Reviewer's report

Title: Exploring Effective Core Drug Patterns in Primary Insomnia Treatment with Chinese Herbal Medicine: Study Protocol for a Randomized Controlled Trial

Version: 2 Date: 3 January 2013

Reviewer: John Norrie

Reviewer's report:

Discretionary revisions

The authors need to attend to the following issues to clarify their protocol:

1. The English writing needs checking throughout - there are various mistakes and in several places the protocol lacks fluency.

2. The design needs to be more carefully explained and justified - for example:
   a. It seems that all eligible patients are seen by the 3 TCM clinicians, including the 50% that will be randomised to placebo - but that it is only those randomised to TCM that are subsequently seen after randomisation by the 3 clinicians - so (a) how then is this a 'blinded' and (b) what is the point of the baseline TCM assessments in the placebo group? They do not appear to be used after they have been taken?
   b. What is the overarching purpose of the trial - the title suggests that this is 'finding the effective core drug patterns' - so is the comparison between placebo and active purely to identify the subset of patients that have responded to then conduct the 'scale free network' analysis to find these core drug patterns?
   c. The protocol states 'At next visits the assignment of group still adopts the randomisation results of the first visit' - so useful to be clear - the patient remains being treated with whatever the initial clinician allocated recommends, but this prescription could be changed and adapt from visit to visit?
   d. But if so doesn't that make the prescriptions from the other two TCM clinicians very artificial - because they haven't been treated according to what they recommended? And in a similar vein even though one of them had their treatment implemented, they don't actually know that for sure due to blinding?

3. There does not seem to be any justification of the sample size - we are told it is a sequential design with looks at 80 and 160, and that the maximum sample size will be 300 - but this is not justified in terms of power to detect an assumed effect size nor what variability is being assumed in the Total Sleep Time (TST) primary outcome?

4. But given the objective is to find the 'core effective drug patterns', this isn't driven so much by the 150 patients, but the 3 TCM clinicians. Three seems a very small number, and in addition all three are described as 'prestigious' and 'expert'. So it would seem (a) we are unlikely to find all the core drug patterns
due to a very small number of clinicians taking part and (b) even then the findings may not be generalisable?

5. We need proper detail and methodological references for the 'multi dimensions association rule and scale free networks method' - and in addition why is this analysis only on those that the treatments proved effective on? And what is the definition of effective for TST?

6. What pharmacologic insomnia treatments will be allowed and how will this be adjusted for in the analysis, if appropriate?

7. What is the justification for having an upper age limit of 65 years old?

8. In addition, the authors should discuss the inclusion / exclusion criteria to explain how generalisable the findings might be? Presumably this is a single site study, as well?

9. Is the primary outcome of TST by patient self report from a diary validated for use like this in a clinical trial?

10. The safety section is very brief and should be expanded. Is there any independent oversight of the trial via a Trial Steering Committee and an independent Data Monitoring Committee?