Reviewer's report

Title: The effect of long-term homocysteine-lowering on vascular structure and function in stroke: a randomized controlled trial and meta-analysis

Version: 2 Date: 16 June 2008

Reviewer: Andrew R Willan

Reviewer's report:

Major Compulsory Revisions

From Figure 1, only 30% (i.e. 162) of the 532 patients that were randomized contributed data to the analysis. This is an unacceptably high rate of loss-to-followup. Since this is a report of a sub-study, the patients were randomized prior to being recruited. This is a huge methodological flaw, leading to a 70% “drop-out” rate and, quite possibly, a biased sample. This issue requires a more extensive discussion in the Limitations Section.

Was the type I error rate used for sample size determination one- or two-sided? According to the objectives it should have been one-sided.

The p-values in Table 1 should be removed. For baseline comparisons they are irrelevant, since any difference had to have occurred by chance. Also, the effect of baseline imbalances are based on the actual difference, not on whether they are statistically significant or not. The p-value is a function of sample size, so that in a large study very small differences might be statistically significant, but irrelevant with regard to their effect on post-treatment comparisons. On the other hand, in a small study a large important difference in a baseline variable might not be statistically significant. The follow-up p-values in Table 1 should also be removed since they are not outcome variables in the treatment comparison.

In Table 2 the p-values for the “Baseline” and “Post-treatment” comparisons should be removed. The confidence intervals (or whatever they are in the parentheses) for the “Baseline” and “Post-treatment” comparisons should be replaced by the standard deviations. Also, the ‘Change from baseline” means, confidence intervals (or whatever they are in the parentheses) and p-values should be replaced by the adjusted mean treatment difference from an analysis of covariance, together with the associated standard errors and p-values. In the analysis of covariance the dependent variable should be the post-treatment value and the independent variables should be the baseline value and an indicator for treatment group.

What biases are the effect sizes corrected for? How is the confidence interval for an effect size determined?

Discretionary Revisions
The sub-groups analyses for the FMD meta-analysis would be enhanced with proper tests for interactions.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.