Author's response to reviews

Title: Protocol for a systematic review of the diagnostic and prognostic utility of tests currently available for the detection of aspirin resistance in patients with established cardiovascular or cerebrovascular disease

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Version: 3  Date: 4 February 2013

Author's response to reviews: see over
Dear Editors

Re: Protocol for a systematic review of the diagnostic and prognostic utility of tests currently available for the detection of aspirin resistance in patients with established cardiovascular or cerebrovascular disease (MS: 7423535198571203)

Please find below our responses to the peer reviewers’ comments. Please do not hesitate to contact me if there are any outstanding queries.

Your faithfully

Janine Dretzke

<table>
<thead>
<tr>
<th>Reviewer 1 Comments</th>
<th>Response</th>
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<tr>
<td>1. It has previously been shown that the timing between pill ingestion and blood sampling to a large extent affects the number of “aspirin resistant” individuals. Including this factor in the analyses is perhaps not important, but the authors may wish to include this parameter in tables (in the article) summarizing previous studies.</td>
<td>We have mentioned in the protocol that methodological differences make it difficult to compare the test results. Given the large number of parameters that may influence test results, we have not listed all in the protocol. However, we have an extensive data extraction form and are extracting data from published studies on this parameter where information is reported. Any findings (or lack of) on this parameter will be reported and discussed in the full report.</td>
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<td>2. The authors state that “Several factors may influence the response of platelets to antiplatelet therapy” and could support this statement by citing e.g.: Interindividuvel variability in the efficacy of oral antiplatelet drugs: definitions, mechanisms and clinical importance by Würtz et al; Curr Pharm Des. 2012;18(33):5344-61.</td>
<td>This reference has been added as suggested.</td>
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<td>3. When alluding to the importance of aspirin compliance one key reference is: Schwartz KA et al. Am J Cardiol. 2005 Apr 15;95(8):973-5.</td>
<td>This reference has been added as suggested.</td>
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<td>4. In the discussion of platelet function tests (second paragraph of Background), the slightly old reviews (2003-4) included in the reference list may be supplemented by newer ones, e.g. Platelet function testing in atherothrombotic disease; Curr Pharm Des. 2012;18(33):5379-91.</td>
<td>This reference has been added as suggested.</td>
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<td>Reviewer 2 Comments</td>
<td>Response</td>
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| 5. Page 6 (i) "diagnostic/prognostic utility..." - how will you define "sufficient" prognostic utility? This seems like a potentially arbitrary designation - are there well agreed-upon cut-offs that you could cite as a guide? | We agree that this was too vague. On page 6 we have now rewritten this and quantified our meaning. We say:  
- To establish whether any of the available platelet functions test to determine "aspirin resistance" has sufficiently high diagnostic/predictive utility (e.g. sensitivity, specificity and positive and negative predictive values close to 1) in order to determine, for individual patients, if treatment modification should be considered based on the test result; |
| 6. Page 7, top - cost-effectiveness analysis - this seems out of scope for this review and could risk stretching the data further than it really should go. I would think that in order to truly determine cost-effectiveness you'd first have to find evidence of effectiveness. In other words, find "test-treat" studies as you suggest on page 15. Platelet function assays could be shown in the review to have excellent prognostic ability, but that doesn't necessarily mean treating patients with alternate or additional anti-platelet therapies will change clinical outcomes. I would suggest either reconsidering the inclusion of the cost-effectiveness study, or, if you do want to include, describe the types of studies you would need to find in order to conduct such analyses in the section describing study selection. | We agree that a cost-effectiveness analysis is only feasible if there is evidence of effectiveness, and that this evidence will most likely not be available (e.g. in terms of the consequences of changing treatment on the basis of a test result). However, as it is part of our commissioning brief to undertake a cost-effectiveness analysis, we will present a speculative model that could be populated with such data if future research is conducted. We will also conduct extensive sensitivity analyses using a range of hypothetical values in order to demonstrate at which point a test may become cost-effective under a number of effectiveness assumptions.  
The following text has been added to the protocol (p17):  

*However, in the absence of strong data, a speculative model will be constructed that could be populated with data if future research is conducted. A speculative model will be subject to extensive sensitivity analysis, using a range of hypothetical values in order to demonstrate at which point a test may become cost-effective under a number of test-treat effectiveness assumptions.* |
| 7. To be useful, it seems that these assays would have to provide incrementally more diagnostic/prognostic information than currently | We acknowledge that this is an important point and we intend to include prognostic models reporting on risk of adverse |
available information such as risk scores, or inflammatory markers like CRP. The described meta-regression and subgroup analyses may provide some information. Studies evaluating the additive contributions of assays to risk prediction would also be useful. It might be useful to frame the choice of study and analysis to more clearly address this issue of incremental value. It may very well be that you find few studies able to answer this question, but framing it in such a way would allow you to more clearly identify an important gap in evidence.

outcomes depending on the presence of potential risk factors including the results of testing for aspirin resistance. Of particular interest would be models that report results both with and without the inclusion of tests results as a parameter in the model, and any findings will be discussed.

The inclusion of studies describing prognostic models with test results as one of the prognostic factors has already been outlined under **Selection criteria, b) Prognostic model studies.**

We have further added these sentences to the protocol:

**Data extraction (p11):**

*Data will also be extracted on any prognostic models, including results of models reporting prognostic risk with and without test results as a parameter.*

**Analysis (p13):**

*If prognostic models report the incremental value of including tests, we will qualitatively summarise the added value reported in each study (e.g. net reclassification improvement, change in C statistic, etc).*