Author's response to reviews

Title: The efficacy and safety of Shaoyao Shujin tablet for knee osteoarthritis: study protocol for a multicenter randomized, double-blind, placebo-controlled trial

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Author's response to reviews: see over
Dear Editors and Reviewer Kent Johnson:

We are very grateful to the editors and the reviewer for the careful and considered comments and for their valuable time. We have accommodated the comments and the paper is revised accordingly. We look forward to hearing from you.

Kind regards,

Ding-Kun Lin, on behalf of authors.

Responses to the comments of reviewer Kent Johnson:

Major essential revisions

1- Have a native English speaking science writer carefully edit the entire manuscript.

Response: We are grateful for this suggestion. At least one native English speaking science writers had edited our manuscript, See figure 1 below.

2- Rewrite all sections that make claims without substantive standards of evidence (well-controlled, randomized trials) – for example lines 103-105. The language needs to be much more nuanced – the science editor should be able to help here. The text needs to reflect the design used in ref 6, and it needs to reflect that delay in degeneration claim has been shown only in animal models (ref 7 & 8). In another area, lines 245-
250, without a careful, critical review of the claims made, I think this material amounts to editorializing and should be deleted.

**Response:** We are grateful for this suggestion. We had noticed there have some confused concepts in background section. Shaoyao Shujin tablet (SST) had been named as Yangxue ruanjian jiaonang before, due to the transfer of patent, this multicomponent Chinese herbal supplement changed its name as Shaoyao Shujin tablet at last. In ref 6-9 both *Yangxue ruanjian jiaonang* and *shaoyao shujin tablet* were the same subject. We had cleared this concept in line 97-98. We had also cleared that ref 6 was a literature about the effectiveness of SST on pain relief of KOA patients and ref 7-8 was a literature about the degeneration delay of KOA articulate cartilage in animal models. Amendment can be seen in lines 99-100. According to Handling editor' comments, we don’t delete lines 246-249.

3- Line 100 – these are only a small part of the toxicity that is seen in the elderly.
**Response:** We agree with the reviewer’s argument. As we know that the current pharmacological approaches on KOA still haven’t a perfect one. We are trying to fine out whether Chinese herbal supplement would have any valuable effectiveness on treating KOA in concerning about more safety or less side-effect, obviously this need more researches.

4- Need a discussion of the duration – 6wk treatment only. Is there any longer term follow-up planned?

**Response:** We agree with the reviewer’s argument. As a short-term study aims to explore the efficacy and safety of SST for the symptomatic management of KOA, we think of 6 weeks treatment and 4 weeks follow-up will be enough to observe whether there are difference among HD group, LD group and the placebo tablet group. We have added a new statement to address this question (pages 8, lines 166-169).

5-Blinding (line 205): Are the treating physicians/health care workers also blinded. This needs to be made explicit. If they are not, then the design is inappropriate.
**Response:** We agree with the reviewer’s argument. In this trial, the treating physicians who are responsible for observations or efficacy evaluations are blinded because the placebo tablet will be manufactured identically to the SST in terms of color and odor. We had changed “assessor” into “treating physicians”.

6-Lines 182-187 – The abstract says rescue medication use is also a secondary outcome, yet it is not mentioned here.

**Response:** We agree with the reviewer’s argument. We agree rescue medication complicates the interpretation of trial results by having an effect on the trial outcome, typically rescue medication tends to make the observed outcome better than would otherwise have been observed. In our study, the rescue medication will be adopted as a covariate in primary outcome analysis. We had revised the statement in abstract. (lines 53 and 56).

7-Statistical analysis: Elaborate on the multi-level regression model to assess rescue medication use. Where did the 18.2 come from – ref 13/Table 2 shows 19.8 to be the overall SD
of the total WOMAC score (although this won’t change the sample size much)?

In the discussion you need to address the possibility that a success conclusion in the primary endpoint analysis might be undermined by the conclusion in the rescue medication analysis - i.e., the SST herbal medicine may win by the WOMAC but if the rescue medication analysis shows more rescue use in the SST herbal medicine patients, then the WOMAC win may not be due to the SST herbal medicine use but to a greater ibuprofen use.

**Response:** We are grateful for this suggestion. We had elaborated rescue medication as a covariate into a multilevel regression approaches (see lines 240-244), and in discussion section, we had adopted the reviewer’s option and discussed underlying outcomes of the rescue medication might given and practical method.(see lines 249-262).

In sample size section, we had realized there have some data mistakes, and we had recalculated our sample size with hypothesis as that WOMAC total score absolute improvement
of 10 in HD group and 5 in LD group are likely the smallest clinically relevant difference compare with control group. We adopt the standard deviation of the total WOMAC score is 19.8 at baseline. Based on these assumptions, in a one-way ANOVA study, we need 77 patients in each group to have at least 80% power ($\beta = 0.8$) and to rule out a two-sided type I error of 5% ($\alpha = 0.05$). Although the sample size is smaller than before, according to our careful recalculation, we consider it will be the right and reasonable size. (see lines 222-232)

8-Why are electrocardiograms being done? Is there any good evidence on the toxicity profile of SST?

Response: We are grateful for this suggestion. Because there were no good evidence on the toxicity profile of SST, and in order to evaluate the safety of SST sufficiently, we think it’s necessary to do a electrocardiogram for patients.
FIGURE 1

EDITORIAL CERTIFICATE

This document certifies that the manuscript listed below was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at American Journal Experts.

Manuscript title:
The efficacy and safety of Shaoyao Shuǐjin tablet for knee osteoarthritis: study protocol for a randomized controlled trial

Authors:
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