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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Version: 2 Date: 14 February 2015

Author's response to reviews: see over
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 comments.

In the table below are each of the reviewer’s comments, with our responses. We have indicated in this table, where changes have been made to the manuscript, as well as highlighting changes as track changes in the revised submitted manuscript.

In addition, as requested, we have removed the ethical approval letter from the additional files section of the re-submission.

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>Reviewer 1 comments</th>
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<td>1. Will the study design adequately test the hypothesis?</td>
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The manuscript presents the protocol of a series of sequential studies. The study design is quite complex and is divided into three series in which patients with optimal TTR and those with low quality TTR will be studied to assess their perception of the disease, quality of life and expectations from therapy (in particular in relation to NOACs). Data from several questionnaires and those on
- The adherence detected in patients with TTR less than 50% will be used for the final phase of the study aimed at evaluating interventions to improve adherence.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

Details of the study are generally well reported but the choice of the TTR threshold less than 50% appears to be rather unclear if we consider that TTR values slightly below 60% already involve a problematic efficacy of therapy with VKAs. Authors must somehow justify the choice of such a TTR threshold.

- Thank you for the suggestion. Following an evaluation of our clinic population, we found there were sufficient numbers at the time of study design, to have a cut-off TTR of <50%. The availability of the novel anticoagulants provides an opportunity to switch patients poorly controlled on VKA, and it was felt that the patients with the poorest control should be given this option to switch first – i.e. be prioritised – hence focusing on the <50% group. Furthermore, having two clear distinct groups (<50% and >75%) and understanding and appreciating the differences between these two groups will ensure that the hypotheses of the study proposed can be tested and if appropriate, a suitable support mechanism can be developed for patients prescribed chronic NOAC therapy where it is anticipated that adherence might be an issue.

- Thank you for the suggestion of clarifying the policy of what is in place for patients who decline to participate or refuse a switch to a NOAC. No formal policy is in place for patients who refuse the opportunity to switch or who do not wish to take part in the study, as ultimately it is up to the individual patient concerned. However, text has been added to the method section to address this comment (line 189-191), so readers are aware that patients who decline a switch to a NOAC, will be followed longitudinally and any outcomes recorded and reported. Those patients who switch to a NOAC, but who do not consent to the study will not be formally recorded, aside from descriptive statistics describing the number where this applies during the course of the study.

3. Does the manuscript adhere to the relevant standards for reporting and data deposition: if not, in what ways?

Yes

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?

This item is not relevant to the kind of submitted
5. Is the writing acceptable?

Yes, although some spelling errors (ie Rosendal instead of Rosendaal, line 152) should be corrected

Many thanks for highlighting this spelling error. This has now been corrected in the revised manuscript.

Reviewer 2 comments

1 Structure of the article

BMC recommendations and other information
- According to the BMC recommendations for the Study protocols submission (http://www.biomedcentral.com/bmchematol/authors/instructions/studyprotocol):
  - Page 1: please specify the trial identifier and registry name. If not yet registered, name of intended registry
  - Page 12: the list of abbreviations must appear before the competing interest
  - Title

If possible specify the study design in the title

This study is not classed as a clinical trial or a registry study. The UK authorities class this study as a clinical research study. Therefore, no trial / registry identifier is required for this type of study.

Thank you – this has now been corrected.

The title informs readers of the 3 key areas being evaluated in this study, i.e. patient’s quality of life, beliefs about medications and illness perceptions and the impact these 3 factors have on patient’s adherence to their anticoagulant treatment. We are of the opinion that extending the title further, will make it unnecessarily wieldy; we have therefore not amended the study title.

2 Background

- The article mentions the vitamin K antagonists (VKA) but not heparin. Please clarify.

- New oral anticoagulants can also be a source of drug-

The study team decided to focus on VKAs and not heparin, as the majority of patients prescribed chronic anticoagulant therapy are prescribed VKA. Evaluating the quality of life issues, beliefs about medication and illness perceptions for patients prescribed heparin will be different (Patel et al., JTH 2012) and our clinic population would not have sufficient numbers of patients to test the study hypotheses for this group of patients. Furthermore, patients prescribed heparin, would not have a TTR calculated, therefore, there would be no means to stratify them into a well-controlled or poorly controlled group.

Many thanks for this comment. We have added
drug and drug-food interactions. The text leads to misunderstanding (l. 63-67)

• “Acknowledging that all patients will have differing beliefs about their medication is the first step in addressing the medication non-adherence problem” [19] (l.87). The reference tells that patients may have different beliefs about their medications but not that this understanding is the first step in addressing the medication non-adherence problem. Please add another reference or modify our text.

3 Is the question posed original, important and well defined?

Originality
• The question posed is original and important.

Nevertheless, we recommend updating the references.

Clarity
• The research question is complex and difficult to understand.

• A lot of hypotheses and objectives are mentioned in the article; but many variables to collect are not specified (e.g. determination of symptomatic vs. asymptomatic patients). This point needs clarification.

4 Are the data sound and well controlled?

• Switch to NOAC

We need to understand better why the switch is proposed only to patients with TTR<50% (is this only an economic argument or are you following some therapeutic policies?). This switch might be clear in UK but it is not outside UK. We also refer to following UK excellence guidelines for AF (ref [23] in the article) saying:

“Trials of the non-VKA oral anticoagulants have shown that the degree of benefit of these agents compared with warfarin may depend on the time in therapeutic range (TTR) of the warfarin group. These trials assessed the degree of benefit in relation to the mean TTR for the warfarin group in that country. However, the inference of benefit is based on a number of assumptions. It is unclear that the population TTR can be extrapolated to decision-making in an individual. If, for example, an individual’s low TTR is a result of poor compliance, it is unlikely that compliance will improve with a non-VKA oral anticoagulant and uncertain whether a non-VKA oral anticoagulant will offer any benefit. Moreover, the threshold of TTR at which a non-VKA oral anticoagulant might offer benefit is unclear. The same question can be extended to include people before they start warfarin treatment, using criteria that prospectively identify those likely to have poor control on warfarin”

Thank you for this insightful comment. Our reasons for choosing a TTR <50% have been outlined in our response to reviewer 1’s second comment. i.e. the key reason being that we wanted to prioritise patients with the worst control and compare the 3 variables of QoL, illness perceptions and beliefs about medications to a group of well controlled patients – in order to test the hypotheses proposed.

We agree with reviewer 2, that if a patient has poor adherence on VKA, it is likely to lead to poor adherence to a novel oral anticoagulant. We therefore do not switch patients in clinic who overtly are non-adherent to VKA, before exploring what specific reasons might underlie the non-adherence. When patients attend clinic, a full and frank discussion is had with them about the importance of adherence with novel oral anticoagulants, if a switch goes ahead.

Reviewer 2 is correct, that the beliefs about medication, illness perceptions and QoL questions could be extended to include patients before they start treatment with a
VKA, using criteria such as the SAMe-TT\textsubscript{2}R\textsubscript{2} score. However, this group of patients will be very different, as they will never have been exposed to VKA therapy, so their experience of anticoagulant therapy will be different to those already established on VKA therapy. Only for the next 2-3 years, does this unique opportunity exist of understanding how things are for patients prescribed chronic VKA who are not well controlled and how their QoL, beliefs about medications and illness perceptions change (if at all), following a switch to a novel oral anticoagulant. Once NOAC are well established in clinical care, this opportunity will not exist, hence our reason for focussing on patients established on VKA with a TTR<50%, at this moment in time.

Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?

Participants:
- Please clarify the design for each sub-study (I, II and III)
- Specify if data will be analyzed according to the intention to treat guidelines.
- Specify which population will be included: AF and/or VTE, other?
- It is not clear if inclusion criteria are applied before dividing the population according to level of TTR or after.
- We do not understand why patients with a TTR between 50 and 75 are not considered; this will decrease the external validity of the results.
- TTR < 75% is not an exclusion criteria but rather a stratifying one.
- Pregnancy is a contra-indication to NOAC; why did you not include in the exclusion criteria?

Data collection
Socio-demographic data
- Please clarify how and when the socio-demographic data will be collected.

Medication adherence
- How adherence to NOAC was assessed? In the article you mention “by pill count and specific adherence screening questions at 1 year”

Text has been added to this study design section to clarify these points, including a statement that analysis will be conducted on an intention to treat basis.

This has been clarified in the text.

An explanation has been added to the manuscript to clarify this point.

As per previous comments, we wish to explicitly compare a poorly controlled group to a well-controlled group. Enrolling patients with moderate control would not be appropriate, in order to test the hypotheses proposed by our study.

Thank you; we have removed this criteria from the exclusion list.

This has been added, as per reviewer 2’s request.

This information will be collected and recorded at visit 1 for studies 2 and 3. Information has been added to table 1, so potential readers are aware.

Table 1 specifies when the pill counts will be conducted for studies 2 and 3. This will be done in clinic by the clinician reviewing the patient.
- Please explain how the pill count will be done (mathematical formula?), when, where and by whom.

- Please clarify which kind of questions will be proposed. A validated questionnaire will be used? Please specify and provide a reference.

- Who administers the questionnaires to the patients (BMQ, IPQ-R, ACTS)? The researcher? The physician? Others?

- Time needed to fill in the questionnaires?

Study I
- Responses between the groups will be compared # specified in the figure and in the abstract but not in the text. Please clarify.

Study II
- Will the results of group 2a and results of group 2b (BMQ, IPQ-R, ACTS) be compared at baseline? Please clarify.
- Will Group 2b (warfarin) be followed during the whole study (from baseline to month 12)? If not, why?

Study III
“The results from studies I and II will be used to create a treatment pathway which will be used for group 3.”
“The findings from the study will be used to inform a treatment pathway which aims to help support patients prescribed chronic NOAC therapy” (l. 116-117)
“The treatment pathway will be informed from the two-month follow-up data collected at visit 3 from patients in group 2 of study I. Group 3 patients will have the same follow-up in clinic as per the schedule outlined for group 2 patients” (l. 194-195)
- Please clarify what is a treatment pathway and what you intend to do?

They will count how many tablets the patient has left and compare this to how many expected tablets the patient should have, following their last review in clinic.

We will be using the Modified Morisky Scale (Aliotta, 2004). Further details have now been included in the main manuscript, explaining this. We will also be asking patients how many doses of their anticoagulation medicine they have missed in the last week – as used in previous studies (Clifford et al., 2008).

The clinician in clinic reviewing the patient will administer the questionnaire. The patient has the option of completing in clinic, or taking home and returning at their subsequent clinic review.

Patients are informed it takes ~20 minutes to complete. Text has been added to the manuscript, to explain this point and the point above.

Text has now been added to the manuscript to clarify this point.

No, as group 2(b) patients decline a switch, they will not have the BMQ, IPQ-R, ACTS compared at baseline. This is because for the hypotheses we are testing, we are interested in comparing differences between the <50% group and >75% group, not between those in the <50% group who decided to switch and those who do not. Our current experience is, that the number of patients who decline a switch is small, so meaningful results are unlikely to be yielded, if this was pursued.

It is not possible to provide this information, as it requires analysis of results from studies I and II to inform this pathway. At this stage, we can only state that an intervention will be instigated from what we learn from studies I
- The pathway will inform the medical follow-up between months 0 and 2; why not extending this to month 12? How will this pathway support the prescription of chronic NOAC therapy? Please clarify.

Will the results of group 2a (study II - NOAC) and group 3 (study III - NOAC) be compared?

Limitations
Identify the possible limitations and bias that could influence the internal or external validity of the results.

6 What are the strengths and weaknesses of the methods? The article presents an interesting design but the methodology is complex and needs to be improved. Readers need to know exactly which data will be collected, why, when, how and by whom. Please provide more details.

Many thanks for your comment. We have added text and clarity to the manuscript, to address this comment.

7 Is the interpretation (discussion) well balanced and supported by the data? Discussion is interesting with comparisons with the literature. However, a reference is missing in the following sentence: "Current cost-analysis which states that these NOAC are cost-effective assumes full adherence to medication" (l. 291).

As these agents are approved by NICE for use, they have undergone cost-effectiveness analysis. References has been added, as per reviewer 2’s request.

8 Can the writing, organization, tables and figures be improved?

- Writing: English needs to be improved
- Organization: the structure of the methods needs major improvements.
- Tables and figures: to understand the study design, the

We anticipate that the adherence intervention will be delivered by the clinician during the outpatient clinic appointments. As the initiation of therapy represents an ideal window in which to establish a regular habit of medicine taking (Phillips, Leventhal, Leventhal, 2013), The primary purpose of the intervention will be to support patients during the first two months when the opportunity to consult with the clinician is still available to the patient.

Yes, the results of group 2a and group 3 will be compared at the end of the study.

The instructions for authors does not request limitations for a methodology paper submission. We have therefore not stated these, as we have not completed the programme of work for the research questions posed and would therefore be second guessing any limitations. Furthermore, in our experience, discussing limitations would be more usual when results from the study are presented - so readers can interpret the results in the context of their limitations. We will therefore do this, at the appropriate time.
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<td>figure 2 is necessary; nevertheless, using a diagram with a timeline could increase clarity.</td>
<td>The instructions for authors state that any legends for figures should appear at the end of the manuscript. Therefore, we have not altered this in the manuscript.</td>
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<td>The list of abbreviations is not complete (the abbreviations used in the table 1 don't appear in the list)</td>
<td>Many thanks – this list has been updated.</td>
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<td>9 Are there any ethical or competing interests issues you would like to raise?</td>
<td>This is because as previously stated, this study is not a clinical trial, and therefore the requirement of reporting adverse events is not formally required. We will of course be recording any events patients who consent to the study suffer, and report these outcomes in our results papers.</td>
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| • Harms
Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct are not specified | Sections have been added to the manuscript to address confidentiality, data recording and data storage. |
| • Confidentiality
How will personal information about potential and enrolled participants be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial? | Please refer to comment above |
| • Data storage
How will the collected data be stored, where and how long? | |
| 10 Are the included additional files (supplementary materials) appropriate? | |
| Yes, Ethics approval has been presented | |
| Level of interest:
An article whose findings are important to those with closely related research interests | |
| Quality of written English:
Needs some language corrections before being published | |
| Statistical review:
No, the manuscript does not need to be seen by a statistician. | |
| Declaration of competing interests:
• Harms
Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct are not specified | Please refer to previous comment. |
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