Reviewer's report

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

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Reviewer: David J Torgerson

Reviewer's report:

I found this paper very interesting and the authors make the point, which is always worth making, that there is spontaneous improvement in many, if not most, clinical areas that are completely unrelated to the treatment effects.

MAJOR

My main criticism, which is a major one, but easily dealt with: is that the authors make no mention of regression to the mean. When patients appear to get better there are three, not two, alternative explanations in addition to a true treatment effect. Placebo and temporal changes as the authors correctly state but also regression effects.

I am surprised that they do not mention it at all as some of their findings are almost certainly due to this phenomenon. For example, on page 9 the say – “It seems likely that spontaneous improvement is more important in trials that include patients with high symptom scores and that do not implement a placebo run-in period.” NO this is regression to the mean – high symptom scores are most likely to have a higher error term and regress more than those near the mean also having a run-in deals with regression to the mean as you are having repeated measures taken. The reason you didn’t see an effect on hypertension trials is that physicians, unless they are incompetent, normally take 3 BP measurements and take the average and only diagnosis hypertension if this is above a certain threshold. This mainly deals with regression effects so if you then enrol these people into a trial those with high values to due to test error have been removed. Psychological tests or any quality of life tests have high error components and are classically subject to regression effects.

There are lots of references to this phenomenon here are some of mine but there are lots of others Stephen Senn as written quite a bit on this:

Torgerson DJ and Torgerson CJ Designing randomised trials in health, education and the social sciences Palgrave macmillan, Basingstoke, 2008 - Chapter 2

Morton and Torgerson BMJ 2003,326:1083-4

So what I recommend is that you include text about regression to the mean and perhaps discuss those areas where it is less likely to occur due to either tests with little error or sequential testing (e.g., hypertension) and interpret your findings in this way.

Unfortunately, I don’t think it is possible to disentangle spontaneous improvement from regression to the mean – you can see where it is less likely but I don’t think you can ever disentangle this from spontaneous improvement.

MINOR

Other less important issues is the type of tests – some will have a ceiling or floor problem. Therefore, those near the top or bottom of the test scores can only go one way, which assuming there is no true change whatsoever, just error you will tend to see a change downwards if it is a ceiling problem because the error can only go to one side – this exacerbates the regression problem (although it is a little different as even if you have a test with no ceiling or floor you will still get regression).

David Torgerson

**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 have no competing interests