Reviewer's report

**Title:** Using meta-regression analyses in addition to conventional systematic review methods to examine the variation in cost-effectiveness results - a case study

**Version:** 4  
**Date:** 6 July 2015

**Reviewer:** Lotte Steuten

**Reviewer's report:**

Review of manuscript: Using meta-regression analyses in addition to conventional systematic review methods to examine the variation in cost-effectiveness results – a case study

**Major Compulsory Revisions:**

**Background:**
- Main aim of the paper is “to explore the usefulness of meta-regression […]” Authors need to determine a priori when the method will be considered “useful” (line 65) or of “added value” (line 70).

**Methods / Analysis:**
- Insufficient amount of detail on the analyses:
  - What were all the a priori expected associations? Now specified as “several bivariate linear regressions” (line 114). What direction was expected re the relations? What was the level of measurement (ordinal, interval, ratio scale)? Which alpha level used for statistical significance?
  - How were missing data handled? Influence on choice of analysis (i.e. bivariate instead of multivariate)
  - Validation check: one-sided in that it considers some associations that were expected and found, but also need to see if associations that are not to be expected were indeed not found.
  - In line 117: “…check if the model predicts what it should predict”. Doesn’t predicting require multivariate analysis? As only bivariate analysis were done may need rephrasing.

**Results:**
- Need more information on the frequency with which the different levels of the covariates were observed (if not reported in Table 1). How many missing values?
- Authors basically describe the results of the meta-regression and mention in a rather ad-hoc manner when something happens to be found using meta-regression that would not have been found based on conventional methods. Results need an explicit and more systematic overview of what the meta-regression analysis tells us about the variation in CE-results and what the conventional systematic review methods would tell us. It is for example relevant
to know if there’s say 50% or 90% overlap between what both methods produce in terms of results. Currently insufficient detail for readers to assess the “usefulness” or “added value” of meta-regression.

- Line 182 – 183: “This was also found by Hill …” In addition to Hill, two more studies (15 and 18) provide results on different (discrete) time horizons. What do they find re longer time horizon?

Table 3:
- The perspectives used are not the standard ones (such as health care system, societal perspective etc.) and need explanation in the text and below the table. How do these differ from each other exactly? Why were these four chosen instead of the usual ones? How many papers / analyses report on each of these perspectives?
- It is unclear whether the assumptions tested are all the assumptions done in the studies or a selection of the most frequent or important ones. This sort of information should be provided in the methods section.

Discussion:
- Needs more depth regarding the “added value” of meta-regression over conventional methods. When providing more details in the results section regarding this, the authors should build on that to put somewhat more beef to the bones of this paper. See also comments on Results.
- While meta-regression may be unique for systematic reviews of health economic evaluations, it is fairly common in other fields. What can we learn from these fields to enhance the meta-regression approach in health economics (for example – how do they deal with missing data?), or vice versa? Generally, comparison with other literature is lacking.
- More elaboration of the implications of using bivariate analyses instead of multivariate analyses is required. Is there a risk overestimating the “added value” of meta-regression now a long list of bivariate analyses was done and may have identified associations that would not have come up in a multivariate analysis? Or may this have led to not picking up on associations that multivariate would have identified?

Minor Essential Revisions:

Results
- Lines 156 – 170: No reference is provided in the text to Table 3, which contains the results for this section.
- Sentence line 195 – 197 is unclear
- Line 205: “…number of stents varied [between] 1(22) and 2.6 (19)…”
- Line 210: “…only one concluded that DES could be cost-saving.” Please mention how many concluded that DES was cost-effective (rather than cost-saving) in order to compare this statement with the previous sentence. The current may be misleading.
- Line 213: “…the following associations are confirmed by the regression but not
significant.” If not significant than the direction may also not be confirmed. Need 95% CI to determine whether the direction is indeed confirmed.

Discussion:
- Lines 241-242: “…this review showed that it is possible to predict the incremental costs based […] ‘meta-level’ (figure 2).” Please reconsider using the word predict here, as only bivariate analyses were done.
- Line 248: “Moreover, other parameters were not significantly associated but also these differences are undesirable and could have influenced the outcomes.” Unclear which other parameters are meant here and why differences would be undesirable and could have influenced the outcome?

Table 1:
- Write out abbreviation NS below table.

Table 2:
- Provide n of CEAs and n of CUAs in table.
- Column 4: Is it Incr repeat vascularizations or Incr repeat revascularisations avoided? The latter would be in line with the text (line 161).
- Beta’s need 95% CI

Table 3:
- Please explain if increment is defined as DES – BMS or vice versa
- Write out abbreviation NA below table
- Please specify Costs currency (€)
- Column 4: Is it Incr repeat vascularizations or Incr repeat revascularisations avoided? The latter would be in line with text (line 161).
- Beta’s need 95% CI
- Write out CABG, PCI and MI below table
- Unclear how the covariate discount rate (yes/no) was scored exactly. For example: no discounting would be appropriate in case of time horizon <= 1. Does that score as yes or no?

Based on the above, see my score on a scale from 1 (very inadequate) - 10 (very adequate) below:
1. Is the question posed by the authors well defined? 6
2. Are the methods appropriate and well described? 5
3. Are the data sound? 8
4. Do the figures appear to be genuine, i.e. without evidence of manipulation? 8
5. Does the manuscript adhere to the relevant standards for reporting and data deposition? 7
6. Are the discussion and conclusions well balanced and adequately supported
by the data? 5
7. Are limitations of the work clearly stated? 7
8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? 7
9. Do the title and abstract accurately convey what has been found? 6
10. Is the writing acceptable? 8

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests