National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726]

You are asked to check the ERG report from LRiG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **14th January 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726]

BMS/Pfizer Response to ERG report

14th January 2015

BMS and Pfizer would like to thank NICE for the opportunity to review the Evidence Review Group (ERG) report from Liverpool Review and Implementation Group (LRIG) for apixaban for the treatment and prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). We welcome the fact the ERG has acknowledged that apixaban is a clinically effective therapy in the treatment period, and that the indirect evidence from the treatment network meta-analysis (NMA) can be considered reliable. However, we are disappointed that their conclusions do not acknowledge the bleeding advantages of apixaban in the treatment and prevention periods and by their failure to accept the long term clinical benefit of apixaban based on the prevention period NMA.

We believe the robust AMPLIFY and AMPLIFY-EXT trials have demonstrated the clinical benefit of apixaban for long term anticoagulation use. This evidence is consistent with that available for other novel oral anti-coagulants (NOACs) accepted by NICE for this indication. In terms of the evidence supporting the long term benefits of apixaban we accept that there is uncertainty associated with the prevention period NMA. However, we would suggest that we have included the best available evidence, extensively tested for inconsistency and/or heterogeneity across trials and presented numerous sensitivity analyses in order to produce the most plausible estimates of treatment effect. Moreover, we would like to take this opportunity to raise our concerns regarding the alternative approaches (vague prior and Poisson) proposed by the ERG in their new set of analyses, which we believe are not appropriate or consistent with methods described in the NICE Decision Support Unit (DSU) Technical Support Documents (TSDs). Therefore, we continue to believe that the prevention NMA in our submission provides the most reliable estimate of the true treatment effect of anticoagulants despite the limitations in the evidence base.

We are also disappointed that the ERG has failed to review the 'secondary analyses' of the AMPLIFY and AMPLIFY-EXT trials, which contained post-hoc analyses from the apixaban trials to support the economic model. These data, along with the AMPLIFY and AMPLIFY-EXT clinical study reports (CSRs), were provided to the ERG with the submission and we believe should have been sufficient to validate the economic model without the need of additional analyses of the apixaban trials requested by the ERG. Failing to review these documents has led to a misunderstanding of the modelling approach which we attempted to avoid by offering on a number of occasions to engage further with the ERG during the clarification process. We believe this raises significant concerns and casts doubt over the ERG conclusions regarding the economic model, given that we do not believe there are any fundamental errors contained within the model. Despite confirmation from NICE that the ERG intends to review the secondary analyses ahead of the Appraisal Committee meeting, we believe this is insufficient to rectify this oversight by the ERG or the conclusions contained within the ERG report.

The modelling approach is based upon that used in the NICE rivaroxaban appraisals and is also similar to the approach used in the dabigatran appraisal (TA327) which have previously been accepted by NICE as appropriate. We are therefore surprised that the ERG has called into question the validity of the model for this appraisal. Furthermore, we are concerned that this will lead to alternative recommendations for apixaban compared to the other two NOACs (rivaroxaban and dabigatran). This is despite the comparative efficacy and price of NOACs and the evidence provided in the treatment and prevention NMAs to suggest apixaban offers patients and clinicians a treatment option with a more favourable bleeding profile.

We would ask the Appraisal Committee to consider these issues in its deliberations. BMS/Pfizer continue to believe the model results represent a credible and robust estimation of apixaban's cost-effectiveness compared to the other anticoagulants considered.

Factual inaccuracies – summary

We have identified a number of factual inaccuracies contained within the ERG report with regards to the interpretation of the evidence presented in the manufacturer's submission (MS). We would highlight the following three major themes based largely on the misinterpretation of the evidence presented in the MS which we discuss in more detail below:

1. **The results of the AMPLIFY-EXT trial are generalisable to the VTE population requiring long-term anticoagulation in England and Wales and apixaban's long term benefit should be clarified in the ERG report**
   1.1 Apixaban provides a novel treatment for patients who require long term anticoagulation and apixaban 2.5 mg BD is the only treatment which has demonstrated both superior efficacy to, and most importantly, a similar bleeding profile to placebo.
   1.2 The evidence from AMPLIFY-EXT is clinically relevant to the broad population requiring long term anticoagulation identified in the scope for this appraisal. This is consistent with evidence accepted in TA261, TA287 and TA327 to support long term anticoagulation for rivaroxaban and dabigatran.
   1.3 AMPLIFY-EXT is generalisable to clinical practice in England and Wales. Patients were included on the basis of prior risk factors for VTE recurrence and these are readily identifiable in clinical practice.
   1.4 The concept of clinical equipoise explored in the AMPLIFY-EXT publication is consistent with the published NICE Guidelines (CG144) that state a patient with an unprovoked PE should be offered a VKA beyond 3 months, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding.

2. **The prevention period NMA provides a reliable estimation of the treatment effect , we undertook extensive testing and scenario analyses which had negligible impact on cost effectiveness results, which has not been highlighted in the ERG report**
   2.1 The prevention period NMA includes the best available evidence and produces the most plausible estimates of treatment effect. Extensive sensitivity analyses were undertaken to explore the uncertainty but none substantially change the conclusion of the economic model results.
   2.2 The prevention period NMA's methods and results are largely consistent with the recent peer reviewed publication by independent Canadian researchers published in the British Medical Journal (Castellucci *et al* 2013).
   2.3 The treatment effects from indirect comparison of other NOACs (rivaroxaban and dabigatran) accepted by NICE in TA327 are similar to those presented in our submission.
   2.4 Alternative methods proposed by the ERG have not previously been tested in this disease area and should be interpreted with caution.

3. **The economic model is a reliable estimate of apixaban's cost-effectiveness, and the results generated can be considered robust for NICE Appraisal Committee's decision making**
   3.1 The ERG has misinterpreted assumptions in our model leading to incorrect identification of errors, specifically treatment discontinuation and all-cause mortality.
   3.2 Failure by the ERG to review important 'secondary analyses' of the AMPLIFY and AMPLIFY-EXT trials that support the clinical evidence and assumptions used in the economic model has led to concerns regarding the original evidence and/or the analytic methods. If this data had been taken into consideration during the modelling review then this may have avoided the ERG unnecessarily calling into question the reliability of the model.
   3.3 Despite the changes/criticisms made by the ERG the resultant ICERs have not changed the conclusion that apixaban is a cost-effectiveness treatment option for the treatment and prevention of DVT and/or PE.

In conclusion, apixaban represents a cost-effective option compared to the standard of care (LMWH/warfarin), and other available oral anticoagulants rivaroxaban and dabigatran, for the treatment and long-term prevention of DVT and/or PE. Based on the evidence that we submitted, BMS/Pfizer believe that apixaban should be recommended in line with other NOACs for the treatment and prevention of DVT and/or PE.

The following sections provide further details on these key points for consideration.

Major factual inaccuracies regarding the ERG report

Issue 1 The results of the AMPLIFY-EXT trial are generalisable to the VTE population requiring long-term anticoagulation in England and Wales and the long term benefit should be clarified in the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
No evidence in patients for whom long term anticoagulation is required In; Section 3.1, para 1, pg. 25 'the ERG considers that the results of the AMPLIFY-EXT trial are only relevant to one of the subgroups of patients identified in the NICE scope i.e., to patients for whom the risks and benefits of extended anticoagulation are uncertain. The extent to which the results of the AMPLIFY-EXT trial are directly applicable to patients who definitely require extended anticoagulation treatment is not discussed in the CS.' Similar points are made in Section 1.4, pg.9 and Section 8.1.1, pg.134. Later, in section 3.6, pg. 30, the ERG notes that there is no data available to support the clinical effectiveness of long term or lifelong treatment with apixaban. ➢ ***We disagree with this***	It should be clarified that apixaban provides a novel treatment for patients who require long term anticoagulation and apixaban 2.5 mg BD is the only treatment which has demonstrated both superior efficacy to placebo and most importantly a similar bleeding profile to placebo. We would ask that the ERG conclusions in Section 8.2.1 are reflected in the Section 1 (Summary) regarding that "if patients in this subgroup are truly representative of patients who whom the benefits of long term treatment could be considered to be	We believe that the evidence from AMPLIFY-EXT is clinically relevant to the broad population identified in the scope for this appraisal requiring long term anticoagulation. The ERG report states that there is no evidence to support the clinical effectiveness of long term treatment, however we believe that AMPLIFY-EXT does provide appropriate evidence. This is consistent with evidence accepted in TA261[1], TA287[2] and TA327[3] to support long term anticoagulation with rivaroxaban and dabigatran. At the time AMPLIFY-EXT was initiated, it was observed in individuals who completed 6 to 12 months of standard anticoagulation therapy for a DVT or PE, that a risk of recurrent VTE remained even after the initial 6-12 months of treatment ended (~3%/year over 10 years). No anticoagulant was approved for the extended treatment of a DVT and/or PE at the time and so AMPLIFY-EXT was designed as a placebo-controlled trial to fully evaluate both safety and efficacy of prolonged anticoagulation. Greater than 90% of the study population in AMPLIFY-EXT consisted of patients with an index VTE that was unprovoked (93.2% for apixaban 2.5 mg and 91.1% for placebo), and the remaining study patients consisted of those with a provoked index VTE event who also had an additional risk for recurrence. It is generally acknowledged that the	This is not a factual error The ERG agrees that the data from the AMPLIFY-EXT trial demonstrated clinical benefit compared to placebo in patients for whom the risks and benefit of continued anticoagulation are uncertain (clinical equipoise). The AMPLIFY-EXT trial did not include patients for whom extended treatment with anticoagulants was clearly appropriate. The ERG is uncertain as to whether the two patient populations can be considered to be the same. The question of long-term treatment depends on what is considered long term. The ERG notes that CG144 states that a clinical trial with 5-year follow-up is needed in order to determine the long-term risks and benefits of anticoagulation treatment for VTE. In the AMPLIFY-EXT trial, treatment was given for 12 months (following pre-treatment of 6 to 12 months). This is similar to the other EXT trials for the other NOACs, rivaroxaban and dabigatran. There are no data available for treatment beyond this duration.

assessment of the AMPLIFY-EXT trial and with the ERGs assertion that the data from the trial does not support the clinical effectiveness of long term treatment with apixaban.	uncertain, then the results of AMPLIFY-EXT trial demonstrate that, over a 12 month period, treatment with apixaban compared to placebo/no treatment is clinically effective."	patients with thromboembolic events of unknown origin have a more than two–fold rate of recurrent VTE in comparison to patients who thrombosis is based on transient risk factors[4]. Therefore, the AMPLIFY-EXT study included patients at high risk for VTE recurrence and who would have definitely required extended anticoagulation treatment beyond their initial 6-12 months of anticoagulation treatment just simply on the basis of risk for recurrence alone. The reason why these patients were entered into a placebo-controlled trial (AMPLIFY-EXT) is because the treating physicians were not certain whether the risk of bleeding with conventional therapy (i.e. vitamin K antagonists [VKA]) would be worth the potential benefit of extended anticoagulation compared to no treatment. The benefit-risk ratio with extended VKA treatment varies among patients with regard to bleeding risk, reliance on INR monitoring, and maintaining consistent anticoagulation due to the multiple drug-drug and drug-food interactions known to affect VKA therapy. Therefore, the risk of bleeding with extended VKA therapy could outweigh the potential benefit in preventing recurrent VTE once the patient had reached equipoise. The results of AMPLIFY-EXT show unequivocally that the potential benefit of reducing the risk of recurrent VTE with extended treatment with apixaban 2.5 mg twice daily for 12 months beyond the initial 6 to 12 months of therapy for the acute VTE event outweighs the potential risk of bleeding (and particularly major bleeding) with apixaban which was found to be no greater than that with placebo.	No amendment is required.
<u>Generalisability of the clinical equipoise population to UK VTE population</u> In section 3.1, para 3, pg. 25,	We believe that population in AMPLIFY-EXT is generalisable to a	Patients were included in AMPLIFY-EXT on the basis of prior risk factors for VTE recurrence and these are readily identifiable in clinical practice. For this reason we believe that AMPLIFY-EXT is generalisable to	This is a matter of opinion and not a factual error. The ERG report states that the patient population in the AMPLIFY-EXT trial may not

the ERG state that no definition of clinical equipoise is described in the published paper for AMPLIFY-EXT or in the CS. The ERG is concerned that the patient population in the AMPLIFY-EXT trial may not be easily identifiable in clinical practice in England and Wales. A similar point is made in Section 8.1.1, pg.135. ➢ ***We believe the trial population of AMPLIFY-EXT does represent a clinically relevant population within England and Wales.***	clinical population in England and Wales and this should be clarified in the ERG report.	clinical practice in England and Wales. In the absence of a universally accepted explicit definition of clinical equipoise, the NICE guidelines advise that a VKA should only be extended if the risk of recurrence is high and there is no additional risk of major bleeding. However, all patients receiving an anticoagulant are at risk of a bleed and there is no unified algorithm in clinical practice to determine a patient's risk of a bleed; the assessment of clinical equipoise is left to the treating physician. To this point, the NICE Guidelines also state that a patient with an unprovoked PE should be offered a VKA beyond 3 months taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding – this is consistent with the concept of clinical equipoise studied in AMPLIFY-EXT. Furthermore, both RE-SONATE (dabigatran) and EINSTEIN-EXT (rivaroxaban) studied similar populations to AMPLIFY-EXT and were included in the prevention NMA for the dabigatran STA (TA327), which NICE has previously accepted as evidence of dabigatran equivalence to rivaroxaban.	be easily identifiable in clinical practice. This is consistent with clinical advice given to the ERG. The ERG agrees the population of the AMPLIFY-EXT trial is similar to the populations of the RE-SONATE (dabigatran) and EINSTEIN-EXT (rivaroxaban) trials that provided the key clinical evidence in the appraisals of dabigatran and rivaroxaban respectively. No amendment is required.

Issue 2 The prevention period NMA provides a reliable estimation of the treatment effect: we undertook extensive testing and scenario analyses which had negligible impact on cost effectiveness results, which has not been highlighted in the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Appropriateness of the</u>	This section and in the introduction and the	We acknowledged within the manufacturer's submission (MS) that there may be uncertainty with	This is not a factual error. The ERG appreciates that the company took steps to

<u>secondary prevention NMA submitted in the MS</u> In section, 4.8.3, pg. 84-5, the ERG considers the methods used to combine data in the secondary prevention period NMA to be inappropriate due to the different lengths of treatment and stated follow-up times of the included trial. The ERG further notes that 'the company discusses both of these sources of heterogeneity in the MS and explains that consultation with experts suggested that the use of different treatment periods and follow up times would not significantly impact the size of relative treatment effects. The ERG does not agree that the outcome data from studies included in the secondary prevention period NMA have been produced using sufficiently similar assumptions; the ERG considers that there are likely to be more events in studies with longer treatment periods and follow up times than in studies with shorter treatment periods and follow up times. This is a fundamental flaw in the secondary prevention period NMA and the ERG considers that the efficacy (and safety) of apixaban versus any active	conclusion should be amended to reflect the following: We would ask the ERG to amend the relevant sections in their summary, critique of our NMA and conclusions such that they acknowledge that the manufacturer has tested this important assumption extensively in sensitivity analyses and demonstrated that apixaban remains cost effective at an acceptable level. Therefore, the prevention NMA should not be regarding as 'fundamentally flawed' and references to this should be removed.	regards to the prevention period NMA and the differences in the follow up times and treatments periods in the trials included in the NMA resulting in heterogeneity in the network of evidence. However, the ERG has failed to acknowledge a number of important pieces of evidence that suggest that this uncertainty is not unduly biasing the relative treatment effects of the NMA: A number of tests were conducted in the MS that suggested that there was no evidence of statistical heterogeneity (pg.103-4, MS) or any statistical inconsistency within the network for the prevention NMA (pg110-111, MS). Furthermore, a number of sensitivity analyses were conducted to explore the impact of different follow ups and treatment periods between and across trials. 'These analyses demonstrated that the base case conclusions were broadly consistent regardless of changes to the network' and also in terms of trials with different follow up or treatment periods (pg.105, MS). The prevention NMAs methods and approach is consistent with the independent NMA approach published by Castellucci et al (2013) in the British Medical Journal (pg.82, MS). Overall, the treatment effects for VKA and other NOACs from this study conducted by Canadian researchers are broadly consistent with those presented in our submission. Moreover, for example, the results of the accepted meta-analysis conducted as part of the recent dabigatran submission to NICE (NICE TA327).[3] demonstrated that the relative risks of dabigatran versus rivaroxaban and warfarin for major bleeding are comparable to the estimates we included in our analysis. Our analysis suggests a relative risk of dabigatran versus rivaroxaban of 0.11 and dabigatran versus VKA of 0.55 (calculated by	measure statistical heterogeneity for each pairwise comparison within the network, and statistical inconsistencies within the network; however, besides the results of statistical tests there are other important considerations when assessing heterogeneity. If the included studies are fundamentally different, as they are in the case of the prevention period network, then it is still inappropriate to perform a NMA despite the results of the statistical tests. Furthermore, in response to the statement that a "number of sensitivity analyses were conducted to explore the impact of different follow ups and treatment periods between and across trials", the ERG notes that the only sensitivity analysis which investigated the effects of inherent differences between included trials, was the analysis that excluded the WODIT DVT/PE studies due to the significantly longer follow-up periods within these trials. This sensitivity analysis does not fully address the fact that there are important differences between the remaining trials in the network; for example, time on treatment ranged from 6 months (RE-SONATE) to 37.2 months (ASPIRE) in the remaining trials. Therefore, the ERG remains of the opinion that the trials in the prevention period are not sufficiently comparable to be combined in a NMA. Although the company shows that the base case clinical effectiveness conclusions, and the cost-effectiveness conclusions are not altered in a number of sensitivity analyses undertaken by the company, none of these sensitivity analyses adequately address the fact that the studies included in the network are not

comparator as secondary prevention is not yet confirmed and that the results of the secondary prevention NMA analysis should be interpreted with caution.' A similar point is made in 8.2.1, pg.136. ➢ ***We believe that the secondary prevention NMA provides an appropriate estimation of the relative treatment effects of apixaban compared to other therapies. This is supported by the evidence included in the MS, which the ERG has not included nor acknowledged in their report***		dividing the relative risk of dabigatran by the relative risk of comparators). This is comparable to the relative risks computed in the dabigatran appraisal of 0.19 versus rivaroxaban and 0.55 versus warfarin. The ERG is concerned that there is a fundamental flaw in our prevention NMA relating to the likelihood that there are more events in studies with longer treatment periods and follow up times than in studies with shorter treatment periods and follow up times; however fails to address the point around whether this would impact the relative treatment effect of therapies. Finally, whilst acknowledging that there may be some uncertainty with regards to the prevention NMA, we note that the ERG is unable to suggest an alternative network of evidence to reduce bias or uncertainty of the results. We believe that the prevention NMA provides a reliable estimate of the relative effectiveness of apixaban based on a published methodological approach, and is consistent with other published NMAs and the network of evidence demonstrating limited or no statistical heterogeneity or inconsistency. Furthermore, the results of the NMA remain largely consistent despite thorough sensitivity testing. It should be noted that the sensitivity analyses were tested in the economic model and these did not change the overall conclusion that apixaban remains cost effective option at acceptable levels.	comparable. No amendment is required
<u>Appropriateness of the continuity corrections used in the treatment and prevention NMA</u> In addition, in Section 4.8.3, pg.85, para 4-5 the ERG has	The methodology we have utilised should be acknowledged as an appropriate method for handling zero events as recommended in NICE TSDs.	The NMA method we have employed in our analysis is appropriate and is a recognised approach for handling zero events, as stated in NICE technical support document (TSD) 2, when the networks are sparse and some treatment links are only informed by one trial.[5] We did add continuity corrections where the analyses would not converge in the base	This is not a factual error. The ERG's comments relate to the robustness of the results obtained from the prevention NMA, not the appropriateness of the methodology used. The ERG acknowledges that the continuity correction method is appropriate for handling zero events. However, the ERG raises

concerns about the methodology used for the initial and secondary prevention period NMA. The company applied continuity correction factors for instance of zero events for certain outcomes. This led to high estimates of RRs for some comparisons, which in turn were used in the economic model and so affected the size of the ICERs. A similar point is made in 8.2.1, pg.136. ➢ ***The continuity correction used in the submitted treatment and prevention NMAs are appropriate methods recommended in the NICE TSD documents. There are limitations with the ERG-preferred NMA that should be highlighted.***	We believe the ERG should acknowledge the limitations of the alternative vague prior NMA approach favoured by the ERG.	case due to the zero events. We note the ERG preference for the alternative vague prior however they fail to note the strong assumptions required for this distribution to be valid. The NICE decision support unit (DSU) TSD 2 outlines this as a "last resort" approach to the issue of zero events in the NMA of binary outcomes. This is unlikely to be an appropriate method for every outcome or every treatment comparison when there is sufficient evidence in the network available and no zero events. We believe the ERG should be transparent in noting the limitations of this approach both in the main body of their report and in their summary of our evidence. On pg.85 of the ERG report, the ERG provides an example to illustrate their concerns with our approach specifically related to the major bleeding estimate of apixaban versus rivaroxaban. In this example, the rate for rivaroxaban is a product of a zero event in the placebo arm (0/590) compared to four events in the rivaroxaban arm (4/598) of EINSTEIN-EXT. This has resulted in an uncertain estimate of effect for rivaroxaban for major bleeding in the prevention period, which has been noted previously by Castellucci et al. Please note that in our submission, we identified this as an area of uncertainty in the prevention NMA network and took steps to try and reduce this by searching the published literature to identify alternative data sources but unfortunately none were available. That said we would like to point out that rivaroxaban does not form a 'loop' of evidence within the network, and as a consequence this uncertainty in terms of treatment effect will not unduly affect the other treatments in the network of evidence for major bleeding.	concerns about an implausibly large treatment effect estimated by the company's analysis, and for this reason the ERG asked for alternative analyses to be undertaken to investigate the robustness of the company methodology. Despite the fact that the company identified the area of uncertainty in the estimate of apixaban versus rivaroxaban in terms of major bleeding, this does not give an idea of how this effect estimate may vary when using alternative methodology. For this reason, the ERG requested the analysis using the vague prior. The company's original analysis uses fixed trial effects in combination with random treatment effects, whereas the ERG requested analysis uses random trial effects in combination with fixed treatment effects. The justification for the ERG requested methodology is that the prevention period network is very sparse with evidence for some treatments being provided by one trial only. Effectively, this means that two parameters (the trial effect and the mean treatment effect for the "unique" treatment) have to be estimated solely from the two counts from the trial. The treatment effect for the unique treatment is then entirely driven by its relative difference in relation to the other treatment and the absolute count is effectively irrelevant. If instead a random trial effect is adopted then the absolute level of the count for the unique treatment is used within the estimate (and the relative difference is still used). The company states that the ERG requested analysis "is unlikely to be an appropriate

		Overall, we believe the continuity correction methodology utilised in the treatment and prevention NMAs is an appropriate and validated approach which has previously been accepted by NICE and the DSU. Accordingly, the results we have produced in our treatment and prevention NMAs are robust and credible.	method for every outcome or every treatment comparison when there is sufficient evidence in the network available and no zero events". The ERG is of the opinion that whilst the issue of not considering the absolute difference becomes more acute when there are zero counts, it is always questionable to use fixed trial effects when there are treatments that occur only in a single trial. For the reasons above, the ERG believes that their requested analyses using a vague prior were an appropriate alternative analysis to investigate the robustness of the results from the company's original analysis. The ERG would like to highlight that results from network meta-analyses are often sensitive to the choice of analysis method, and it is very difficult to assess the appropriateness of either random or fixed effects to fit the data set in question. Therefore, it is a sensible approach to investigate an alternative methodology in situations where implausibly large treatment effects have been estimated.
<u>Appropriateness of the alternative ERG NMA derived using a Poisson assumption</u> The ERG note in Section 5.5.7, pg.117 that they carried out two additional analyses using a Poisson assumption relating risk to the time of follow up exposure, using Bayesian and non-Bayesian methods, which are highlighted in Appendix 7. ➢ ***It should be noted in the ERG that the NMA derived***	In the main body of their report and appendix 7, we would ask the ERG to highlight the strong assumptions required regarding the use of a Poisson distribution to be justified within their report. Furthermore, we note that ERG has not tested this assumption and this should be flagged as a limitation	NICE DSU TSD2 states that "a key assumption of the Poisson model is that in each arm of each trial the hazard is constant over the follow-up period. This can only be the case in homogeneous populations where all patients have the same hazard rate. In populations with constant but heterogeneous rates, the average hazard must necessarily decrease over time, as those with higher hazard rates tend to reach their end-points earlier and exit from the risk set". As suggested by expert opinion consulted and noted in the ERG conclusion (section 8.2.1, pg.136), the events of interest were assumed to occur in higher frequency early on (i.e. hazards of treatment arms will not be constant over the treatment and follow up periods).	This is not a factual error. The alternative Poisson model approach is appropriate in situations where the risk of events is approximately proportional to the exposure time, and is therefore a natural basis for assessing most outcome measures. By contrast comparisons which make no adjustment for different durations of follow-up implicitly make the very strong assumption that all risk is confined to the follow-up period of the shortest trial, and that no further risk exists from extended exposure to any other treatment. The ERG considers this to be an unreasonable basis for comparison. No amendment is required.

using a Poisson assumptions requires strong assumptions that may not necessarily be valid with regards to the disease area and calls into question the validity of their results	of their approach. We would suggest that these analyses should be reviewed with caution. For this reason we continue to believe the submitted prevention NMA remains the most credible estimate of treatment effects.	In addition, we note that the use of the Poisson distribution requires the calculation of hazard rates using an appropriate measure of follow up for each study. It would have been difficult to identify which time point would be used for each study (inconsistent reporting of follow up- mean, median etc.) and the calculation of the hazard rates would also require a number of assumptions. The assumptions and methods used by the ERG are not clear on this point and should be clarified to ensure the reliability of the estimates produced.	

Issue 3 The economic model is a reliable estimate of apixaban's cost-effectiveness, and the result generated by it can be considered robust for NICE Appraisal Committee's decisions

Description of problem	Description of proposed amendment	Justification for amendment	
<u>AMPLIFY and AMPLIFY-EXT trial secondary analyses to support the economic model</u> In section 1.6 (para. 3, pg. 11) and section 5.5.8 (para. 1, pg. 117) the ERG suggests that "The submitted model uses parameter values derived from the AMPLIFY and AMPLIFYEXT clinical trials to represent the various AEs suffered by VTE patients during the trial follow-up periods (i.e. recurrent VTE events, VTE related fatality, death from other causes, major bleeding events, CRNM events, IC bleeding, CTPH and	The statement that any supporting information was not provided and should be deleted.	When we submitted on the 13th October 2014 we included in the reference pack 'secondary analyses' of AMPLIFY and AMPLIFY-EXT, which included analyses that were undertaken to support the development of the economic model. Specifically, this contained the event rates and risks per model cycle including outcomes such as VTE and VTE related death and major bleeding. This document may have addressed the concerns regarding the original evidence and/or the analytic methods used to generate the clinical (model) parameters. Consequently, if this data had been taken into consideration in the modelling review then this may have avoided the ERG unnecessarily calling into question the reliability of the model.	The ERG accepts that the secondary analyses were missed and the text in the ERG report will be amended accordingly. However the secondary analyses did not include the ERG's requested information concerning the time-to-event variables analysis, where the secondary analyses provided only the same parameter values included in the model without any supporting trial data.

PTS), as well as treatment duration. The sources for these model parameters are described in the model as "AMPLIFY/AMPLIFY-EXT secondary analysis" but without any supporting information describing the original evidence or the analytic methods used to generate the values used." ➢ ***These documents were provided in the reference pack along with the AMPLIFY and AMPLIFY-EXT CSRs***			
<u>Incorrect identification of an error in the time to treatment discontinuation used in the model</u> In section 5.58 (para. 4, pg. 118) the ERG suggests that "The rate of discontinuation of treatment in the two 3-month cycles of the model has been estimated as though the duration of the trial was 12 months, rather than the true duration of 6 months. As a consequence, the calculated rate used in the model is only half the true rate of discontinuation." This is also referred to in other sections: Section 1.6, para 2, Pg. 8; Section 1.6, para 3, pg. 11; and Section 5.5.8, para 5-6, pg. 118. ➢ ***This statement is an***	The ERG found no error in the calculation of parameters; rather they misinterpreted assumptions used in the model. The ERG's incorrect suggestion concerning an error in the rate of discontinuation in the model should be deleted.	The ERG suggestion that applied discontinuation rates in the model contain an error is incorrect. Instead, the ERG appears to have misunderstood the definition of 'other' treatment discontinuation used in the model. In the model, the rates were not estimated over a 12 month period, rather a 6 month period. Treatment discontinuation was modelled as a result of bleeding events or as a result of adverse events unrelated to bleeding and VTE events. Discontinuation due to withdrawal of consent, loss of follow-up, administrative reasons, subject to no longer meeting study inclusion criteria or other reasons were not included in the discontinuation rates due to: • These reasons not being incrementally different between the treatments • These reasons not reflecting reasons of discontinuation in the real-world • Maintaining conservatism in the model as	The ERG accepts that the disparity between the Kaplan-Meier (K-M) time to discontinuation data and the model estimates is not attributable to the calculation of model parameters. However, closer comparison of the K-M data and the model trace results at 90 days confirms the existence of important discrepancies. Section 5.5.8 of the ERG report will be amended to read: **<u>Time to treatment discontinuation</u>** The ERG's comparison of the time to treatment discontinuation results from the AMPLIFY trial with the corresponding Markov trace model results has revealed important discrepancies. After 90 days treatment 8.7% of apixaban patients had discontinued treatment, whereas the

incorrect interpretation of the time to event data provided to the ERG to validate the model **<u>Reliability of the model and the cost effectiveness results</u>** Based on the apparent error highlighted above, in section 5.58 (para, 5, pg. 118) the ERG questions the validity of the economic model and notes that "This finding confirms the ERG belief that all similar model parameters should be independently validated against the original trial data. Without access to the requested K-M analyses, it is not possible for the ERG to determine whether or not this calculation error has been repeated across the whole range of time-to-event model variables, rendering the calculated ICERs wholly unreliable" ➢ ***ERG has found no error in the calculation of parameters; rather they have misinterpreted assumptions used in the model and therefore the model results can be regarded as reliable estimates of the cost-effectiveness of apixaban***		higher discontinuation rates benefit apixaban Discontinuation due to adverse events excluding bleeding and VTE was used as adverse events can vary between treatments causing incremental differences. Furthermore as demonstrated in scenario analysis setting treatment discontinuation to 0 (MS, pg.212, 215, 218) resulted in higher ICERs for apixaban. Therefore, it is evident that higher discontinuation rates benefit apixaban versus LMWH/VKA regimens, suggesting that the assumption used is conservative. Use of lower discontinuation rates is consistent with approaches used in TA261[2] and TA287[3] which chose lower discontinuation rates from their review for the long-term period for conservatism. The rate of other treatment discontinuation included in the submission for the LMWH/VKA arm of 0.0521 per 6 months is comparable to the risk used in TA261,[1] TA287,[2] and published evaluations of rivaroxaban[6], which was 0.019 and 0.0213 for DVT and PE patients respectively per 3 month cycle base (converted to 6-month event rate of 0.038 and 0.043 respectively). We therefore find that discontinuation rates have not been underestimated in the model. However, as noted in the submission, we find treatment discontinuation of anticoagulants over time to be a parameter of uncertainty, therefore conservative estimates were used and extensive scenario analysis was conducted in the submission. Please note that had all cause discontinuation been included in the model, results produced would have been much more favourable for apixaban. In addition predictive validation in the MS (pg.189-190) showed that the model replicated AMPLIFY and AMPLIFY-EXT with some deviations in all-cause mortality and treatment discontinuation which were justified and found to be unfavourable to apixaban.	company model indicates only 7.7% discontinuations. For patients assigned to conventional therapy the trial data show 9.8% of patients had stopped treatment compared to 13.0% estimated by the model. **This finding confirms the ERG belief that all similar model parameters should be independently validated against the original trial data. Without access to the requested K-M analyses, it is not possible for the ERG to determine whether or not similar discrepancies are present in other time-to-event model variables, which may render the calculated ICERs unreliable.**

		"When evaluating all-cause mortality excluding events modelled in AMPLIFY, apixaban had a benefit vs. VKA in the trial beyond the mortality benefit observed due to reduction in VTE and bleeding events. This is not included when assuming the same background mortality resulting in a less favourable but conservative model prediction for apixaban. Treatment discontinuation reported in the model was that related to discontinuation due to non-IC major bleeds and discontinuation unrelated to the events modelled. The lower number of discontinuations observed can be attributed to patients discontinuing treatment on the occurrence of VTE or CRNM bleeds in the trial, whereas in the model we allowed for these patients to remain on treatment." In addition we note that the predictive validation included numbers from AMPLIFY to denote treatment discontinuation from adverse events, which could have been cross-referenced back to Table 2 in the AMPLIFY publication,[7] highlighting the definition used for treatment discontinuation. The ERG however did not seek any clarifications on this matter. Therefore, the model provides an accurate and correct estimation of the cost effectiveness of apixaban. Furthermore, the predictive validation of the model, demonstrated that the calculated ICERs represent a conservative estimation of the cost effectiveness of apixaban compared to LWMH/VKA.	
<u>Incorrect calibration of all-cause mortality from AMPLIFY trial by the ERG</u> In section 5.5.8 (paragraph 3, page 119) the ERG suggests that "The company's base-case short-	We believe that the approach that we have taken in appropriate and that there is no error in the all-cause mortality in the model	The ERG's analysis is flawed with respect to several key aspects: • Use of an exponential function to model all-cause mortality, assuming a constant risk of death over time	This is not a factual error. The ERG has carried out an exploratory analysis of the AMPLIFY trial results in order to assess the degree of correspondence between the submitted model and the data from which it was calibrated – a standard

term model results indicate an undiscounted survival advantage for apixaban of only 15.6 days, suggesting that the submitted model is incorrectly calibrated from the AMPLIFY trial data" using the area under the curve method of a 2-phase survival model fitted by the ERG as evidence ➢ ***This statement is factually inaccurate as the ERG's analysis has limitations and cannot be used to assess mortality benefit. The model has not been incorrectly calibrated to AMPLIFY trial data.***	and we ask that this is acknowledged in the ERG report. We would suggest that the section in the ERG report titled "Time to death from any cause" should be amended as the ERG evidence provided suffers from lack of validity as well as being inconsistent with the methods described in the published NICE methods guidance. We would also ask that the section be amended to reflect the limitations associated with the ERG's analysis, rather than refer to it as a gold standard.	• Lack of compliance with published NICE methods guidance in terms of internal and external validity • Extrapolation based on less than 2% of the modelled population dying • Incorrect comparison of all-cause mortality in the DVT population to all-cause mortality in the overall VTE population These issues are further expanded in the sections below. The ERG's analysis suffers from lack of internal and external validity and does not follow NICE methods guidance as they have not assessed the validity of their approach in relation to historical cohort datasets and/or clinical trials.[8] NICE suggests that: "*The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources such as historical cohort data sets or other relevant clinical trials."*[8] The ERG has provided external data sources surrounding the patterns of all-cause mortality in their report to criticise lack of accumulation of history of recurrent VTE, rather than validate their findings. We therefore refer to section 5.5.2 of the ERG report which provides evidence that the risk of mortality in patients with VTE increases over time, at odds to the distribution used by the ERG to extrapolate long-term mortality which assumes a constant risk. Furthermore, the ERG's analysis suffers from lack of incorporation of time-varying effects as their analysis uses a constant risk without accounting for ageing. The ERG has extrapolated all-cause mortality based on less than 2% of the population in AMPLIFY[7] dying	approach to validating the reliability of any decision model. The methods used for this analysis have been used previously on multiple occasions in NICE appraisals and accepted by Appraisal Committees. Where the methods used by the ERG do not correspond with those contained in a Decision Support Unit document this simply reflects the fact that there are a variety of academic opinions on most of the issues considered by the DSU. It should be noted that DSU reports always contain the following statement "Please be aware that whilst the DSU is funded by NICE, these documents do not constitute formal NICE guidance or policy." It should also be noted that the method used by the ERG for estimating survival gain in the AMPLIFY trial is independent of the selection of any specific parametric projective function, since the only requirement is that when time-shifted the long-term portions of the two survival curves converge to follow the same trend and that there is clinical reason to believe that the long-term experience of surviving patients in both arms of the trial would be similar if they continue thereafter to receive similar treatment. No amendment is required.

		rendering their estimates highly uncertain. The published NICE methods guide also states: "*Internal validity should be explored and when statistical measures are used to assess the internal validity of alternative models of extrapolation based on their relative fit to the observed trial data, the limitations of these statistical measures should be documented*".[8] The ERG has not presented any details of alternative statistical distribution or outputs of their analysis. We have therefore been unable to exactly replicate their analysis. However, based on the graphs presented in Figure 9 of the ERG report it would appear that the annual rate of mortality post 46 days would be approximately 0.03 annually. This suggests that using the ERG's analysis that the annual mortality rate of patients with VTE at the age of 76 and above is lower than that of the general population (e.g. mortality rate for general population aged 80 is 0.05).[3] Finally the ERG compares all-cause mortality figures from the DVT population to the overall VTE population which is not appropriate and is flawed. Overall, we agree with the ERG that mortality benefit has been conservatively underestimated in our model as acknowledged in the predictive validation (MS pg.189-190): *"When evaluating all-cause mortality excluding events modelled in AMPLIFY, apixaban had a benefit vs. VKA in the trial beyond the mortality benefit observed due to reduction in VTE and bleeding events. This is not included when assuming the same background mortality resulting in a less favourable but conservative model prediction for apixaban."* That said, had the ERG's estimate of all-cause mortality been incorporated into the model as an alternative scenario, results produced would have been	

		even more favourable for apixaban as demonstrated by the scenario analysis setting other cause mortality rates to be equal to the general population as used in TA261,[1] TA287[2] and TA327,[3] a scenario that highlighted more favourable ICERs for apixaban (MS, pg.212,215, 218). In conclusion, we do not agree with the suggested ERG approach as it is not appropriate for the VTE treatment population. We believe that our approach utilising conservative estimates of all-cause mortality have enabled a more accurate prediction of costs and QALYs gained albeit potentially overestimating mortality and the ICERs of apixaban.	
<u>Kaplan-Meier analyses requested in clarification questions</u> In section 1.6, para. 3, pg.11 The ERG state that the company was asked via the clarification process to provide 12 K-M analyses. Only two analyses were provided to the ERG.	We would ask that the wording is changed to reflect that BMS/Pfizer provide responses to all priority question the two K-M analyses.	We would like to emphasise that during the clarification process we endeavoured to respond to all questions and provided the two Kaplan-Meier questions that were marked 'Priority Question 27 and Priority Question 28'. Please note we believe that if the 'secondary analyses' had been reviewed by the ERG this would have been sufficient to validate the economic model without the need of additional analyses of the apixaban trials. Furthermore, during the clarification process, no economic questions were received despite BMS/Pfizer raising this issue with NICE.	This is not a factual error. It is incorrect that there were no economic clarification questions. The ERG requested a number of K-M analyses as Economic Issues since they are needed to allow assessment of the company's cost effectiveness submission. However, the letter that was sent from NICE had been modified to combine these with the Clinical Effectiveness questions. Both NICE and the ERG were expecting responses to all clarification questions. The ERG notes from the company letter accompanying this form indicates that the company had offered on a number of occasions to engage further with the ERG during the clarification process. The ERG was not made aware of any such requests.

Further factual inaccuracies regarding the interpretation of the evidence by the ERG

Issue 4 Evidence in provoked VTE patients

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Evidence in provoked VTE patients</u> The ERG notes that the AMPLIFY study population does not include patients with provoked VTE (with no risk factors for recurrence). Section 1.4, para. 1, pg. 9 & Section 3.1, para. 7, pg. 26 & Section 8.1.1, para. 3. The ERG has some concerns about this assumption as no clinical data are available from the AMPLIFY trial to support the use of apixaban in patients with a provoked index event without risk of recurrence. ➢ ***It should be noted that the apixaban 3-month efficacy and safety data is consistent with the apixaban's SPC and the EMA decision regarding apixaban in this population.***	It should be clarified that apixaban is effective in patients with provoked VTE as efficacy and safety has been demonstrated at 3 or 6 months.	As described in the MS (pg.97), AMPLIFY studied patients with a persistent risk factor for recurrence as this warranted six months of treatment. In clinical practice and per the guidelines patients with provoked VTE with no persistent risk factor for recurrence and patients with unprovoked VTE receive the same drug and dosing regimen but for differing treatment durations. The 3-month efficacy and safety data provided to the ERG confirms that apixaban is suitable for 3 or 6 month treatment and is consistent with the apixaban SPC based on the EMA decision, which states that short duration of treatment (at least 3 months) with apixaban should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation).	This is not a factual error. The ERG is concerned that the AMPLIFY trial did not recruit patients with a provoked DVT and no risk of recurrence. Thus, there are no specific clinical data available from the AMPLIFY trial to support the use of apixaban in patients with a provoked index event without risk of recurrence or in patients with distal DVT. The ERG is aware and noted in the ERG report (p25 and p133) that the EMA was satisfied that, having been shown to be clinically effective in patients at higher risk of recurrence, apixaban is also likely to be effective in patients who are at a lower risk of recurrence. The CS presented a subgroup analysis of the AMPLIFY trial that demonstrated the clinical effectiveness of apixaban vs warfarin at 3 months. This was reported in the ERG report (p51). . No amendment is required.

Issue 5 Age and generalizability of the AMPLIFY and AMPLIFY-EXT trials

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Age and generalizability of the AMPLIFY and AMPLIFY-EXT trials</u> The ERG suggest that the mean age of patients with VTE in UK clinical practice is different from the mean age of patients participating in AMPLIFY and AMPLIFY-EXT trials. The ERG notes that the eligibility criteria of AMPLIFY mean that the patient population is likely to be somewhat different the population treated in standard clinical practice in England and Wales. Section 1.4, para.1, pg.9 & Section 4.3.2 para.1, pg. 39 & Section 4.9, para.9, pg.88 & Section 8.1.1, para1, pg.134. ➢ ***It should be noted that the apixaban trials are likely to be eneralizable to a population in England and Wales and that the age of patients within the trials are within the range of patients seen in England and Wales.***	The amendment should acknowledge that the age range in Martinez et al. 2014 is 45 to 82.9 years. Therefore, this statement should be amended to indicate that the mean age of patients recruited in AMPLIFY and AMPLIFY-EXT trials falls within the age range expected to be routinely treated in clinical practice.	Although there were no trial sites for the AMPLIFY study in the UK, there were 7 trial sites in the UK which participated in the AMPLIFY-EXT study. The UK withdrew participation prior to initiation of the AMPLIFY trial due to the colour of the warfarin tablets used as a comparator. The colour was different to that used in the UK and was a concern for confusion. Data on the age distribution of patients in AMPLIFY and AMPLIFY have been presented have been presented in Table 10.1.1 (AMPLIFY CSR) and Table 10.1.2 (AMPLIFY-EXT CSR). It should be acknowledged that patients in the Martinez cohort study referred to by the ERG presents a mean age of 64±18.9 and therefore, age of patients with unprovoked VTE ranged from 45 to 82.9. This range encompasses the mean age of population recruited in AMPLIFY and AMPLIFY-EXT trials. Therefore, this is reflective of patients routinely treated in the NHS	This is a matter of opinion and not a factual error. No amendment is required.

Issue 6 Dose reduction not applicable for the treatment and prevention of DVT and/or PE

Description of problem	Description of proposed amendment	Justification for amendment	
Dose reduction not applicable for the treatment and prevention of DVT and/or PE In Section 3.2, para.5, pg.27 it is reported that patients with serum creatinine ≥1.5mg/ml (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5mg twice daily. ➢ ***This is not relevant for treatment and prevention of DVT and/or PE indication***	The referred text should be removed. There are no dose reduction criteria for the treatment or prevention of DVT and Pes with apixaban.	Per Section 4.2 of the apixaban SPC, there are no dose reductions required when treating patients for DVTs and/or Pes and for long term prevention of DVTs and/or Pes. Dose reductions are only applicable to patients with non-valvular AF who are receiving apixaban for stroke prevention and who fulfill the criteria described in the SPC. Apixaban 2.5 mg is a licensed dose for the long-term prevention of DVTs and Pes.	This is an error and the text will be amended.

Issue 7 Data and interpretation should be marked academic in confidence

Description of problem	Description of proposed amendment	Justification for amendment	
Request for text to be marked academic in confidence We request the following section (Section 4.5.1 para.10,	We request that this section of text is marked academic in confidence.	This is data from the AMPLIFY CSR and should be considered academic in confidence, as this data has not been published yet.	The text will be marked accordingly.

pg.49) should be marked academic in confidence given the data and interpretation is taken from the AMPLIFY (clinical study report) CSR : For the primary analysis no imputation methods were used in the case of missing data. [redacted] ➢ ***We request that this section of the text is marked academic in confidence.***			

Issue 8 Aspirin and no treatment inclusion in the treatment period NMA

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Aspirin and no treatment inclusion in the treatment period NMA</u> In Section 4.8.3, para 6, pg.85 it notes that the ERG have a minor concern in relation to the	To confirm that these comparators were not included in the treatment period NMA and this paragraph can be removed.	The RRs used in table 58, 61 and 63 of the MS represent the RRs used for aspirin and no treatment when patients are switched to these treatments for second line use. They are derived from the prevention NMA.	Thank you for confirming this. Section 4.8.3 will be amended to: A minor concern that the ERG has in relation to the initial treatment period NMA is that the description of the NMA data and analysis is unclear. Tables 58, 61 and 63 in the CS all show RRs for aspirin and no treatment versus

treatment period NMA and whether we included aspirin and no treatment in the network of evidence for this NMA. This is also referred to in Section 8.2.1, pg. 136. ➢ ***Aspirin and no treatment were not included in the treatment period NMA***			apixaban for the initial treatment period, although further clarification (via the factual error check) reveals that aspirin and 'no treatment' were not included in the treatment period NMA, and that these RRs were derived from the prevention period NMA. The ERG has tried to replicate the company's findings from the initial treatment period NMA using the network of evidence as provided in Figure 10 of the CS, but was unable to obtain the same results as the company. Section 8.2.1 will be amended to: The ERG was unable to reproduce the results of either the company's initial treatment period or the company's secondary prevention period NMA using the information included in the CS. The ERG notes that the information about the comparators included in the initial treatment period NMA that is presented in the clinical section of the CS is not the same as the information that is presented in the economics section. Specifically there are results for two additional comparators (no treatment and aspirin) listed in Table 58 of the economics section. The legend for Table 58 is not sufficiently detailed to allow understanding of any additional assumptions/analyses that have been carried out by the company to explain this discrepancy. Further clarification (via the company's factual error check) has revealed that 'aspirin' and 'no treatment' were not included in the meta-analysis calculations for the treatment period NMA.

Issue 9 Inconsistency in the bolding of significant differences

Description of problem	Description of proposed amendment	Justification for amendment	
In Table 30, pg.81 of the ERG report, a number of significant differences have not been highlighted that demonstrate that apixaban reduces major or CRNM bleeding compared to other treatments. ➢ ***There is inconsistency in the highlighting of significant differences in Table 30, pg. 81***	Please consistently highlight the statistically significant differences between comparators	Inconsistency in the highlighting of the statistical differences may be misleading for the reader.	Table 30 will be amended accordingly.

Issue 10 Similarity in AMPLIFY and AMPLIFY-EXT population and modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	
Similarity in AMPLIFY and AMPLIFY-EXT population and modelling approach In section 1.6 (para.2, pg.11) and section 5.5.1 (para.1-2, pg.110) the ERG suggests that two separate models should have been developed to model short term versus long-term treatment and states that "This approach to model design is problematic since the populations included in the two	This suggestion of separate models is at odds to submitted models previously accepted by NICE (TA327)[3] as well as the clinical course of VTE and should therefore be removed. The populations of AMPLIFY and AMPLIFY-EXT are similar based on the baseline	The most recent dabigatran appraisal (TA327) utilised data from their short term trial (RE-COVER)[9] to model the first 6 months of treatment and data from their extended trials (RE-MEDY and RE-SONATE)[10] when comparing to warfarin and rivaroxaban for treatment and secondary prevention.[11] As RE-MEDY included only patients at high risk of VTE[10] and RE-SONATE specifically excluded these, use of this data in their model would be subject to the same limitations. We note however that despite this, NICE and their ERG has previously accepted this approach.[3] This approach is consistent with the disease course of VTE, that is, a continuous	There is no factual error relating to the ERG's opinion that two separate models is preferable to a combined model. Essentially apixaban is being considered for two distinct indications (early preventive treatment of an index event, and long-term continuation treatment of patients without recent VTE recurrence) and each comparison would be more simply and clearly presented separately. The ERG's concern about incompatibility between the two apixaban trials does not

trials are clearly dissimilar. ” ➢ ***The statement is inaccurate as the baseline characteristics of the trials are similar and the modelling approach is consistent with previously accepted approaches by NICE.***	characteristics. Therefore, this statement to the contrary should be revised.	disease state as well as evaluating the resource implications of initiating therapy. Furthermore we note that baseline characteristics between AMPLIFY[7] and AMPLIFY-EXT[12] are largely similar in terms of age, gender, initial VTE diagnosis, clinical presentation and active cancer (MS, pg. 48-49). AMPLIFY enrolled approximately 16% [5]of patients with previous VTE whilst AMPLIFY-EXT enrolled 13%.[12] The ERG note in Section 5.5.1, patients who have previously experienced a recurrence are at a higher risk of subsequent recurrences. Scenario analysis submitted in the MS pg.212, 215, 218 where the baseline risks of recurrent VTE were increased to the upper confidence interval test this assumption highlighted a negligible difference (-6% to -3%change) in the ICERs when compared to LMWH/VKA, LMWH/dabigatran and rivaroxaban but a substantial reduction in the ICER versus LMWH/VKA followed by no treatment (MS, pg. 218) (from £17,917 to £11,902). We therefore find the impact of our modelling approach to be negligible in terms of cost-effectiveness results and favouring comparators.	relate to disparities in baseline characteristics, but to the incompatibility of transitioning patients from a pure AMPLIFY cohort to a mixed population with different types of prior treatment and durations of treatment. The ERG accepts that the last sentence in paragraph 2 of section 5.5.1 is inaccurate. See amendment below.
<u>Reliability of short term analysis based on long-term survival parameters</u> In Section 4.5.1 (para.2, pg.110) the ERG states that “The results of the assessment of short-term apixaban treatment may also be called into question if the parameters drawn from AMPLIFY-EXT to represent long-term survival cannot be shown to be relevant to the AMPLIFY	This statement should be removed as parameters to represent long-term survival are not drawn from AMPLIFY-EXT.	The ERG has misunderstood the use of data from AMPLIFY-EXT in the short term (treatment period) analysis and we have outlined the use of data in the model for recurrent VTE, bleeding and mortality in the model below. Risk of recurrent VTE post 6 month treatment in the short term analysis was based on the prospective cohort study[4] consistently with TA261,[1] TA287[2] and TA327[3]. Risks of bleeding post 6 month treatment were drawn upon from the AMPLIFY-EXT placebo arm. It should	Paragraph 2 of section 5.5.1 will be amended to read: This has implications for modelling the cost effectiveness of long-term preventive treatment with apixaban, since the model begins with a pure AMPLIFY population then applies long-term outcome effectiveness parameters derived from a very mixed population from which all patients surviving a prior recurrent VTE have been excluded. This essential incompatibility of the two parts of the model may compromise the results of the

population." ➢ ***The statement is factually inaccurate as long term survival parameters in the short-term analysis are not drawn from AMPLIFY-EXT***		be noted that post the 6 month treatment duration patients are exposed to the same risks regardless of treatment initiated on in the model. Use of risks of major and CRNM bleedings post the 6 month period is at odds to assumptions used in TA261,[1] TA287[2] and TA327.[3] In these models no risk of bleeding was assumed post the 6 month duration. Modelling of a background bleeding risk post discontinuation is conservative to the apixaban arm as it exposes patients who have survived the first 6 months to a risk of bleeding and death that decreases overall survival and QALY gains. Given the risk of events is the same between treatments post 6 months, and more patients are alive in the apixaban arm at the end of 6 months it is evident that this assumption decreases the QALY gains associated with apixaban Long-term survival was modelled based on UK life-tables and adjusted using a hazard ratio[13] to reflect excess mortality in patients who did not experience any events. For patients in the semi-absorbing health states of IC bleeds[14] and CTEPH[15] a similar approach was used. Data from published literature[13-15] was utilised to do so, therefore data from AMPLIFY-EXT was used to represent long-term survival.	long-term preventive assessment of apixaban.

Issue 11 Incorrect assessment of impact of lack of incorporation of the history of recurrent VTE events

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Incorrect assessment of the impact of lack of incorporation of history of recurrent VTE events</u>	Statements suggesting that the effects of apixaban health gains are exaggerated should	This assumption is unfavourable to apixaban for both the short-term and long-term analysis, the latter acknowledged by the ERG. Despite this acknowledgement the summary on page 11	The ERG has amended several of the identified paragraphs in light of the concerns expressed by the company.

In section 1.6. (para.5 pg.11) and section 5.5.1 (para.12 pg.112) the ERG states that lack of accumulation of history of recurrent VTE events is "likely to lead to exaggerated estimates of the long-term health gains for apixaban" and that "The company acknowledges this limitation in their model and considers that its effect is to understate the advantage from apixaban treatment through reduced risk of bleeding events. The ERG recognises this argument in relation to long-term apixaban treatment, but considers it of limited applicability to the assessment of short-term apixaban use." ➢ ***Both statements are inaccurate as this assumption would lead to more favourable results for apixaban and the argument provided is applicable to both short and long term analysis***	be removed, as should the statement referring to the limited applicability to short-term apixaban use. A statement that the exclusion of an age-adjusted bleeding risk in the model was conservative should be added.	suggests that the ERG considers this assumption to exaggerate health benefits across all analyses. It may be that the ERG is unclear as to the impact in the short-term analysis as we have shown a slight increase in the number of recurrent VTE events in the apixaban arm, observed due to longer life-expectancy in apixaban treated patients that exposes them to the risk of recurrent VTE over a longer period of time. This argument is however applicable for short-term apixaban use as the submission has shown that the treatment effects in reducing recurrent VTE in the acute period are favourable for apixaban. The impact of including accumulation of history of recurrent VTE events would be increased costs, mortality and utility decrements associated with patients in the recurrent VTE health states i.e. the consequence of applying a high recurrence risk to patients in the recurrent VTE health state. Varying these parameters by their 95% confidence intervals keeping all else equal did not appear in the tornado diagrams versus LMWH/VKA in the short term analysis due to negligible impact. Further to the above the ERG fails to comment on the overall conservatism in the model with regards to adjustment in major bleeding and rather only mentions recurrent VTE. A systematic review of case control and cohort studies on risk factor for intracranial haemorrhage (ICH) conducted on the general population found that the risk increased by age, with a crude relative risk for age every 10 year increase to be 1.97 (1.79-2.16).[16] Further to the above evidence, an open cohort study using data from general practices in England showed that the risk of gastrointestinal bleeding increased with age,[17] and older age is a commonly cited risk factor for gastrointestinal bleeding.[18] These studies also cite	1.6 last paragraph will be amended to read: In addition, the company model does not incorporate the impact of an accumulating history of recurrent VTE events on future risks; an omission that may lead to unreliable estimates of long-term health gains for apixaban. Furthermore, the ERG considers that background mortality is inadequately represented, treatment costs have been underestimated, incorrect UK utility values have been employed, and an excessive mean body weight estimate for a UK population has been applied. 1.8 final 2 bullet points will read: • The company model does not incorporate the impact of an accumulating history of recurrent VTE events on future risks; an omission that may lead to unreliable estimates of long-term health gains for apixaban • The ERG considers that, within the company model, background mortality is inadequately represented, treatment costs have been underestimated, incorrect UK utility values have been employed and an excessive mean body weight estimate for a UK population has been applied 5.5.9 second bullet point will read: The company acknowledges that no attempt has been made to incorporate the impact of accumulating history of recurrent VTE events through increasing future risks (including background mortality), as is attested in the literature. This may lead to unreliable estimates of long-term health gains for

		prior bleeding as a factor that increases the risk of future bleeding,[17,18] which highlights a further conservative aspect in our model as the risk of bleeding was not increased to account for increased risk in recurrent bleeds or haemorrhages. This approach has been accepted by NICE in their assessment of NOACs in atrial fibrillation.[19,20,21]	apixaban. 5.5.1 last paragraph will to read: The natural consequence of the company model design is, therefore, that long-term estimates of future VTE events (including deaths) will be increasingly underestimated, resulting in understated event costs and disutilities, and overestimated cohort survival. The company acknowledges this limitation in their model and considers that its effect is to understate the advantage from apixaban treatment through reduced risk of bleeding events. The ERG recognises this argument in relation to long-term apixaban treatment, but considers it of limited applicability to the assessment of short-term apixaban use where initial apixaban therapy replaced by long-term conventional therapy. However, there is no obvious model modification available to the ERG that would correct this important weakness in model structure; the only reliable approach would be to redesign the model completely to incorporate progressively increasing VTE recurrence rates by introducing several additional patient states for those experiencing second and subsequent recurrent events. Populating such a model may prove challenging.
Incorrect assessment of impact of increasing recurrent event incidence, fatality rates and general mortality rates over time	This sentence should be removed or revised appropriately to demonstrate the impact of the assumptions	The impact of the model on increasing recurrent event incidence and case fatality rates within recurrent VTEs would increase survival gain and decrease event-related costs for apixaban as noted above. This is due to favourable treatment effects for	The ERG will amend the identified paragraph in light of the concerns expressed by the company: The impact on the model of increasing recurrent event incidence, fatality rates and

In section 5.5.2 (para.1, pg.114) the ERG suggests "The impact on the model of increasing recurrent event incidence, fatality rates and general mortality rates over time would be to increase the net cost of further events while also reducing the average survival estimates in both trial arms and thereby proportionately reducing the estimated survival gain and incremental QALYs attributable to treatment with apixaban." ➢ ***The statement is incorrect as the impact of increasing risks of VTE recurrence and case fatality (on recurrence), would increase QALY gains for apixaban and increase the reduction in event related costs.***	being unfavourable to apixaban.	apixaban in the short term, and reduction in VTE events in the long-term analysis as highlighted above. Therefore we believe the ERG's statement is inaccurate. The ERG's statement with regards to the impact of increasing mortality rates over time is true; however increasing mortality estimates is contradictory to arguments posed in section 5.5.8 which suggest mortality rates were overestimated.	general mortality rates over time would be to increase the net cost of further events while also reducing the average survival estimates in both trial arms. The net effect on cost effectiveness of incorporating these time-varying risk parameters into the submitted economic model is difficult to anticipate without much more detailed analysis of the AMPLIFY and AMPLIFY-EXT trial data together with data from longer-term trials of apixaban and comparator products.
<u>Appropriateness of data available to model increasing risk of recurrence for VTE</u> The ERG use the Beyth et al study of evidence of VTE recurrence in patients with second recurrence in Section 5.5.1, pg.112 para.3. The ERG go on to conclude that there is no obvious model modification available to the ERG that would correct this important weakness in model structure; the only	We believe that the ERG should acknowledge that redesigning the model on this basis relies on appropriate data to model the assumption. We are not aware of data that would support this change in the model to predict second and subsequent recurrent events. The data provided by the ERG is	We are unaware of data that would be able to support this modification of the model. Furthermore, the ERG state that there is evidence for VTE recurrence on the basis of a patient cohort of 124 patients who underwent unilateral venography between 1984-5 in the USA.[22] The cohort is unlikely to be representative of patients currently receiving therapy in the UK. The high percentage of patients with cancer (27%)[22] means the rate of recurrence is likely to be over stated in this study and is, therefore, inappropriate for the population modelled in the economic evaluation.	As noted for Issue 11 (<u>Incorrect assessment of the impact of lack of incorporation of history of recurrent VTE events)</u> above, the last paragraph of Section 5.5.1 will be amended to read: The natural consequence of the company model design is, therefore, that long-term estimates of future VTE events (including deaths) will be increasingly underestimated, resulting in understated event costs and disutilities, and overestimated cohort survival. The company acknowledges this limitation in their model and considers that its effect is to

reliable approach would be to redesign the model completely to incorporate progressively increasing VTE recurrence rates by introducing several additional patient states for those experiencing second and subsequent recurrent events. ➢ ***The ERG implies that the model should have been designed to increase the risk of recurrence without acknowledging the data gaps***	inappropriate given that there is low generalisability to the current UK clinical practice and a high proportion of patients in the study had cancer. The ERG should acknowledge the limitations of the data provided as evidence of the rate of recurrence or remove the data.		understate the advantage from apixaban treatment through reduced risk of bleeding events. The ERG recognises this argument in relation to long-term apixaban treatment, but considers it of limited applicability to the assessment of short-term apixaban use where initial apixaban therapy would be replaced by long-term conventional therapy. However, there is no obvious model modification available to the ERG that would correct this important weakness in model structure; the only reliable approach would be to redesign the model completely to incorporate progressively increasing VTE recurrence rates by introducing several additional patient states for those experiencing second and subsequent recurrent events. Populating such a model may prove challenging.

Issue 12 Increasing hazard ratio of mortality versus the general population

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Misinterpretation of other cause mortality and its constituents</u> In section 5.5.2 (para. 2, pg.113) the ERG suggests the hazard ratio applied to background mortality rates to estimate	The ERG should either move this statement to section 5.5.1 where this criticism is relevant or completely remove this from section 5.5.2. Alternatively, paragraph	The statement the ERG makes, suggests that death unrelated to VTE should incorporate increase in the risks of recurrent VTE events. However mortality related to recurrent VTE was taken into account in its respective disease state and was omitted from the background mortality to avoid double-counting. As the model assesses VTE-related death and other	This is not a factual error. It is more a difference of opinion. The point being made here is that the sequelae of multiple VTE events include general deterioration in a patients condition including progressively worsening disability (unrelated to specific past VTE events), which

mortality unrelated to VTE events "do not take into account that the risks of recurrent VTE events and that mortality increase progressively with each VTE event." ➢ ***The statement is correct however the implication is factually incorrect. As per the definition of other cause mortality in the model (i.e. excluding deaths related to VTE), increased deaths due to VTE should not be accounted for in this outcome.***	1 on page 113 should be removed and replaced by a description of all-cause mortality.	cause mortality separately this statement is not applicable to other cause mortality, rather VTE recurrence and VTE related death and overall all-cause mortality projections. The criticisms provided by the ERG are not relevant to other cause mortality.	in turn increase the risk of both cardiovascular and non-CVD events unrelated to new VTE events. The result is that 'other cause' mortality increases more rapidly over time than is reflected in a simple multiple of the general population mortality rate. To capture this effect would require a more sophisticated model structure which can accumulate events and measures of disability as modifiers of 'other cause' mortality rates. The derivation of a single hazard ratio (4.41) from the Flinterman results is not clear, and is not obviously consistent with some of the evidence shown (e.g. calculating the ratio of cumulative incidence for Idiopathic vs Control in Table 2 suggests a rapidly accelerating multiplier over time which seem unlikely to be attributable wholly to VTE related deaths). It is difficult to see how adjustment could be made to exclude VTE and bleeding deaths in a consistent manner since these data were not included in the Flinterman paper. No amendment is required.
<u>Irrelevant evidence to denote that the hazard ratio of mortality versus the general population for patients with VTE increases over time</u> In section 5.5.2 (para.2-3, pg.113) the ERG provides evidence on increasing mortality risks for patients with PE and DVT as well risk of death due to stroke, MI, other vascular deaths increasing over time and suggest this is	The evidence provided by the ERG could be misleading and should be removed.	The ERG has not provided evidence to suggest the hazard ratio of mortality versus the general population increases over time. The ERG has also suggested that mortality rates and risk of death increases over time. However this does not suggest whether the increase is proportional, lower or higher than the increase in mortality rates observed in the general population. Therefore providing such evidence to suggest the hazard ratio (being the rate of mortality [unrelated to bleeds and VTE] in VTE patients divided by the rate of mortality in the general population) increases over time is	Please see above (Misinterpretation of other cause mortality and its constituents)

evidence that "the RR risk applied to standard life table mortality risks may increase over time as additional VTE events accumulate among the 'at risk' population" ➢ ***The statement is assumption-based and could be misleading as the ERG has provided no evidence of an increasing hazard ratio, rather evidence of an increasing risk which by definition is different. Evidence from the literature does not suggest the hazard ratio increases over time.***		misleading to the reader. Further critique on the evidence provided by the ERG is detailed below: The ERG refers to the long-term mortality hazard ratio (PE versus non-PE) in their report increasing by 2.7% each year; however this analysis and number are not reported in Klok et al,[23] nor are any statistical tests to determine whether these effects are significant.[23] Examination of the overall survival curves in Klok et al do not suggest an increasing hazard ratio rather one that appears to decrease and increase at different time-points which is consistent with findings from Flinterman et al.[13] The Flinterman paper suggests that the relative risk of death was highest in the first three years, with the calculated HRs provided thereafter not following a distinct increasing or decreasing pattern (HRs of mortality are 14.4, 7.1, 4.2, 1.7, 2.5, 1.8, 2.1 and 3.8 in years 1-8 respectively[13]). We therefore conclude that there is no evidence to suggest the HR increases over time.[13] Use of an average HR over an 8 year follow-up is therefore deemed appropriate. Risk of death due to stroke, MI and other vascular deaths is included in the Flinterman estimates. This study is one of the largest conducted on VTE mortality following up 4,947 patients with first venous thrombosis following up patients over a period of 8 years (mean follow-up of 5.5 years).[13] Therefore patients with these co-morbidities would be included and followed up over time, with their natural progression being reflected in mortality estimates, We note this would also be included in background life-table for the general population, therefore we find the evidence provided by the ERG to be irrelevant. Finally with regards to increasing mortality and	

		disability due to IC bleeds as above in relation to recurrent VTE, this evidence is only relevant to the IC bleed state. If this aspect were incorporated the outcome would be beneficial to apixaban due to its favourable bleeding profile.	

Issue 13 Suggestion that treatment costs have been calculated incorrectly

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Suggestion of incorrect calculation of treatment costs and flawed revision</u> In section 1.6 (para.5, pg.11) and section 5.5.3 (para.1-2, pg.114) the ERG suggests that the method of calculation of treatment costs is inaccurate for both the first cycle and subsequent cycles. The ERG offers an alternative method of calculation, assuming wastage associated with oral anticoagulants and that these are prescribed on a quarterly basis. ➢ ***We believe the alternative method of calculation of treatment costs is inaccurate.***	Statements suggesting treatment costs are calculated inaccurately should be removed. Alternatively the ERG should clarify that treatment costs have been calculated assuming no wastage and comment on the appropriateness of the assumption also taking into account the potential wastage associated with enoxaparin, rather than just oral anticoagulants.	A consistent approach was used in calculating treatment costs which assumed no wastage across treatments. Treatment costs were calculated using the widely accepted and recommended half-cycle correction for Markov models.[24] Therefore the method of calculation is not incorrect; rather the ERG may be concerned with the assumption of no wastage which should be clarified. Although we understand the ERG's rationale, the correction proposed is one-sided as it assumes wastage associated with oral anticoagulants but disregards that associated with enoxaparin. Sacco et al. suggest that the costs of drugs that are administered based on weight or body surface area, are underestimated when the mean weight or body surface area is used and the underlying distribution of weight and thereby distribution of vials/syringes required in the average population is not considered.[25] Including the true wastage for enoxaparin would increase its cost and potentially lead to more favourable ICERs even when incorporating the ERG's correction. We note that the ERG's correction	This is not a factual error. This model amendment applies a sensitivity analysis which indicates the extent of possible uncertainty involved in costing oral medications. The use of the average number of patients on treatment at the start and end of each period implies no wastage at all, which is clearly unrealistic for patients who spend any time during each 3-month cycle in the community. The alternative of assuming the full cost of prescriptions applies from day 1 of each cycle demonstrates the maximum possible wastage of oral medications on discontinuation. Various intermediate scenarios are possible with corresponding intermediate estimates of wastage. Clinical advice suggests that monthly prescribing may be most likely, so that the effect on the ICER would be approximately mid-way between the two extremes. Testing this model amendment also on enoxaparin costs has a very small effect on the ICER (+£8/QALY). No amendment is required.

		improved estimates versus dabigatran and rivaroxaban. Therefore the ERG should acknowledge that assuming no wastage for all treatments is conservative for apixaban, or provide estimates incorporating wastage for enoxaparin. Further to the above as highlighted in the KM analysis provided to the ERG patients can discontinue treatment or die within the first 5-7 days. As a large proportion of these patients are hospitalised on index VTE, oral medications would not necessarily be discarded if patients discontinue or die within that time-period. Moreover clinical experts suggest that follow-up of patients is more frequent upon initiation of therapy, therefore it is likely that prescriptions are filled monthly decreasing wastage. As the ERG assumes these are filled quarterly it should be stated that this is an assumption that is not necessarily validated with experts and may overestimate costs.	

Issue 14 Suggestion of incorrect utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
<u>Suggestion of incorrect utility values attributed to wrong age bands</u> In section 1.6 (para.5, pg. 11) and section 5.5.4 (para.4-6, pg.115-116) the ERG suggests that the mean utility values are incorrect and attributed to patients at the wrong ages • "However, the Kind et al paper does not include any utility values. The original source document for this UK national survey is the Centre for Health	The statements regarding mean values being attributed to the wrong ages and not matching those published are incorrect and should be removed. Further the ERG should note that the baseline utility value used reflects EQ-5D VAS that was previously used in the appraisals of rivaroxaban, marginally different from the utility used by the ERG (0.825	The Kind et al. paper[26] provides a figure (Figure 1) with the age-varying EQ-5D values that are consistent with those included in the model. These values are extracted from the Kind paper in Szende et al. 2004.[27]. Whilst we agree with the ERG that these values are based on the EQ-5D survey using the visual analogue scale, rather than aggregated using NICE's preferred time trade off,	This is not a factual error. Referencing a secondary source which misrepresents original published study results cannot be considered a valid justification for using erroneous data. The MVH time-trade-off is accepted as the primary UK EQ-5D utility tariff, as VAS values were only used as confirmatory to the main analysis (being inherent biased by the absence of negative scores in VAS). No amendment is required.

Economics (CHE) Discussion Paper 172 published in 1999." • "the mean values do not match those published, and are ascribed to different age-bands" • "The consequence of these errors is that mean utility values are incorrect, having been attributed to patients at the wrong ages" ➢ ***The mean values match those published and are attributed to patients in the right ages.***	vs. 0.823).	these values were used for consistency with TA261[1] and TA287[2]. We note that the ERG's amendments did not alter the conclusions of the base case analysis.	
<u>Overstating the impact of using standard deviation in the PSA</u> In section 5.5.4 (paragraphs 3-4 pages 115-116) the ERG states that "The standard error figures in the company model are in fact standard deviations. The uncertainty associated with these utility parameters are seriously overstated (by more than 17 times in individual age-bands, and by 58 times for the overall utility estimate) calling into question the results of the PSA" ➢ ***The ERG inaccurately implies that use of standard deviations has a major impact on results, despite this being negligible***	The statement should be revised, to provide clarifications as to how the PSA results are called into question and allude to the potential impact of this error as the ERG inaccurately implies that this has a major impact.	We agree with the ERG that in fact the utility parameters were varied using standard deviations instead of standard errors. The ERG however inaccurately implies that this has a substantial impact when in fact the correction has negligible to no impact on PSA results.	This is not a factual error. The statement is factually accurate. It is for the Appraisal Committee to consider its significance. No amendment is required.

Issue 15 Suggestion that mean body weight used is excessive

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Suggestion that the mean body weight applied is excessive</u> In sections 1.6 (para.5, pg. 11) and section 5.5.6 (para.1, pg. 116) the ERG suggests that the mean weight used should reflect that reported in the Health survey for England "The cost of LMWH treatment is based on a daily dose of 1.5mg/kg of body weight. In the company model the mean body weight is 84.6kg as reported for the AMPLIFY trial population. However, this is noticeably higher than the mean adult population weight of 77.4kg reported from the Health Survey for England for 2012." ➢ ***The ERG inaccurately suggests that excessive mean body weight has been used disregarding evidence relevant to the UK VTE population***	The ERG should remove statements suggesting use of excessive mean body weight. We suggest that the body weight of the VTE UK population rather the average UK population or provide rationale as to why the general population would be a better reflection in comparison to the VTE population.	It is unclear, why the ERG believe that that Health Survey for England is more appropriate than the AMPLIFY study. We note the CPRD analysis provided in the (MS, Appendix 13f, Section 10.31) on patients with VTE suggests that the mean body weight is 84.07 much closer to the average weight observed in AMPLIFY. This analysis was examined in scenario analysis highlighting no incremental difference on results. In addition if the weight of the population was indeed 77.4kg, assuming no wastage this would merit use of the cost of enoxaparin of the 120mg syringe used TA261[1] and TA287[2] which would result in a daily cost of £9.45 as compared to £9.02 in the base case. This would suggest that the ERG's estimated ICER using this scenario is incorrect assuming no wastage. Incorporation of wastage may have resulted in a higher estimate of enoxaparin costs than the base case even with the lower weight estimate of 77.4kg.	This is not a factual error. Although the CPRD study shows a similar mean body weight to that of patients in the AMPLIFY trial, there are important differences which suggest that the similarity may be coincidental: the mean CPRD age is [redacted] years vs 56.9 years in AMPLIFY. Males constitute [redacted] of the CPRD cohort vs 58.7% in AMPLIFY. Index PE was only [redacted] of the CPRD cohort vs 43.5% in AMPLIFY. The company acknowledges that the two populations are not comparable. The ERG applied body weight data from the general UK population matched by age and sex as an exploratory sensitivity analysis to indicate the potential uncertainty associated with body weight estimation. No amendment is required.

Issue 16 Secondary analyses not provided within the submission

Description of problem	Description of proposed amendment	Justification for amendment	
<u>AMPLIFY and AMPLIFY-EXT trial secondary analyses to support the economic model</u> In section 1.6 (para. 3, pg. 11) and section 5.5.8 (para. 1, pg. 117) the ERG suggests that "The submitted model uses parameter values derived from the AMPLIFY and AMPLIFYEXT clinical trials to represent the various AEs suffered by VTE patients during the trial follow-up periods (i.e. recurrent VTE events, VTE related fatality, death from other causes, major bleeding events, CRNM events, IC bleeding, CTPH and PTS), as well as treatment duration. The sources for these model parameters are described in *the* model as "AMPLIFY/AMPLIFY-EXT secondary analysis" but without any supporting information describing the original evidence or the analytic methods used to generate the values used." ➢ ***These documents were provided in the reference pack along with the AMPLIFY and AMPLIFY-EXT CSRs***	The statement that any supporting information was not provided and should be deleted.	When we submitted on the 13th October 2014 we included in the reference pack 'secondary analyses' of AMPLIFY and AMPLIFY-EXT, which included analyses that were specifically undertaken to support the development of the economic model. Specifically, this contained the event rates and risks per model cycle including outcomes such as VTE and VTE related death and major bleeding. This may have addressed the concerns regarding the original evidence and/or the analytic methods used to generate the clinical (model) parameters. Consequently, if this data had been taken into consideration in the modelling review then this may have avoided the ERG unnecessarily calling into question the reliability of the model. .	The ERG accepts that the secondary analyses were missed and the text in the ERG will be amended accordingly. However the secondary analyses did not include the ERG's requested information concerning the time-to-event variables analysis, where the secondary analyses provided only the same parameter values included in the model without any supporting trial data.

Issue 17 Minor typographical errors in description of model and inputs

Description of problem	Description of proposed amendment	Justification for amendment	
<u>Typographical error in description of model</u> In section 5.4.6, pg. 99 the ERG states that "Risks of recurrent VTE and bleed events in patients who had discontinued treatment (i.e. those in the post-CTEPH and post-IC health states) were based on data from the placebo arm of the AMPLIFY-EXT trial. The risks of recurrent VTE events beyond the end of the AMPLIFY-EXT trial were based on those reported in a prospective cohort study." ➢ ***The description is inaccurate for the short term analysis and contains a typographical error***	This statement should be revised to clarify that in the 6-month analysis recurrent VTE risks post-treatment cessation were based on the data from the prospective cohort study (Pradoni et al). Data from AMPLIFY-EXT were only used for treatment durations above 6 months. In addition the parenthesis should be revised to (i.e. those in post DVT and post PE health states) as this appears to be an error.	This statement is only true for the long-term treatment and secondary prevention analysis. As the ERG calls into question the applicability of short term apixaban results in light of use of data from AMPLIFY-EXT it should be clearly stated the risks of recurrent VTE post the 6 month duration in the short term analysis were not based on AMPLIFY-EXT rather the prospective cohort study[4] consistently with TA261,[1] TA287[2] and TA327[3]. Post CTEPH and post-IC health states are semi-absorbing health states indicating that patients are not exposed to any further risks other than death. We therefore believe that inclusion of these health states in the parenthesis to denote patients who had discontinued treatment may have been a typographical error.	The text will be amended in line with the company's suggestion.
<u>Typographical error in description of model input</u> On page 100, Table 43 Baseline utility value the ERG states that the baseline utility value used in the model is 0.8224 ➢ ***Typographical error in the***	The baseline utility value should be revised to 0.825	Typographical error in the description of the baseline utility value that is inconsistent with the model input.	0.8224 is the baseline utility value presented in the company's report (Table 67, p170). However, the ERG acknowledges that the value of 0.825 is that which is actually used in the company model. An appropriate amendment will be made to the ERG report.

utility value			
<u>Typographical error in the date of the searches</u> In Section 5.2.1, para. 1, page 89 ERG report, paragraph 1, line 2. There appears to be some minor typographical errors with regards to the dates used in the searches: 'ERG states that 'the TA287 review considered articles published between 1 July 2011 and 25 October 2015...' 'The ERG state that the 'time horizon for the search was 25 October 2014 to 15 July 2013' ➢ ***Typographical error in the date***	The dates of the searches need to be revised.	The rivaroxaban NICE submission systematic review was conducted up to the 25th October 2012. The update of the Systematic Review was carried on the 15th July 2014 (Date span: 25th October 2012 to 15th July 2014).	The ERG will amend their report to correct the typographical errors identified by the company

References

1. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. National Institute for Health and Care Excellence TA261. Available from: http://www.nice.org.uk/guidance/TA261 (accessed 14 January 2014)

2. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. National Institute for Health and Care Excellence TA287. Available from: http://www.nice.org.uk/guidance/TA287 (accessed 14 January 2014)
3. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and / or pulmonary embolism. STA report. National Institute for Health and Care Excellence TA327. Available from: http://www.nice.org.uk/guidance/ta327(accessed 14 January 2014)
4. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007;92(2):199-205
5. Dias s, Welton JN, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Available from: http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf (last accessed: 13 January 2015).
6. Lefebvre P, Coleman CI, Bookhart BK, et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. *Journal of medical economics* 2014;17(1):52-64
7. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *The New England journal of medicine* 2013;369(9):799-808
8. National Institute of Clinical Excellence (NICE);Guide to the methods of technology appraisal 2013, 04 April 2013. Available from: http://publications.nice.org.uk/pmg9 (accessed January 2015)
9. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
10. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368(8):709-18.
11. Buller HR. Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism. The EINSTEIN-Extension study. Blood (ASH Annual Meeting Abstracts). 2009;114(22):LBA-2.
12. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013b;368(8):699–708.
13. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, Rosendaal FR. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. *PLoS medicine* 2012;9(1):e1001155

14. Prandoni P, Trujillo-Santos J, Sanchez-Cantalejo E, et al. Major bleeding as a predictor of mortality in patients with venous thromboembolism: findings from the RIETE Registry. *Journal of thrombosis and haemostasis:JTH* 2010;8(11):2575-2577
15. Ng AC, Chung T, Yong AS, et al. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circulation. Cardiovascular quality and outcomes* 2011;4(1):122-128
16. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* 2003;34(8):2060-2065
17. Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. *BMJ (Clinical research ed.)* 2014;349:g4606
18. Valkhoff VE, Sturkenboom MC, Kuipers EJ. Risk factors for gastrointestinal bleeding associated with low-dose aspirin. *Best practice & research. Clinical gastroenterology* 2012;26(2):125-140
19. Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. National Institute for Health and Care Excellence TA275. Available from: https://www.nice.org.uk/guidance/TA275/resources (accessed 14 January 2014)
20. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. National Institute for Health and Care Excellence TA256. Available from:https://www.nice.org.uk/guidance/TA256/resources (accessed 14 January 2014)
21. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. National Institute for Health and Care Excellence TA249. Available from: https://www.nice.org.uk/guidance/TA249/resources (accessed 14 January 2014)
22. Beyth RJ, CohenAM, Landefeld S. Long term outcomes of deep vein thrombosis. *JAMA Intern Med* 1995; 155:1031-7
23. Klok FA, Zondag W, van Kralingen KW, et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. *American journal of respiratory and critical care medicine* 2010;181(5):501-506
24. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2012;15(6):812-820
25. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PloS one* 2010;5(1):e8933
26. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ (Clinical research ed.)* 1998;316(7133):736-741
27. Szende A, Williams A. Measuring Self-Reported Population; The EuroQol Group's International Task Force on Self-Reported Health 2004