Author's response to reviews

Title: Anticoagulated patient's perception of their illness, their beliefs about the anticoagulant therapy prescribed and the relationship with adherence: impact of novel oral anticoagulant therapy - The Switching Study

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Author's response to reviews: see over
Dr Peter O’Donovan  
Editor  
BMC Haematology

Dear Dr O’Donovan,

Re: MS: 7491772681446721  
Anticoagulated patient’s perception of their illness, their beliefs about the anticoagulant therapy prescribed and the relationship with adherence: impact of novel oral anticoagulant therapy – The Switching Study

Many thanks for the opportunity to revise our manuscript in light of the reviewer’s additional comments made, following our second revision.

In the table below are the additional comments made by the reviewer, along with our responses to these. In order to make it clear where changes have been made, we have accepted all previous track changes in revision 2 submitted, and made new track changes to this document.

We look forward to hearing the outcome of your review.

On behalf of the manuscript authors,

Yours sincerely,

Vivian Auyeung, PhD  
Lecturer in Medicines Use and Health Psychologist  
King’s College London

<table>
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<th>Comments</th>
<th>Author responses</th>
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<td>Thank you for your review, which increased the study methodology. This represents a huge study (&gt;700 patients), and a very complex design; Figure 1 helps understanding it. There are still weaknesses in the methodology (e.g. how is persistence measured in GP summary care records; this is not obvious to the readers;</td>
<td>The aim in study II is to report longitudinal adherence and persistence in those patients who switch to a NOAC. We will use the GP summary care record to report this, which reports the number of NOAC prescriptions issued from the time prescribing was handed over to the GP from the specialist anticoagulation clinic. In this way, the proportion of days covered will be calculated and coupled with the Morisky 8-item adherence scale, as assessment of adherence and persistence will be reported at the 1 year</td>
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describe which novel anticoagulant patients will be switched to;

study III is missing in the abstract).

The reference list needs to be checked again, as example references 10 and 11 are missing.

Reference 21 is old and refers to an abstract only; this reference is weak for this very important aspect in methodology.

There are other updated references of the 8-item Morisky adherence scale.

Line 76: authors referred 9 publications, all from the same authors and no original cost-effectiveness papers. The literature search has to be refined.

There are still typo errors in the text, for example 'Additionally, there are currently no antidotes currently' (line80). Text needs to be checked carefully.

Line 67: 'relatively fewer drug-drug interactions'; this statement is misleading as NOAC are substrates of the P-glycoprotein and P450 CYP3A4, and are therefore

time-point.

All NOACs available in the UK will be used for patients in the Switching study, with the patients specific clinical circumstances dictating the choice of NOAC prescribed. The details of which NOACs were prescribed will be reported in results papers of the switching study.

We have structured the abstract, so that the entire programme of work is described. We have purposively not referred to specific studies. The following statement is made at the end of the method section in the abstract, which describes study III: The results from these sub-studies, will inform a treatment pathway to support patients on these novel agents, which will be evaluated in an independent group of patients.

We are unsure about this comment. Reference 10 and 11 were present in revision 2 submitted. We have double checked this.

This reference has been changed.

We are aware that there more up to date references to this scale. However, we have referenced the original 8 item Morisky adherence scale, as that is what we are using in the Switching study. We feel it would be inappropriate to use any other reference for this.

The 9 publications which the reviewer refers to are NICE guidelines. As NICE guidance in the UK is driving the change in anticoagulation prescribing, we feel it’s important the guidelines are highlighted to interested readers, particularly as these guidelines have impact internationally. As part of the NICE approval process, a full cost-effectiveness analysis is done and by virtue of receiving NICE approval, the agent is deemed to be cost-effective.

We thank the reviewer for highlighting this to us. We have changed the text and re-read the entire paper to ensure there are no other grammatical errors.

We have removed this statement from the introduction, as per the reviewer’s request.
both vulnerable of inducers and inhibitors of these enzymes, leading to many interactions. This has been reflected in the exclusion criteria: ‘taking concurrent interacting drugs which are contra-indicated’ (Line 229) but not in the background section.

<table>
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<tr>
<th>Line</th>
<th>Original Text</th>
<th>Suggested Change</th>
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<tbody>
<tr>
<td>143</td>
<td>‘Anticoagulated patients who meet the inclusion criteria, defined by their TTR’. Please specify the inclusion/eligibility criteria more clearly.</td>
<td>We feel the opening statement in the method section helps set the scene for the study. At this stage, we purposively do not define the specific TTR cut-off points. These are defined in detail in the detailed descriptions of studies I, II and III, within the methods section.</td>
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<tr>
<td>170-190</td>
<td>specify more clearly that included patients in study 1 do not switch to NOACs (pre-switch study).</td>
<td>We have added text, to clarify this, as requested.</td>
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<td>215-216</td>
<td>‘The findings from group 2 patients will then be compared to the findings of group 3 patients. Authors should specify how they will match the patients of groups 2 and 3 as they are not randomized, with a risk of bias. I do not think that the design is controlled as stated in the manuscript. It is rather a case-control study. It will be difficult to test the effectiveness of the intervention. Why not doing a RCT or using alternative designs like the stepped-wedge design?</td>
<td>Patients in study II and III who are switched to a NOAC, will not be case-controlled. Patients are recruited from the anticoagulation clinic consecutively and the results from study II will inform what support will be provided for subjects in study III. We agree that a gold standard RCT is the optimal design, however, the purpose of our programme of work is to develop the ‘intervention’ or ‘treatment pathway’, through the completion of studies I and II. The current design allows within group changes to be assessed and we therefore feel the current study design is best for the hypotheses being tested.</td>
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<td>211</td>
<td>please give a definition of ‘Treatment pathway’. Is this the intervention on adherence that will be tested? By reading the manuscript, I got the feeling that you are using the psychometric outcomes of the studies to build up the intervention. Please clarify the intervention and the way you intend to proceed to build it up.</td>
<td>As per above, the results of study I and II will inform the ‘treatment pathway’. We therefore cannot describe what that will look like at this stage. This will of course be reported in results papers, as results begin to emerge.</td>
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<td>281-282</td>
<td>I think there is an important, ethical problem here as all patients should be offered the standard of care or local guidance, i.e. switch to NOACs if eligible, and then they should be introduced to the research study, and not reverse as described in the manuscript.</td>
<td>The switching study has received independent ethics committee approval, in its current form. We have made a statement to this effect, at the end of the methods section of the paper.</td>
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<td>327-330</td>
<td>it is not clear which outcome authors use to calculate the sample size of the intervention?</td>
<td>Adherence is the outcome we used to calculate our sample size.</td>
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