Reviewer's report

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

Version: 3 Date: 3 May 2011

Reviewer: Kent Johnson

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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”

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.

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.

4-Need explanation of “pattern differentiation of TCM” (Setting and Overall Study Design) and why it is important enough to be a stratification factor.

5-In revised form the article should be reviewed by a biostatistician.

References:
