Reviewer’s report

Title: Predictors for major cardiovascular outcomes in stable ischaemic heart disease (PREMAC): Statistical analysis plan for data originating from the CLARICOR (clarithromycin for patients with stable coronary heart disease) trial

Version: 0 Date: 19 Oct 2016

Reviewer: Ben Van Calster

Reviewer's report:

This manuscript describes a statistical analysis plan of an interesting topic that nicely fits the scope of the journal. In that sense this protocol submission is valuable, but before it can be acceptable the manuscript needs to clarify and explain several issues.

1. Overall I think the problems and suggested methods are not carefully described, with a few unclear sentences/paragraphs. Examples:
   a. P9: The part from 'the set of candidate predictors' to 'redundancy may be an issue' is unclear. Further, this study is mainly seen as hypothesis generating, and this should be more clear upfront (e.g. in the abstract).
   b. The last paragraph on p9 is unclear to me, there seems to be an issue with the measurement of GFR?
   c. Are the first 2 paragraphs on p11 still on the issue of selection bias?

2. The authors mention that they will control for standard predictors, but I have not seen a description of the evidence from the literature about what standard predictors are in this context. The authors only state that they consider standard predictors to be those demographic/hospital/biochemical variables available in most Western hospital laboratories. This is very thin as an explanation, certainly given the fact that they seem to label >25 variables as standard predictors. This needs further justification.

3. This is a statistical analysis plan, and in this respect I would expect a more detailed account of some of the planned analyses.
   a. The discussion mentions the rarity of missing values, but there is no information as to how many missing values there are or as to how this issue is addressed (complete cases, imputation, …). Also, it is stated that biochemical values may be missing because collection of blood specimens was not carried out 'for one reason or another'. That is no convincing argument to state that missing values are most likely MCAR.
b. The issue of skewness remains too vague throughout the text. What is specifically meant with this, and how will this specifically be investigated?

c. How are the PH and linearity assumptions addressed?

d. Given the amount of standard predictors, are there enough events?

e. P8: is it necessary to have a significant effect when used alone AND after correction for standard predictors? What if it is only significant after correction, or what if effects before and after correction are in the opposite direction?

f. What do you mean with lives saveable? How is this quantified?

4. Is it necessary to have six outcomes? Would you expect strongly different predictors?

5. C statistic does not represent a frequency of correct triage decisions.

6. Second sentence in the methods section of the abstract is difficult, I suggest to reword.

7. Write C in full in abstract.

8. What is meant with 'we plan to assess each of the advanced biochemical quantities in individual publications and then assess their combined effect in final publication'? The authors cannot really suggest to write a separate paper for every advanced biochemical predictor, and then a final paper? More than 10 advanced predictors are listed.

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