Reviewer’s report

Title: Spontaneous improvement in randomised clinical trials: meta-analysis of three-armed trials comparing no treatment, placebo and active intervention

Version: 3 Date: 30 November 2008

Reviewer: Jesse Berlin

Reviewer’s report:

I appreciate the response provided by the authors, which largely takes into account my previous concerns. (The bar chart looks great.)

I also thank the authors for consulting another statistician, who makes some very valid points about the reasons for not pursuing meta-analytic methods that rely on within-study comparisons. His point about the use of ratios, in particular, was a helpful reminder that the scale of the analysis was the SMD, and not an odds ratio or risk ratio. My apologies for my earlier confusion.

Just as a point of clarification, however, the lack of statistical stability within a trial, is an admitted weakness of within-trial analyses. The fact that the SMD is a scale that crosses zero is a problem that is NOT unique to any within-trial calculation of the percent contribution of “no-treatment” or placebo effects. If the overall treatment effects had been “almost zero” (averaged over all trials), then the division by “almost zero,” in the calculation of a percent contribution, could also have been a problem.

I don’t want to quibble, but the meta-analytic principle of making comparisons within-study could still, I think, have been implemented. Within each trial there is a difference (not a ratio, with apologies again) between the change scores (regardless of what variance estimate was used) in the no-treatment arm, the change score in the placebo arm, and the change score in the active treatment arm. These within-trial differences could have been pooled (and the authors note they did this and got similar results), thereby making the comparisons among treatment arms within each study, thereby preserving the randomized nature of the comparison within each study. Figure 3, I believe, speaks to the possibility of using within-study differences, and to the apparent stability of such analyses. Again, I make the point simply for clarification at this stage.

In any case, I’m happy for now to accept the authors’ claim that the within-trial analyses gave similar results. As the statistical response notes, the three summary numbers do speak for themselves.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I continue to be a full-time employee of Johnson & Johnson Pharmaceutical Research and Development. I know of no specific conflict related to this methodologic paper.