Reviewer's report

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

Version: 1 Date: 31 August 2008

Reviewer: Jesse Berlin

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1. Abstract: It’s not immediately obvious how the percentage contributions were calculated. I understand that you may not have room in the abstract to show calculations, but the same comment applies to the Results section of the paper. At a minimum, you need to make it very clear in the abstract that the SMD given in the Results section of the abstract is for pre-post change?

2. In the Results section of the body of the paper, you need to show calculations of percent contribution. No treatment SMD = -0.44; Placebo = -0.54; and active = -1.27. You say the contribution of spontaneous improvement is 35%. Is that .44 / 1.27 = 0.35 (after rounding)? This is just a matter of clarification. You might also provide a footnote for Table 2, giving the calculations? In particular, how did you define the contribution of placebo? Is that subtracting out the effect of spontaneous improvement?

3. Page 4: What was the basis for the selection of outcome measure? Specifically, what do you mean by the outcome that you “found most relevant?” How was relevance defined and determined? Was there a consensus process?

4. Page 5: With respect to the use of pre-post data, let’s assume we just accept the idea of ignoring the pairing in calculating effect sizes. First, you should probably acknowledge that ignoring the pairing implies that we are willing to assume that the effect of the ignored correlations between pre- and post-intervention measurements is the same in all situations. That may not be a realistic assumption, but I agree with the idea that various approaches to imputing missing correlations, correcting variance estimates, etc., would make little difference to the conclusions.

5. Correlations aside, your approach doesn’t seem to take the randomization into account, unless I’m misinterpreting your calculations. Wouldn’t it be possible to get a within-study measure of the relative contributions? These are all 3-arm studies, so the effect of spontaneous improvement, within a study, could be defined as “change from baseline on no treatment / change from baseline on active treatment.” I think I’m advocating using a very similar approach to what you did, but if I’m interpreting correctly, your current calculations are based on the “ratio of the means” rather than the “mean of the ratios.” I hope that’s clear. The point is that you may be introducing potential confounding, if “study” is related to both outcome and treatment assignment? I don’t believe this will make
a substantive difference in your conclusions, but it might, for example, if the allocation ratios are substantially different from 1:1 in some of the studies.

6. Page 5: The difference in pre and post sample sizes could reflect bias in the effect sizes if, for example, the subjects who dropped out did so because of reduced efficacy or increased risk of adverse effects. It’s true that studies with loss to follow-up would be down-weighted, (and I know you’re aware of this potential bias), but you might want to note this issue as a potential limitation.

7. General: Is the analysis here really a multivariate problem? You’ve focused separately on acute versus chronic conditions and observer-reported versus patient-reported outcomes. Could the nature of intervention (psychological versus physical versus drug) matter? I realize it wouldn’t be possible to separate out these effects, because not all types of interventions occur with all clinical conditions. I’m not sure you have enough studies to do real multivariable modeling, but please give this some thought.

Minor Essential

8. Introduction, paragraph 2: Needs a bit more elaboration on spontaneous improvement? Just add something that completes the thought. Patients seek treatment and enroll in trials when Sx are at worst, …, so natural variability means they will be less severe over time (assuming the natural variability is “reversible”, not just increasing deterioration).

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