Reviewer's report

Title: Comparing methods to estimate treatment effects on a continuous outcome in multicentre randomized controlled trials: A simulation study

Version: 3 Date: 19 January 2011

Reviewer: Ruth Pickering

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I felt the paper read better this time, though it was still difficult following the quantity of results presented in tables. Its the difficulty of assimilating so many scenarios and varying factors. Only a really dedicated reader is going to go through the tables and text results in sufficient detail to absorb all the trends described.

Discretionary revisions

1 Abstract, background, line 3, 'This approach overlooks the potential for clustering within centres'. The stratified analysis, or fixed centre effects approach, to my mind treats centre effect differently than a random effects model, I'm not sure that overlooking clustering is quite accurate.

2 Page 6, 5th-2nd lines from the bottom. 'The mixed model supplies a natural way to extend inference from a sample to a bigger population of centres.' I think this sentence is confusing in the context of the model without centre*treatment interaction. The results show that random main centre effects, because they recover inter-centre information in unbalanced situations can give more precise estimates of the treatment effect than the fixed centre effects models. The reader might assume that the phrase extending inference from a sample to population of centres related to the main objective of the trial the treatment effect, but without centre*treatment interaction, I'm not sure how this is achieved, particularly with a more precise estimate of treatment effect. The same point comes up in the Discussion, page 26, lines 13-15, 'Some believe that the random-effects model should be employed for glocal estimatres'. I think those who believe this are thinking of a model including random centre*treatment interaction, not just random main centre effects.

3 Page 18, 5th-4th lines from the bottom, 'Models B and C yielded more accurate estimates of the standard deviation of the treatment effect estimator'. I would call this the standard ERROR not DEVIATION of the estimate, as done in Table 3. In Tables 4a, 5a, & 6 the average of the model based standard errors of the effect estimates is also called the Ave. SE at the top of the relevant columns. However in these latter tables the standard deviation of the treatment estimates obtained empirically over the 1000 repeated simulations is also called a standard error (SE), whereas I would call this one a standard deviation (SD). The authors should check through the entire text of the results to ensure that however they
choose to call these things its done consistently throughout the document.

**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