Author’s response to reviews

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

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Author’s response to reviews: see over
Reviewer: Torbjørn Wisløff

**Major compulsory revisions**

1. Abstract, methods: The following sentence needs to be rephrased: «We identified and reviewed all modelling studies published until January 2012». You attempted to identify all, and can never be certain that you actually did find all. When doing a similar, but not systematic search a few years ago, I also found the following HTA report:


   This report is referred in the HTA database with the following accession number: 32004000872

   *We agree with the reviewer that a systematic review always aims to include all eligible articles but it is never certain that all studies are actually included. To increase the sensitivity of our search we first checked previously performed systematic reviews performed by Ligthart et al. (4), Hill et al. (2), and Neyt et al. (3). to make sure that our search identified the studies that should be included in our review.*

   Regarding the study from Canada (32004000872) this study was found in our literature search but was considered ineligible according to our inclusion and exclusion criteria since it does not report incremental costs and incremental effects separately; furthermore, this publication focussed on the total health care budget.

   *Changes to manuscript – abstract: We attempted to identify and review all modelling studies published until January 2012*

2. Methods, lines 113-115: The choice of explanatory variables in the regression is peculiar. A more common and unbiased method is to include in your regression only those variables that you believe can have an impact on the outcome. An analysis with all these included should be the primary output. Bivariate analyses could be added as sensitivity analyses.

   *The parameters chosen in the regression analyses were the most likely general study characteristics (e.g. population, time horizon, funding) that are reported in conventional systematic reviews. In addition, we added the most important input parameters (e.g. cost of procedure, relative risk of repeat revascularization, probability of repeat revascularization, utilities) that are used in a model to estimate the cost-effectiveness. These key parameters are often varied in deterministic sensitivity analyses. Furthermore, we wanted to see if modelling assumptions (e.g. oculo-stenotic effect) influenced the incremental outcomes. Lastly, the quality of the studies was assessed and the associations between the quality of the study and incremental outcomes were estimated.*

   *Changes to manuscript – methods:*
The parameters chosen in the regression analyses were the most likely general study characteristics (e.g. population, time horizon, funding) that are reported in conventional systematic reviews. In addition, we added the most important input parameters (e.g. cost procedure, relative risk repeat revascularization, probability of repeat revascularization, utilities) that are used in the model to estimate the cost-effectiveness. These key parameters are often varied in deterministic sensitivity analyses. Costs were converted to Euros (5) and corrected for inflation if necessary (6) to present the costs as 2012 Euros. Furthermore, we wanted to see if modelling assumptions (e.g. oculo-stenotic effect) were of influence on the incremental outcomes. All assumptions reported in the studies were monitored. Lastly, two reviewers (LB & FW) independently assessed the quality of the models using the Philips et al. checklist (7) for the assessment of model-based economic analyses.

Changes to manuscript – discussion:
Moreover, meta-regression analyses (bivariate or multivariate) help to explain variation in outcomes, however it also identified associations that were not expected a priori. For example, type of study had an influence on the incremental costs which is not logical since the type of study only affects the incremental effects. Covariates that are on beforehand implausible (e.g. type of study and incremental costs) should not be included in future meta-regression analyses since it leads to false positive outcomes.

3. Methods, line 114: When performing linear regressions, you assume normality. Have you tested whether that is appropriate here? It is, for instance, often more appropriate to do generalized linear model with gamma family on costs. If you choose not to perform other types of regressions, this should, at least, be mentioned as a limitation.

We agree that the regression models could have been improved using different types of regressions. However, since this was a test case and the number of observations was large (which, given the central limit theorem, supports the assumption of normality) we decided to focus solely on linear regressions. We have included this point in the discussion section.

Changes to manuscript – discussion: In this case study, linear regression models were used to estimate the associations of study characteristics on the outcomes (incremental costs, incremental QALYs and repeat revascularizations avoided) since the number of observations was large. However, regression models could be improved by first considering if the dependent variable (e.g. incremental costs) can best be modelled using a different function (e.g. gamma).

4. It is essential to include the average of all three outcomes (costs, QALYs and repeat revasc.) in table 2, so that readers can relate the results of table 3.
Changes to manuscript – Table 2: The averages of the three outcomes are added to Table 2.

5. Table 3 would be more informative if standard errors were included

Changes to manuscript – Tables 3-5: We have included standard errors in Table 3. Since Table 3 became very large after including the standard errors and number of observations, we were forced to create two additional tables. Tables 3-5 show the results of the regression analyses of the different outcomes separately.

6. Table 3: number of observations with each value would make the table more useful

Changes to manuscript – Tables 3-5: We have included the number of observations in Table 3. Since Table 3 became very large after including the standard errors and number of observations, we opted to create two additional tables. Tables 3-5 show the results of the regression analyses of the different outcomes separately.

Changes to manuscript – methods: Some studies reported both incremental effects and incremental QALYs for a specific analysis. Since the incremental costs associated with both outcomes is the same we only included one of the two analyses for the regression analyses on the incremental costs to avoid double counting.

Minor essential revisions

1. Abstract, methods: The reference to Philips is too brief and is not helpful unless the reader has knowledge about this specific check list.

In the methods section of the abstract we have now provided some more information. The abstract already mentions that the Philips checklist is used to assess the quality of the model. We have added that Philips is a checklist.

Changes to manuscript - abstract: We extracted general study information (e.g. funding), modelling methods, values of input parameters, and quality of the model using the Philips et al. checklist.

2. Background, second sentence: Please rephrase the sentence.

Changes to manuscript – background: Often for a specific decision problem different economic evaluations are conducted. The results of these studies may differ substantially between studies: from interventions being dominated to being dominant.

3. Background, line 54: “exist”, not “exists”
Changes to manuscript - background: corrected

4. Background, line 56: what if other relationships than linear exist?

Some linear relationships are very obvious (e.g. an increase in the costs per stent will lead to proportionately higher total costs) but some relationships are not linear and therefore a meta-regression analysis could be useful. For example, the quality of the studies or funding do not have a linear impact on the cost-effectiveness.

Changes to manuscript - background: Other associations with input parameters that do not have a linear association with the outcome (e.g. probabilities leading to changes in costs and effects) or study characteristics (e.g. funding) could be identified using meta-regression analyses in addition to conventional systematic review methods.

5. Methods, line 80-81: the first sentence should be made more explicit; is it published online or in print.

Changes to manuscript - methods: A systematic literature search was performed to identify all English-language (online or print) publications (at any time before January 2012) of CEAs using decision analytic models to compare the costs and consequences of DES (sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), everolimus or zotarolimus-eluting stent (ZES)) versus BMS for patients who require a stent implantation due to an atherosclerotic lesion of the coronary artery.

6. Methods, line 97: When only one reviewer screened titles and abstracts, that should be mentioned in Limitations.

Changes to manuscript - discussion: Furthermore, title and abstract screening was performed by one reviewer, which could be seen as a limitation of the study. However, checks of whether the studies included in previously published reviews were also identified with the search, increased the sensitivity of the search and thereby reduced the chance of missing a relevant publication.

7. Methods, line 119: “as long incremental cost of incremental” should be “as long as incremental costs OR incremental”.

Changes to manuscript - methods: corrected

8. Results, line 152: “overall” should be replaced by “average”
Changes to manuscript – results: The average overall quality of the models was moderate (59%±15% of a maximum possible score of 100%).

9. Results, line 209: Please check whether it is two or three studies that concluded DES was cost-effective among the sponsored. You write “three”, but do only have two references.

We have changed the manuscript and included the third reference, which was missing.

Changes to manuscript – results: (15, 17, 20)

10. Results, line 220: “Meta-regressions” should be “Meta-regression”

Changes to manuscript - results: corrected

11. Discussion, line 228: Please add “of economic evaluations” at the end of the first sentence

Changes to manuscript - discussion: This study explored the usefulness of meta-regression analyses in combination with a systematic review of economic evaluations compared with conventional review methods.

12. Discussion, line 250: You refer to ISPOR task force. Firstly, this should be “ISPOR-SMDM”. Secondly, it seems a bit odd to refer to ISPOR-SMDM here, but use Philips in your quality assessment. This should be discussed further.

We agree with the reviewer that both guidelines provide guidance for transparent reporting. We have included both suggestions.

Changes to manuscript - discussion: It is important for authors to follow the recommendations of the ISPOR-SMDM task force for modelling good research practices (27) and the recommendations based on the Philips et al. checklist (7) for modelling studies to increase the quality of the study and generalizability of the results.

13. Discussion, line 260: You could add a sentence stating something like: “Regardless of these limitations, we found statistically significant effect of quality on the outcome repeat revascularization.

Thank you, the following sentence has been included

Changes to manuscript – discussion: “Regardless of these limitations, we found a statistically significant association between quality and the outcome of repeat revascularization.”
14. Table 3: “0.000” does not make sense. Do you mean “<0.001”?

*Changes to manuscript – table 3: this has been corrected*

15. Table 3: other possible explanatory variables: Publication year and country

*Changes to manuscript – table 3: additional associations have been included*

16. Figure 3: Have tested whether the figure looks better with a logarithmic x-axis?

*Perhaps it would be improved if it were plotted on a logarithmic x-axis. However, negative values of the incremental effects (x-axis) are included in the graph, making it impossible to use a logarithmic x-axis.*

*Changes to manuscript – figure 3: none*
Reviewer: Lotte Steuten

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).

_We have included in the introduction some comments regarding when we consider meta-regression analyses useful._

_Changes to manuscript – background:_ Meta-regression analyses may be useful if they provide more information, in terms of associations with the outcomes, than conventional systematic reviews and sensitivity analyses.

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?

_We have included additional information regarding the analyses in the methods section. The choice of the variables and their measurement._

_Changes to manuscript – methods:_

The parameters chosen for the regression analyses were the most likely general study characteristics (e.g. population, time horizon, funding) that are reported in conventional systematic reviews. In addition, we added the most important input parameters (e.g. cost of procedure, relative risk of repeat revascularization, probability of repeat revascularization, utilities) that are used in the model to estimate the cost-effectiveness. These key parameters are often varied in deterministic sensitivity analyses. Costs were converted to Euros (5) and corrected for inflation if necessary (6) to present the costs as 2012 Euros. Furthermore, we wanted to see if modelling assumptions (e.g. oculo-stenotic effect) were associated with the incremental outcomes. All assumptions reported in the studies were monitored. Lastly, two reviewers (LB & FW) independently assessed the quality of the models using the Philips et al. checklist (7) for the assessment of model-based economic analyses.
The level of measurement was ordinal or ratio, depending on the covariate. The model assumptions and study characteristics (e.g. funding) were measured on an ordinal scale. Input parameters such as the probability of repeat revascularization were measured on a ratio scale. Conclusions about statistical significance were based on an alpha level of 5%.

How were missing data handled? Influence on choice of analysis (i.e. bivariate instead of multivariate)

Due to non-transparent reporting of many studies we were unable to obtain values for all covariates for all studies. It seemed imprudent to use imputing methods to overcome this limitation since it would have led to invalid values. Therefore, as mentioned in the discussion, we performed only bivariate analyses.

Changes to manuscript – methods: Multivariate analyses with all of the parameters that were significant in the bivariate analyses could not be performed due to a high frequency of missing values caused by incomplete reporting.

Changes to manuscript – discussion: A solution could be to include a smaller number of input parameters with only common input parameters (e.g. cost of procedure, time horizon etc). However, this will lead to fewer associations between outcomes and covariates.

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.

We agree with the reviewer, we included some examples of associations that were not expected a priori.

Changes to manuscript – discussion: Moreover, meta-regression analyses (bivariate or multivariate) help to explain variation in outcomes, however it also identified associations that were not expected a priori. For example, type of study was associated with the incremental costs, which was not logical since the type of study mainly influences the incremental effects. Covariates that are on beforehand implausible (e.g. type of study and incremental costs) should not be included in future meta-regression analyses since it leads to false positive outcomes.
- 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.

**Changes to manuscript – methods:** Including associations that could be predicted beforehand (e.g. type of lesion, price stent) are included in the regression analyses since it could be seen as a validation check if the analyses also show these associations.

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?

**Changes to manuscript – table 3:** The number of observations per covariate is included in Table 3, which makes it possible to determine the number of 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.

A conventional systematic review of economic evaluations does not usually investigate which study characteristics or model input parameters explain variation in the outcomes. Individual studies have conducted univariate sensitivity analyses and subgroup analyses that show the impact of changing input parameter values and subgroups on the results. We actually do say what associations could have been found by looking at individual studies; see, for example, lines 180-187:

Again, the meta-regression analyses found associations with incremental QALYs that were expected (Table 4). Relative risk reduction of repeat revascularizations and the initial probability of restenosis after BMS were associated with a greater QALY gain, as seen in individual sensitivity analyses (2,14,15,21,22,24). Furthermore, analyses showed that non-elective patients, patients with a high risk of a repeat revascularization, patients with complex vessels or lesions or older patients will benefit more from DES, something that was also recognised in the individual studies (2,12,17,21,24). In addition, we found a significant positive association between time horizon (continuous) and
incremental QALYs. This was also found by Hill et al. (22) and Ekman et al. (15), who varied the time horizon in the sensitivity analyses.

More comments on the usefulness of meta-regression analyses have been added to the results section:

Changes to manuscript – Results 2: These factors could have been predicted beforehand since subgroup analyses and sensitivity analyses of the individual studies show the same conclusions.

- 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?

This results section focuses on the incremental QALYs and therefore we did not mention reference 18 (Polanczyk et al.) since this study does not report incremental QALYs. In the study by Ekman et al. it was unclear whether the time horizon affected the incremental QALYs since the incremental QALYs are not presented for the 24 months time horizon, only the ICER. However, the authors did state that the ICER became lower when the time horizon increases due to additional repeat revascularizations for BMS and this mechanism may affect both incremental QALYs and incremental costs.

Changes to manuscript – results: This was also found by Hill et al. (22) and Ekman et al. (15) who varied the time horizon in the sensitivity analyses.

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?

The perspectives were based on the perspectives that were reported by the publications. The frequency of perspectives used in the studies is now found in Table 3.

Changes to manuscript – table 3: we have included the number of observations in Table 3.

- 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.
All assumptions reported in the studies were monitored.

Changes to manuscript – methods: all assumptions reported in the studies were monitored.

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.

We have included additional text to the discussion to show the added value of meta-regression analyses.

Changes to the manuscript – discussion: This study explored the usefulness of meta-regression analyses in combination with a systematic review of economic evaluations compared with conventional review methods. The aim of conventional systematic reviews is to show relevant publications on the cost-effectiveness of certain treatments in a systematic manner. When possible, conventional reviews describe associations between study characteristics, input parameters and outcomes. However, it is not possible to statistically determine if the association actually exists, which covariates explain the variation best, to correct for interactions or to predict the incremental outcomes. This case study was inspired by meta-analyses of treatment effectiveness studies that are frequently performed to obtain a single summary estimate. More interesting than meta-analyses are meta-regression analyses that try to relate the size of a treatment effect to one or more characteristics of the included studies (1). Using meta-regression analyses to explore the associations between the incremental outcomes and input parameters is unique for a systematic review of economic evaluations and could help to explain variation in cost-effectiveness outcomes between studies. We used meta-regression to explain variability in the outcomes of cost-effectiveness studies (i.e., incremental costs and effects) of DES versus BMS and found that, besides confirming associations that could be predicted from individual studies, associations at a meta-level also exist, such as an association between outcomes and the quality of the models.

Changes to the manuscript – discussion: This study has showed that meta-regression analyses can be used to explore relationships between study characteristics and cost-effectiveness outcomes and can draw from the methodology used in other fields even though it is not yet fully developed. Compared with conventional review methods or sensitivity analyses of individual studies meta-regression
analyses can be of added value since it identifies significant associations that could not be identified before.

- 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.

**Changes to the manuscript – discussion:** To improve this case study lessons can be learned from meta-regression analyses and meta-analyses that are performed for the clinical effectiveness of interventions. More specifically, it could provide guidance in how to handle missing data (31), how to treat study heterogeneity, how to include covariate interaction (32). In addition, it shows limitations of the methods (1).

- 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?

We agree that it is important to ensure that only valid conclusions are drawn about the added value of meta-regression based on the analyses we could perform in this study. At present, this added value is limited because of incomplete reporting in economic evaluations.

**Changes to the manuscript – discussion:** In addition, transparency in documentation is a major issue leading to a high frequency of missing values that made it impossible to perform multivariate analyses with all of the parameters that were significant in the bivariate analyses. Consequently, we were unable to: 1) take into account interaction effects, 2) determine the most influential covariates, and 3) create a prediction model. A solution could be to include a smaller number of input parameters with only common input parameters (e.g. cost of procedure, time horizon etc). However, this will lead to fewer associations between outcomes and covariates.

**Minor Essential Revisions:**

Results
- Lines 156 – 170: No reference is provided in the text to Table 3, which contains the results for this section.

**Changes to manuscript – Results: included**

- Sentence line 195 – 197 is unclear

**Changes to manuscript – Results:** The meta-regression analyses showed that studies using real-world evidence compared with angiographic follow-up leads to a reduction in incremental QALY gain. The added value of meta-regression analyses is limited in explaining the variation in incremental QALYs, although it identified modelling assumptions that were significantly associated with incremental QALYs.

- Line 205: “...number of stents varied [between] 1(22) and 2.6 (19)...”

**Changes to manuscript – Results: corrected**

- 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.

**Changes to manuscript – Results:** Of the studies that were not funded by a manufacturer (N=8) only one (10,11) of them concluded that DES could be cost-effective.

- 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.

**Changes to manuscript – Table 3: the standard error and number of observations are included in Table 3. In addition we provided the 95% CIs in the text.**

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.
Moreover, this review showed an association between the incremental costs and absolute risk reduction in repeat revascularizations on ‘meta-level’ (Figure 2).

- 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?

Moreover, other parameters were not significantly associated with outcomes (e.g. wait time and incremental costs, or funding and incremental QALYs). These parameters could have influenced the outcomes but are undesirable since e.g. funding should not play a role in the outcomes of the study.

Table 1:
- Write out abbreviation NS below table.

Table 2:
- Provide n of CEAs and n of CUAs in table.

Table 3:
- 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
- Write out CABG, PCI and MI below table
Changes to manuscript – Table 3: corrected/included, number of observations and standard errors are included

- 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?

We determined the association with discount rate only for studies with a time horizon longer than 1 year.

Changes to manuscript – Table 3: A footnote is inserted in the Tables.