# Itemised responses to peer review comments

## Introduction

This document tabulates the comments from the peer reviewers, together with our responses and the actions taken to address the comments. Our submission includes a copy of the revised manuscript with tracked changes. Within this document changes are also marked using the comments feature, where coded of the following format are added: “Rx Cy” . Here x refers to the reviewer (1 or 2) and y refers to the comment from that reviewer. For example, sections marked R2 C2 are made in response to the second comment from the second reviewer.

## Table of reviewer one’s comments and our responses

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| **Number** | **Comment** | **Response** | **Action Taken** |
| 1 | The methods section described 8 distinct cohorts being modelled (p.6, line 42). However, Table 1 only described 4 cohorts (males/females aged 50/65 years). Please clarify. | The reference to ‘eight distinct cohorts’ is out of date. Previously we considered each combination of: male/female; age 50/age 65; and initial CHADS­2 scores of 0/1, and so eight combinations in total. The initial CHADS2score distinction was removed, leaving four combinations.  We apologies for not correcting this reference. | Changed reference from ‘eight distinct cohorts’ to ‘four distinct cohorts’. |
| 2 | The authors stated that the aim of the paper was to determine the cost-effectiveness of TTE vs no TTE, and not to make recommendations on the most appropriate OACs (p.7, line 23). However, separate analyses were carried out for individual OACs and results for individual OAC scenarios were presented in Table 4. Readers might be tempted to draw the conclusion that dabigatran is superior to rivaroxaban based on the lower ICERs in the table. Is this an appropriate conclusion? Perhaps the addition of a brief discussion would be helpful. | We agree that it would be tempting to compare the OACs in this way, although this was not the purpose of the model developed. A model designed for this purpose should perhaps be slightly more sophisticated and, for example, explicitly model bleed risk using the HAS-BLED instrument, and allow sequences of OAC treatment to be compared rather than single treatments.  We will include a full incremental analysis in the appendix, but also emphasise the limitations of our model in addressing this decision problem. | Added a sentence to the discussion section emphasising that the aim of the assessment was to compare TTE with No TTE, but this depends on the consequences of a decision to treat, and so OAC.  Add an appendix showing the full incremental analysis results |
| 3 | Although the interpretation of the quadrants was briefly described on p.9, labelling the quadrants on the PSA scatterplot would be helpful for readers. Also, it would be more helpful to provide the cost-effectiveness acceptability curves to summarise the uncertainty around the estimated ICERs. | We will add these labels as requested to the scatterplots.  We had previously included cost-effectiveness acceptability frontiers (CEAFs) rather than cost-effectiveness acceptability curves (CEACs), as CEAFs show answers to the more clinically meaningful question “What is the probability that the option with the greatest expected net benefit (i.e. the adoption decision) is cost-effective?” But, we had excluded them due to space constraints and the clinical focus of the journal. We will include CEAFs as appendices, including brief descriptions of how to interpret these figures. | Labelled the quadrants as follows:  Less effective, more costly/ more effective, more costly  Less effective, less costly/ more effective, less costly  Added CEAFs as appendices. |
| 4 | Deterministic sensitivity analysis was only performed on the sensitivity and specificity of TTE in detecting ABN. This seems quite limited. | There were effectively two forms of deterministic sensitivity analysis (DSA): 1) The effect of the OAC provided following identification of a positive feature; 2) The effect of assuming different levels of joint sensitivity and specificity for TTE, presented in for three scenarios within the main article, and also in appendix B.  A third DSA has been added to the appendix: the effect of the true prevalence of the high risk feature (TPHR) on the mean ICER. We hope our exploration of structural sensitivity analyses in this way is now sufficient. | Added TPHR DSA to appendix (Appendix H). |
| 5 | The limitations of the study described on p.12 (CHADS-VAS score; dabigatran dose; ABN not age adjusted). What are the potential implications of these limitations? | We acknowledge that the potential implications of these limitations have not been thoroughly investigated, and would welcome further research to be conducted to quantify the effects of these limitations. | We have discussed the limitations in more detail within the limitations section, and made more detailed recommendations in the implications for further research section, with more emphasis on these areas. |

Table Comments from first reviewer

## Table of reviewer two’s comments and our responses

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| **Number** | **Comment** | **Response** | **Action Taken** |
| 1 | Most importantly, it's not clear what happens to patients when they reach age 75. Their CHADS2 score appears to be incremented, but are all patients prescribed an OAC at that point (per guidelines)? | We thank the reviewer highlighting that this needs clarifying. | Added a statement saying that when a patient reaches the age of 75, their CHADS2 score is increased by one, and if this means they are now at the treatment threshold, they are now treated. For newer OACs with a threshold at CHADS2 of 1 this means they are treated. |
| 2 | Other characteristics in CHADS2 may also evolve over time, something that can be fairly readily handled in this modeling approach. If this isn't done, however, some comment should be made about the directional impact of excluding this progression (in my thinking it would result in poorer cost-effectiveness since the TTE test has a shorter window of time to influence treatment). | We agree this is an important issue, especially with regard to diabetes. The limitations and implications for further research sections now discuss this issue more clearly | Further discussion regarding these points have been added to the limitations and implications for further research sections |
| 3 | The consequences of a severe ICH (page 9, line 16) isn't clear. The manuscript notes that there is no QALY gain, but that seems self-evident for a disabling event. | We thank the reviewer for pointing out that this wasn’t clear. A GOS 2 state (coma) is not the only possible outcome of a severe ICH. Other GOS states are also possible. The utility multipliers associated with these lesser states are now presented in the appendix, and the wording has been amended to make this clearer. | The following has been added to the ‘modelling long term events’ section  “If a patient suffers a severe  intracranial haemorrhage leading to a coma (GOS category 2) as a result of taking OACs, their life expectancy was reduced to a maximum of 3.6 years, over which period they experienced no quality of life and so no QALYs were gained. [13] Other degrees of disablement following an ICH (GOS 3, GOS 4 and GOS 5) could also occur, which were assumed to affect quality of life but not longevity. Further details are provided in the appendix.”  Appendix A has also been amended, and now contains table X below. |
| 4 | the text on the bottom of page 7 is garbled a bit | Thank you for pointing this out. On the version of the manuscript we have access to this is not the case. | None |
| 5 | the use of MAICER instead of the equivalent and much more common willingness-to-pay (WTP) threshold is odd. | We will change this term. | Changed all references of MAICER to willingness-to-pay (WTP) threshold |

Table Comments from second reviewer

**TABLE X** Assumed relationship between GOS and mRS, and estimated utility multipliers for each GOS state

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| **GOS state** | **Assumed equivalent to** | **Utility multiplier** |
| GOS 2: vegetative state | mRS 6: dead | 0 |
| GOS 3: severely disabled | mRS 4: moderately severely disabled; and mRS 5: severely disabled | 0.226 (95% CI 0.221 to 0.231) |
| GOS 4: moderately disabled | mRS 2: slight disability  *and*  mRS 3: moderate disability | 0.642 (95% CI 0.638 to 0.645) |
| GOS 5: good recovery | mRS 0: no symptoms  *and*  mRS 1: no significant disability | 0.895 (95% CI 0.892 to 0.898) |