Reviewer's report

Title: Meta-regression models to address heterogeneity and inconsistency in network meta-analysis of survival outcomes

Version: 1 Date: 11 May 2012

Reviewer: Nicky Welton

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This paper presents some models to incorporate study-level covariates in a network meta-analysis (NMA) of survival data, where treatment effects act on both the shape and scale parameters of a Weibull distribution. The models are illustrated with an example. Although models to incorporate covariates in NMA have been presented before, this is the first application where treatment effects act on 2 separate parameters. The paper will be of interest to readers of BMC Methodology, however I have some comments below.

Major Comments

1. The authors understandably make the simplifying assumption that the covariate only interacts with the treatment effects on the scale parameter (and in fact that heterogeneity only acts on the scale parameter), but I think the paper would benefit from a more general formulation to show how, in principle, heterogeneity/covariate effects could act on both parameters, even if not illustrated with the example. Interpretation of parameters could be a problem, and you could discuss this.

2. The paper would also benefit from showing how covariates/heterogeneity could be incorporated for higher-dimensional models e.g. fractional polynomials. Again, this needn’t be illustrated with the example.

3. This doesn’t seem to be a very good example! There is no evidence of heterogeneity (random effect model doesn’t fit much better than fixed effects), and any heterogeneity that there is is not explained through the dose covariate! Also, from the model fit statistics given I can’t assess whether the Weibull is a good fit or not. The residual deviance can help assess this &/or comparing observed values with fitted values. Is the Weibull model a good fit to the data? What about other models?

4. A big problem with these models is identifiability (as you found when trying to fit your most complex model to your example). An expansion of your discussion of this would be useful ... what data would you need to be able to identify these models? Is IPD enough? Or does the covariate spread need to be even across studies in the network? There are other possibilities for the model that could help with identifiability e.g. exchangeable beta’s.

5. An alternative approach would be to treat each treatment & dose combination as a separate treatment. I suspect that if you do this your network will no longer be connected (I wasn’t clear from Fig. 2 whether there are any trials comparing
one drug high dose with another (or the same) low dose? The models you fit therefore allow you to connect the network and perform a synthesis. You should add this as a discussion point.

Minor Comments (I’m counting the page starting INTRODUCTION as p.1, since no p.no.’s)

1. Abstract line 3: replace “indirect comparisons” with “network meta-analysis”
2. Intro line 4 “Even with” should be “Even when”
3. Intro 1st paragraph. Mixed Treatment Comparisons and Network Meta-Analysis are the same thing, and should be introduced as such i.e. different names for the same thing. MTC is not simply for 3 treatments, and introducing it in this way is confusing with the use of the terminology in the large literature on the subject.
4. Intro line 5 “more refined” Do you mean “more precise”?
5. Intro 3rd para “transitivity assumption” Define what you mean by this (also known as the consistency equations)
6. p2 1st equation. This is a little abstract. Maybe say “function f, for example log or logit”
7. p2 2nd equation. Cite NICE Decision Support Unit Technical Support Document #2 or MDM paper (currently in press, but authors are aware of) for this model.
8. p5 Model 3. Give some intuitive examples where this might be a reasonable assumption. E.g. when the covariate is risk of bias and may only expect this in active vs placebo trials rather than active vs active (Dias et al stats in medicine)
9. p6 last para. How did you extract the data from the curves? What is the format of the data? What is the likelihood? You actually answer all these questions later on, but it would be easier to read if it was either described here, or you say something like “(see below for details)”
10. p7 2nd para “adjusted for the subjects censored” how have you done this? What assumptions are made?
11. p8 2nd line of text delete “no” at end of line
12. p8 “no ground to select the fixed effect over the random effect” Isn’t this the other way around? i.e. nos grounds to select the random effects model over the fixed effect model?
13. p9 2nd para You use log and ln in the same equation. Be consistent – which do you mean?
14. p10 Say a bit more about how to get p(best) when you have multi-dimensional treatment effects – could be one treatment effect best on one dimension and another on another dimension. Need to collapse into a single summary on which to compare the treatments.
15. Use model numbers in tables t help reader match results with models
16. Fig. 6 Why report high and low dose separately? Doesn’t the treatment
decision include choice of dose? Or have I misunderstood the dose covariate?

**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 declare that I have no competing interests