Reviewer's report

Title: Systematic review of methods for individual patient data meta analysis with binary outcomes

Version: 3  Date: 5 January 2014

Reviewer: David Fisher

Reviewer's report:

Firstly, thankyou to the authors for a very interesting study, which has given me various thoughts and ideas regarding my own area of interest (meta-analysis of time-to-event data). In general the authors should be commended for the subtlety of their reviewing. My main concern (detailed below) is that such subtlety may be getting confused given the constraints of word limits etc.

Major compulsory revisions:

1. There are several ways in which a meta-analysis may be classified, and the authors attempt to describe all of them to some degree. However, I am concerned as to whether these facets are adequately separated, and whether the manuscript is too confused as a result. For clarity, I refer to:
   a) aggregate-data vs IPD
   b) one-stage vs two-stage
   c) adjusting the treatment effect for (prognostic) confounding vs analysing treatment effect modifiers (e.g. with interaction terms)
   d) random trial effects vs random treatment effects.
   e) [there may be others]

   The authors state that "a one-stage approach... reduce[s] the potential for ecological bias that may occur when meta-regression is used in conventional two-step MA". However, methods exist for analysing treatment-covariate interactions with a two-stage (IPD) approach, and these in fact are guaranteed to be free of ecological bias (see e.g. Fisher, JCE 2011).

   In a later paragraph, the authors state "IPD-MA are not prone to ecological bias" which is only true if the data are analysed correctly -- this should also be clarified.

   In the section "The effects of covariates", the sentence "these studies included the covariate and/or interaction terms between treatment and covariates" requires clarification. Are the authors enumerating all studies that included any covariate and/or interaction adjustment? To me, a treatment effect adjusted for confounder(s) is quite different from a model estimating treatment-covariate interaction(s), and the two should be enumerated separately. Indeed, what exactly is the difference between the 58% of MAs here and the 67% of MAs in the subsequent sentence?
2. The introduction states, justifiably, that a "random-effects" approach may involve random-effects on the trial coefficient and/or the treatment coefficient, and the authors' ambition in describing the use of both possibilities is admirable. However, their subsequent use of the terms "random-effects" and "fixed-effects" is then made a bit more vague, and should be clarified. For instance, in the "Statistical methods" section, it is stated that "all patient data from these studies were combined in a GLMM, accounting for clustering among patients in the same trial by including random effects". Is this really true -- that *no* MAs used a fixed trial-membership effect?

Minor essential revisions

3. In the section "Heterogeneity", the sentence "it was unclear if any measure of heterogeneity was used in about six? Studies" needs correcting.

4. The 5th paragraph of "Discussion" ends "this likely reflects the greater comfort with and availability of [the] random effects model in health research". I assume the authors are implying that the only thing previously holding researchers back from using one-stage models was the lack of random-effects routines in mainstream statistical packages? If so this could be made clearer -- possibly with reference to other outcome types, e.g. time-to-event outcomes, where one-stage random-effects routines are still not generally available.

5. The 10th paragraph of "Discussion" (beginning "heterogeneity should be quantified and described") is currently badly worded and requires revision. (although I agree with the point being made.)

Discretionary revisions:

4. It would be helpful for the included MAs to be explicitly referenced somewhere within main text -- possibly in the second paragraph of "Results"? (I am aware that the MAs are explicitly listed in the Supplementary Information, which is great.)

**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