Reviewer's report

Title: An empirical study using permutation based resampling in meta-regression

Version: 2 Date: 7 December 2011

Reviewer: David Fisher

Reviewer's report:

Major Compulsory Revisions

None - in general this is a well carried-out empirical study of a previously-proposed and simulated methodology (Higgins et al, 2004)

Minor Essential Revisions

Statistical Analysis: Exploration of Heterogeneity, Para 1

“Therefore, the presence of statistical heterogeneity was tested using Cochran’s #2 test or Q test” – these are of course the same thing. Maybe replace with “was tested using Cochran’s Q test (which follows a #2 distribution)” or similar?

Statistical Analysis: Exploration of Heterogeneity, Para 2

“...items 2, 4 and 5 of the jaded scale...” needs correcting to “Jadad scale”

Discretionary Revisions

1. Since the backwards stepwise procedures used to generate Tables 3-5 resulted in relatively few covariates significant at the 5% level, would it be worthwhile specifying a 10% significance level instead, in order to generate more data, especially on ‘borderline significant’ p-values? Basing conclusions on just 9 cases seems a little premature.

2. It is well known that meta-regression on summary patient characteristics (e.g. age, sex) is subject to aggregation bias and may be uninterpretable (except possibly in cases where the distributions are so different as to effectively constitute a trial difference, e.g. studies in adolescents vs those in the elderly). On the other hand, the outcomes considered here are mean differences, and therefore individual patient baseline values are undeniably important. Could the authors comment on the methods used in these trials to adjust for baseline effects – were they mean differences of unadjusted final values, changes from baseline, final value adjusted for baseline, or something else? This may have a great impact on the interpretation of meta-regression coefficients of baseline values. In general, my personal opinion is that patient-level baseline characteristics are not suitable for analysis using meta-regression, and that properly adjusted mean differences should be sought directly from the trial authors where possible.
**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