Author's response to reviews

Title: Study protocol: a randomized double-blind placebo-controlled trial of Classic Yin and Yang Tonic Formula for Osteopenia

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Author's response to reviews: see over
June 1, 2011
Doug Altman; Curt Furberg; Jeremy Grimshaw; Peter Rothwell, Kent Johnson
Marissa Lassere, Editors-in-Chief, Trials

Dear Editors and reviewers:

We would like to resubmit our manuscript “Study protocol: a randomized double-blind placebo-controlled trial of Classic Yin and Yang Tonic Formula for osteopenia” (MS: 1725176005228941) to the Trials for consideration for publication. We have carefully addressed all questions raised by reviewers and provided ‘point-to-point’ replies to reviewers’ comments (please see the appendix). There is no financial conflict of interest for all authors involved in this study.

Sincerely,

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Appendix: (reply marked with blue)

Reviewer: Kent Johnson
Reviewer's report:
I have two general problems with this article.
1-LANGUAGE: The article needs to be edited by an English-fluent biomedical writer. There are numerous instances of poor language construction. To take the first paragraph (“Background”) as an example.
Line 4 “long drug therapy” should be “long-term drug therapy”
Line 5 “and side effect” should be “and side effects”
Lines 7/8 “research the mechanism of efficacy” would be better expressed as “to investigate the mechanism of efficacy”

Reply: Thanks for reviewer’s comment. We have already modified the manuscript and corrected the English grammar (marked in red). The revised
2-PREMISE OF THE PROTOCOL: The primary hypothesis is that the BMD change in the intervention arm will be significantly different from the BMD change in the placebo arm. The article is premised on the assertion that these BMD differences will then translate in fracture reduction changes, yet there is no good evidence that this is the case and there is some evidence that it is not the case with certain classes of drugs directed at BMD. Different classes of anti-osteoporosis drugs have different effects on BMD and fracture reduction, and no analysis of all osteoporosis drugs has shown that BMD changes translate into fracture reduction changes as seen, for example, with other “validated” surrogates. For example the LDL-cholesterol differences in trials of statins versus placebo translate into a statistically significant stroke reduction (1), a finding that affirms the assumption that a new statin will have a similar stroke reduction benefit as previous statins. Additionally, observational BMD / fracture data alone cannot affirm or refute the assertion that a treatment related change in a surrogate translates into a treatment-related improvement in outcome, as has been shown in certain high profile failures in the past (2). Therefore, the tone of the article is incorrect. Osteoporosis trials for drug registration for a claim of fracture reduction have typically been three years in duration and used vertebral fractures or all clinical fractures at their primary endpoint. The three year duration arises from the natural history of BMD change. The trial size proposed here, 102 patients per arm for six months, will fall far short of adequate power for a fracture endpoint trial. Given this, one option would be to rewrite the article, delete the implications that a BMD demonstration translates into a reduction in fractures, and call it a trial to evaluate BMD.

Reply: After carefully reviewing literatures and considering reviewer's comments, we have decided to remove the observation of fracture reduction. Our study is to examine effects of a Chinese herbal intervention to increase bone mineral density of patients with osteoporosis. We have rewritten the ‘Methods/Design’ section and provided more detail information about outcome measurements and sample size considerations. We also have corrected the tone in the revised manuscript.

A few other points:
3-It is not clear that the treating physician is blinded. If not, the term double-blind should not be used.

Reply: In this study, the treating physicians, subjects, and investigators will be blinded to treatment assignment. That will make sure the trial is double-blind.
4-Need explanation of “pattern differentiation of TCM” (Setting and Overall Study Design) and why it is important enough to be a stratification factor. 
Reply: “pattern differentiation of TCM” is also translated into “syndrome differentiation of TCM”. Syndrome, as related to illnesses in Western medicine, are composed of a set of signs and/or symptoms classified by Traditional Chinese Medicine practitioners. TCM Syndrome differentiation based on symptoms help to identify a subset of disease.

5-In revised form the article should be reviewed by a biostatistician. 
Reply: We have rewritten the ‘Statistical Analysis’ section in the revised manuscript, which has been read and modified by a biostatistician.

Reviewer: Marissa Lassere  
Reviewer’s report: 
see comments by Dr Kent Johnson 
Reply: Thanks for reviewers’ comments. We have carefully addressed all questions raised by Dr.Kent Johnson.

Level of interest: An article whose findings are important to those with closely related research interests. 
Reply: Findings of this study will provide evidence regarding the value of the Chinese medical herbs as an intervention to increase BMD in patients with osteoporosis.

Quality of written English: Not suitable for publication unless extensively edited. 
Reply: We have already corrected the English grammar and improved the quality of written English. The revised manuscript has been read and edited by an English-fluent biomedical writer.

Statistical review: No, the manuscript does not need to be seen by a statistician. 
Reply: Thanks for reviewers’ comment.

Declaration of competing interests: 
I declare that I ahve no competing interests. 

Reply: All authors of this article declare that they have no competing interests.