Title: Efficacy of cognitive enhancers for Alzheimer's disease Protocol for a systematic review and network meta-analysis

Version: 3 Date: 3 May 2012

Reviewer: Kerry Dwan

Reviewer's report:

Major Compulsory Revisions

Minor Essential Revisions
2. There are still comments included in your revised manuscript, please delete.

3. Eligibility criteria – it is unclear what the final sentence adds regarding subgroups of interest. Are these items you will look at in subgroup analyses?

4. Methods/design - Studies should not be excluded if they have not reported the outcomes of interest as they may have measured them. This was not sufficiently addressed from the first comments, the text states “To be included in this systematic review....”

5. Methods/design – It is not clear why you will further refine outcomes using the process you suggest. Surely this should have been done during the production of the protocol? Outcomes should not change between protocol and full review.

6. Study selection process - How will the inclusion and exclusion criteria be revised? This was not addressed from my first comments as I was talking about the first paragraph in study selection process.

7. Methodological quality/ risk of bias –please edit the sentence you have included as it states “use GRADE to and to assess"

8. Methodological quality/ risk of bias – the reference for publication bias has not been included.

9. Synthesis of included studies - Measures of treatment effect for dichotomous and continuous outcomes should be stated. This has not been addressed from my first comments i.e. will mean difference and 95% confidence intervals be used or risk ratios or odds ratios etc?

10. Synthesis of included studies - For heterogeneity, what do you consider statistically significant for chi squared, p<0.1?

11. Synthesis of included studies – Please check references, they jump from 26 to 33 and several are included as names not numbers and several are included
as full references – please read over this new section.

12. Synthesis of included studies – more details are needed regarding the sensitivity analyses i.e. how will you split instrument used for primary outcome? What will you do about average adherence between groups? Will you combine observational studies with RCTs here?

13. Synthesis of included studies - you have stated that there needs to be three studies included before a meta-regression is to be conducted. However, typical guidance suggests 10.