline (symptom score before treatment) and the 4th day (symptom score after treatment). The sum of all symptom scores is the cumulative TUM symptom score. The change in cumulative TUM symptom score is assessed by the percentage of symptom score reduction (PSSR). The improvement of TUM symptoms will be assessed by the therapeutic effect evaluation system. Based on this system, it will be categorized into clinical recovery (PSSR≥70%) and invalid (PSSR< 70%). The improvement of TUM symptoms will be estimated with descriptive analysis for number and proportion of patients achieving clinical recovery (PSSR≥70%). We added the detail in the revised manuscript (Page 12).

Response to Reviewer #1 (Zehuai Wen, M.D.) as follows:

1. Thank you for your suggestion. A main task in our study is to compare the means of the time to fever relief (a primary outcome in our study) using an F test (one-way analysis of variance) for three randomized groups. Therefore, we used “One-Way Analysis of Variance F-Tests using Effect Size” in PASS (version 15.0.5) to estimate sample size with a significance level of 0.05. However, to our knowledge, no preliminary study reported the effective size related to the time to fever relief in our target population (patients with common cold). Thus, we used η² as an alternative measure of effect size to estimate the sample size [1-3]. Generally, the effect size can be defined as follows: An η² = 0.0099 ≈ 0.01 is a small effect. An η² = 0.0588 ≈ 0.06 is a medium effect. And, an η² = 0.1379 ≈ 0.14 is a large effect [1-3]. In our study, we would like to determine the sample size required to detect a medium effect when the power is 0.90. Therefore, total sample of 204 subjects (68 for each group) would be required. Assuming an overall 15% drop-out rate of our subjects, 80 subjects should be recruited in each group. Finally, the total
sample size is determined to be 240 patients. We added the detail in the revised manuscript (Page 15).

References


2. Using a stratified block randomization method, 240 participates are stratified by study center (Page 10).

3. We have a procedure to deal with accidental unblinding in the trial. An emergency letter including random sequence and assignment has been prepared in each center. In any emergency medical situation, such as serious adverse event or deteriorative condition, unblinding process will be started after contacting the sponsor and the primary investigator. The investigator should record the details of the urgent unblinding and make sure the corresponding patient is excluded. We added the details in the revised manuscript (Page 10).

4. Thank you for your suggestion. The primary analysis set for efficacy is the full analysis set (FAS) with an intention-to-treat (ITT) principle, in which all patients treated with at least one dose of study drug and clinical observation record should be involved. According to an ITT principle, the last-observation-carried-forward (LOCF) imputation method will be used to approach for missing data. Comparisons among three groups will be conducted by an analysis of variance (ANOVA) and Bonferroni method. Covariates designated as potential confounders will include: age, gender, Body Mass Index (BMI), and duration of symptomatic illness prior to enrollment. Prespecified subgroup analyses and sensitivity analyses involving covariance analysis will evaluate the primary outcomes according to the age and gender. We added the detail in the revised manuscript (Page 16-17).