Reviewer's report

Title: Dealing with Heterogeneity of Treatment Effects: Is the Literature Up to the Challenge? A Systematic Review

Version: 3 Date: 23 March 2009

Reviewer: Gerta Rücker

Reviewer's report:

- Major Compulsory Revisions

(1) In my original review, the main point was that the authors "seem to ignore the fundamental problem of assessment of individual variability that is associated with usual parallel group trials ...". I requested that the authors discuss the problem of variation due to intra-individual reasons (e.g., a drug may or may not be working in this patient on a given day) more carefully.

It is good that the authors now include refs [12,13] and insert three short sentences on each of three places I proposed. However, instead of this, I'd prefer a thorough discussion of this issue at one place in the beginning of the ms (p.5/6). What about taking the sentence from the "Response to reviews": "Subgroup effects may be due to random intra-individual variability, which is impossible to estimate in a parallel group trial."

(2) n-of-1 trials (p. 5/6, one of the three places where the point is mentioned): The authors say that "However, n-of-1 trials are ... subject to random within-patient variability ...". This is misleading, because in the view of the problem described above it is a strength, not a weakness of the n-of-1 trial that it accounts for within-patient variability. In principle, such trials enable researchers to investigate intra-individual variability, what parallel group designs don't.

- Minor Essential Revisions

(4) I did not find answers to the interesting points 1-3 of reviewer 2 (Rochelle Fu) or the points of reviewer 3 (David Moher).

- Discretionary Revisions

(3) "Bivariate analyses" (p.11, 14): From a statistical point of view, I would not describe simple contingency table analyses as "bivariate". A bivariate analysis is one with a bivariate outcome, modelled in terms of a couple of parameters that may influence the outcome. Please replace "bivariate analysis" by "contingency table (analysis)".

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.