ERG Response to factual inaccuracies 17th March 2011

Issue 1 The generalisability of the RE-LY trial to the UK AF population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On several occasions, the ERG report states that the population considered in the MS is (on average) at higher risk of stroke than the population at-large in the UK or that detailed in the final scope (e.g. page 6, 14, 17 etc), thereby querying the degree of applicability of the RE-LY population to the decision problem. It also states that the addition of "…people over 65 with AF but no other risk factors for stroke…" would better reflect the NICE scope (e.g. page 14). We believe these to be incorrect interpretations of the scope and of the factors influencing eligibility for treatment.	The ERG report should concede that the risk profile of the RE-LY trial population is not greatly different from that which would be expected in UK practice.	The final scope states that dabigatran etexilate (DBG) is to be appraised within its licensed indication for the prevention of stroke and systemic embolism. It does not state that it should be appraised according to the stroke risk algorithm presented in NICE Clinical Guideline 36. Although not mutually exclusive, there are differences between the two. The key issue is the interpretation of "eligible for anticoagulation". It is not sufficient to simply state that this refers to those at "moderate to high risk" as per the NICE algorithm. In the NICE algorithm, patients defined as moderate risk (which would apply to patients aged over 65 with no other risk factors) are eligible for either warfarin or aspirin. In particular regarding the moderate risk group the guideline states the following: "*Owing to lack of sufficient clear-cut evidence, treatment may be decided on an individual basis, and the physician must balance the risk and benefits of warfarin versus aspirin. As stroke risk factors are cumulative, warfarin may, for example, be used in the presence of two or more moderate stroke risk factors.*" That is, the guideline indicates that warfarin may be considered in patients at the higher end of the moderate risk spectrum due to lack of evidence. It is therefore curious that the ERG relies on this subgroup to make its point regarding applicability.	The manufacturer has not presented a factual inaccuracy. To be clear the ERG observes that the trial data does not represent the patient group currently eligible for anti-coagulation therapy (with the difference likely to become increasingly marked over time as the threshold for treatment with warfarin decreases) and recommends caution in extrapolating results beyond the trial population. The ERG explores the effects of using patient characteristics from a non-trial AF population and finds that dabigatran is less cost-effective.

		As the ERG correctly points out, the clinical consensus on the appropriate cut-off for eligibility for anticoagulation has shifted downwards in recent years. With this in mind the inclusion criteria for the RE-LY trial was flexible with regards to this definition, i.e. it stipulated only that patients had to have at least one of a series of additional risk factors for stroke. This means that it was possible for patients with a $CHADS_2$ score of 0 (low risk) or 1 (moderate risk) to be included in RE-LY (2.5% and approximately 30% of randomised subjects had a score of 0 or 1 at baseline, respectively). To criticise the applicability of the RE-LY trial population as of insufficiently low risk in general, and specifically for not including patients of age over 65 with no additional risk factors, seems to be very unfair given that the trial inclusion criteria went further by including lower risk patients than clinical consensus may have advocated at the time of the start of the trial.	

Issue 2 Fixed and variable costs of INR monitoring

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states on several occasions that the cost of INR monitoring has been overestimated in the MS (e.g. page 14 and16) due to the inclusion of fixed costs. This criticism directly contradicts the method used to calculate the same	Whilst we concede that there is uncertainty regarding this parameter, the ERG report should also concede that the base case assumption for the cost of INR monitoring in the MS is reasonable based on the available evidence and the reference case. The ERG's supposition that the cost has been overestimated	It is extremely difficult to accurately measure the cost of INR monitoring. The provision of this service not only varies considerably across and within regions with respect to setting and resources, but also by individual patient according to the intensity of monitoring required by each. The MS uses the cost proposed in NICE's own Clinical Guideline, inflated to current prices, as a reasonable assumption for the base case, which is varied in sensitivity analysis. The ERG fails to propose a validated alternative, quoting only one other value based on a clinical trial (i.e. not real-world practice). Further, the ERG's value is based on a different target INR range (2.5 - 3.5) and resource	The manufacturer has not presented a factual inaccuracy, but a disagreement about how monitoring costs should be estimated. The ERG aims to highlight the assumptions being made by the manufacturer and present the results of three alternative costing scenarios. The manufacturer's analysis assumes that all costs of INR monitoring will be eliminated with the introduction of dabigatran. The ERG argues that this is

cost in NICE's own cost-effectiveness analysis within Clinical Guideline 36 (Atrial Fibrillation). Worryingly, the ERG report also states: "These [fixed] costs will only be eliminated if anticoagulation clinics are shut down and clinicians diverted to other activities" (page 96). This is completely inaccurate.	should be either removed or supported by better evidence. In addition, the ERG's assessment that fixed costs can only be released by closing clinics should be removed outright. If it wishes to opine on this issue then the ERG should instead highlight the rare opportunity afforded by this innovation for efficiencies through genuine service redesign.	use from 2001-2 (pre-dating the estimate used in the MS). Accordingly we believe the ERG's claim to be an unjustified over-simplification of the true cost of INR monitoring. In the construction of a cost-effectiveness analysis we regard it as our responsibility (as per the reference case) to use the full economic/opportunity cost that could potentially be realised by use of the technology under appraisal. It is not for the manufacturer (or the ERG in such an arbitrary fashion) to limit the potential for efficiency savings and define what proportion is a fixed or variable cost to the NHS, particularly in this case where services vary so widely. Rather the true economic cost of providing the service should be presented as far as possible, with the subsequent onus then on NHS commissioners and providers to make services as efficient as possible if the technology is recommended. Importantly, the introduction of an effective product that does not require anticoagulation monitoring is a clinical advance not seen in this therapeutic area for over 50 years. This innovation therefore represents an extremely rare opportunity for the NHS to engage in true redesign of an established service, to the benefit of the NHS, taxpayers and patients, which perfectly aligns with the NHS QIPP agenda. We vehemently disagree with the ERG that this redesign could only be achieved by simply closing clinics, and refute this claim as mere conjecture.	accurate only for per patient costs. As some patients will remain on warfarin, anticoagulation clinics will still be needed. Therefore fixed costs will be accrued. The manufacturer's inclusion of fixed costs on the warfarin arm overestimates the costs of warfarin. We explore the cost-effectiveness of dabigatran when fixed costs are not offset by its use. The ERG base case uses costs from HTA 2007 11 in which variable (per patient) costs of monitoring were included but not fixed costs. To be clear, the ERG does not state that the INR monitoring costs estimated in clinical guideline 36 are inaccurate. This guideline estimates total costs of INR monitoring (fixed and variable costs). Therefore, not all the costs included in the guideline will be offset by dabigatran. We have added more text to p.96 of the ERG report to define fixed and variable costs and clarify our analysis.

Issue 3 The ERG claim that a contraindication to warfarin would also mean a contraindication to DBG and the relevance of the aspirin comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states: "The relative effect of dabigatran to aspirin monotherapy in patient (sic) whom warfarin is not suitable remains unknown, therefore this aspect of the NICE scope has not been addressed. However, given a contraindication to warfarin would also mean a contraindication to dabigatran…" (page 14, 29,) These statements are significant errors.	These statements should be removed and the conclusions based on them re-contextualised. Anticoagulation (of whatever form) for eligible AF patients is unquestionably superior to aspirin for the prevention of stroke and systemic embolism. This is not debatable and the ERG report should retract its suggestion that the relative effect of DBG to aspirin is unknown. Further the population ineligible for warfarin but eligible for DBG will be much larger than the ERG predicts, therefore their report should give greater emphasis to the comparison of DBG versus aspirin for these patients than is currently evident, as presented in the MS and required by the final scope.	It is wrong for the ERG to suggest that the relative effect of DBG compared to aspirin is "unknown". Far from being unknown, the weight of available evidence and clinical consensus is compelling: 1) It was already universally accepted that warfarin is superior to aspirin for eligible patients in this indication. 2) The results of RE-LY detailing the relative effectiveness and safety of DBG compared with warfarin are well documented in the MS and ERG report. 3) The recently published AVERROES clinical trial (Connolly *et al, NEJM* 2011, Feb 10), compared apixaban (another new oral anticoagulant in development) with aspirin in patients who are eligible for anticoagulation but "unsuitable" for warfarin. Based on the above it would not be unreasonable to question the need for AVERROES. Accordingly, and unsurprisingly, this trial was halted early due to clear superiority of apixaban. 4) The MTC presented in the MS provides further compelling evidence of the clear superiority of anticoagulation (both DBG and warfarin) compared to aspirin, across a multitude of outcomes. It is well known that warfarin is a complicated medicine with many drug-drug and drug-food interactions, not to mention independent potential difficulties with INR control. For illustration, the above mentioned AVERROES trial (Table 2 in the publication) presents no less than twenty separate reasons for unsuitability of VKA (warfarin) treatment that do not preclude treatment with a new oral anticoagulant, such as DBG. It is important to be clear that there exist absolute contraindications to any anticoagulation therapy (usually related to elevated bleeding risk), and	The manufacturer has not highlighted a factual inaccuracy. No studies of dabigatran vs. aspirin exist in the sub-group of people for whom warfarin is not suitable. We have amended the wording slightly to state " …whom warfarin is not suitable has not been studied in a clinical trial" The manufacturer stated on P8 in their response to the ERG's points of clarification: "it is expected that patients contraindicated for warfarin (due to haematological reasons) would also be contraindicated to DBG." This view was also conveyed by the clinical experts advising the ERG.

		relative contraindications particular to individual treatments, of which warfarin has many more than DBG. It was for this reason, and therefore because this subgroup represents a significant number of patients, that aspirin was included as an important comparator in the final scope.	

Issue 4 The ERG sensitivity analysis which assumes that INR is "consistently within target range"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG analysis highlighted in the summary on page 15 and detailed on page 111, which modifies our base case by applying it only to sub-population of patients able to maintain their INR in the target range, can only be of academic/theoretical interest and should not be used as a basis for decision making. It is therefore extremely disappointing that it has been given a disproportionate and misleading level of significance. That is, on page 16 it states: "[these results]…	The ERG should, at the very least, properly contextualise this extreme analysis as purely theoretical and inapplicable to any real-life AF population. Of even greater concern, the report goes on to use this analysis to justify a recommendation that all patients should be "tested" on warfarin before DBG is considered. The ERG has stretched the significance of this analysis far beyond any logical interpretation, i.e. that 100% TTR can be used to justify a recommendation that DBG is not cost-effective in patients achieving "good" control. If the ERG wishes to make this recommendation, then it should define "good" or "poor" control and propose an evidence-based continuation/switching rule. We submit that no such definition or rule does, or could, exist.	In this extreme analysis, the ERG assumes that warfarin patients remain in target range 100% of the time. There are several problems with this: The ERG incorrectly uses the data from the study by Walker *et al* (2008). This study represents a general AF population that has variable TTR over a relatively short time period. However the ERG assumes that this data can be applied to a cohort of perfectly controlled patients over their full duration of warfarin treatment, howsoever long. Further, 100% TTR is very rare. For example in RE-LY (which has median follow-up of 2 years), only 50 patients (0.8%) achieved 100% TTR, of which only 1 was a UK patient (0.9% of the UK cohort). Importantly, INR control in a clinical trial such as RE-LY is known to be superior to real world practice (see for example van Walraven *et al*., 2006 – reference 107 to the MS), making real-world observation of 100% TTR even less likely. Therefore the ERG analysis could only realistically be applied to an extremely small subgroup of patients who are <u>never</u> out of target range, including during initiation. Moreover, this would require that it is known *a priori* who the 100% TTR patients will be and that their identification is costless. This is	The ERG advocates exploring the cost-effectiveness of dabigatran as second line therapy to warfarin because INR control is a very sensitive factor in the model and given the data and model supplied by the manufacturer the ERG could undertake no further analyses. To clarify this point we have changed p.16 to say " at the same time highlight the need to **explore <u>the scenario of</u>** warfarin as first line treatment with dabigatran as second line".

at the same time highlight the need to test warfarin as first line treatment with dabigatran as second line". This conclusion simply cannot reasonably be drawn from this analysis and we object to it in the strongest possible terms.	Rather, based on the weight of evidence in the MS, and considering that this extreme analysis was the only analysis that the ERG could present which questions the cost-effectiveness of DBG, the ERG should instead recommend that DBG is made available as an option for all eligible patients. Ultimately, the only way a switching rule could be implemented is by clinician judgement. Therefore, based on the cost-effectiveness results presented (both by us and the ERG) it is clear that clinicians should be provided with the flexibility to choose which anticoagulant is most appropriate for their patients, rather than forced to "test" them on a potentially sub-optimal treatment. The ERG report must be amended to this effect.	of course impossible and therefore the derived ICER from this analysis could never apply in any real-world setting. Since patients that may or may not achieve acceptable INR control cannot be prospectively identified, the ERG is advocating withholding a treatment with superior efficacy and safety (DBG 150 mg bid) in order to perform a warfarin testing period where some patients will be at increased stroke and/or bleeding risk. The ethics, costs and consequences involved in this proposed "test" period are not considered by the ERG. Whilst we recognise the purpose of the analysis is to highlight the sensitivity of the results to INR control, it is irresponsible for the ERG to make a recommendation that could affect thousands of patients, without any proposal for how this would be operationalised in practice, based only on an incorrectly executed hypothetical analysis.	The comments indicated by the manufacturer will be important to test.

Issue 5 The use of INR monitoring to assess compliance with warfarin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG reports states: "It is worth noting that INR monitoring offers a benefit of warfarin over dabigatran in clinical practice, as a person not complying with warfarin would be identified by poor INR control." (page 32). This is an alarmingly inaccurate statement.	This statement should be removed.	We have found no evidence, and nor does the ERG present any, to support this statement. INR control can be affected by any of a myriad of factors. It is perfectly plausible for a patient to be compliant with their warfarin therapy and yet have poor INR control, and vice versa. To suggest that INR monitoring can be used as an effective tool to identify non-compliance is factually incorrect.	The ERG agrees that INR control is due to a myriad of factors. However, our clinical experts stated that poor INR control can help identify patients with poor warfarin compliance.

Issue 6 DBG shows "little or no benefit in patients achieving good INR control"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states: "…in people achieving good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with dabigatran." (page 37) This over-simplistic claim is based on an	The ERG report should be amended to account for the following: 1) The subgroup analyses stratified by individual patient TTRs (iTTR) used to justify this claim are inherently subject to bias because they do not preserve randomisation. It is preferable to perform TTR subgroup analyses stratified by centre (cTTR) which preserve each centre's randomisation (Wallentin *et*	The iTTR analyses, such as those used by ERG to justify this claim, introduce serious bias since stratification occurs only in the warfarin arm (i.e., only one of the three treatment arms of RE-LY). While such an analysis may be performed as a sensitivity analysis to assess the overall robustness of study findings, it is inappropriate to use these results as the basis of decision making. In fact, we have performed similar sensitivity analyses on the primary efficacy and safety endpoints, the results of which are provided in the RE-LY clinical trial	The manufacturer has not presented a factual inaccuracy. Whether the benefit of dabigatran over warfarin is maintained across all patients irrespective of their INR control when on warfarin is an important consideration. This was not fully explored in the MS and so the ERG referred to the analysis reported by the FDA. Referring to the more appropriate analysis now supplied by the manufacturer, the

analysis which is subject to bias and is therefore not accurate.	*al*., *Lancet* 2010 Sep 18;376:975-83). 2) The cTTR analyses show that the benefits of DBG 150mg bid at reducing stroke, DBG 110mg bid at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. 3) Other important outcomes, such as intracranial haemorrhage (ICH), should also be considered. The benefit of DBG compared to warfarin in ICH is also preserved across all TTR subgroup analyses.	report (see attached document for ease of reference). In these exploratory analyses a subgroup analysis for the TTR of <65% and ≥65% for the primary endpoint and the safety endpoint 'major bleed' is presented. The superiority of DBG 150mg bid and the non-inferiority of DBG 110mg bid are maintained even against warfarin > 65% TTR, reinforcing the consistent results of RE-LY, even when ignoring the fundamental bias that is inherent in this subgroup analysis. Nevertheless we maintain that these sensitivity analyses are not suitable for making definite assessments on the relative efficacy and safety of DBG. The analyses stratified on centre TTR (cTTR) – a method that maintained randomisation within a centre (Wallentin *et al*., *Lancet* 2010 Sep 18;376:975-83) - should carry more weight. The publication of the cTTR analysis states: "In the absence of any indicator of anticoagulation status in the dabigatran groups, the average TTR each centre achieved in its patients treated with warfarin was used as an approximation of quality of INR control for all its patients (centre's mean TTR [cTTR]) receiving warfarin." Overall, the cTTR analysis is associated with considerably less bias than an analysis based on individual TTRs. Results of the cTTR analysis clearly confirm the overall results of RE-LY. There was no interaction between cTTR and the primary endpoint, thus supporting the robustness of the	results presented are very similar to those in the ERG report (Comparison of Table 2 of Wallentin and Table 10 in the ERG report (reproduced from the FDA document)). Whilst the test for interaction reported by Wallentin et al. does not reach statistical significance the conclusions drawn from these two sets of data would be the same. Wallentin et al. also present an analysis by mean time in therapeutic range for composite outcomes and the pattern of results is similar to that seen for the primary outcome, and these do reach statistical significance. The authors of that paper conclude that "Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives". This is in line with the point made by the ERG.

		RE-LY findings across all INR values achieved for warfarin. The study authors note that "… there were no significant interactions between cTTR and stroke and systemic embolism with either dose of dabigatran versus warfarin" (please see Table 2 and Figure 2 in the Wallentin publication). Finally, the authors state the following in the discussion section: "Thus, these findings support the superiority of 150 mg dabigatran twice daily and the noninferiority of 110 mg dabigatran twice daily versus warfarin for protection against stroke in atrial fibrillation irrespective of the quality of INR control that a centre can achieve." It is also important to note that the risk of intracranial haemorrhage (ICH) observed with warfarin was not affected (i.e., did not decrease) by TTR and was substantially reduced by both doses of DBG, irrespective of the quality of INR control.	

Issue 7 The ERG's claim that if systemic embolism (SE) was included in the economic model, then so should have been pulmonary embolism (PE)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states: "PE, however, was not included in the model. The manufacturer justified this decision by stating that PE was a rare event that occurred at similar rates across the treatment arms. SE, however, was included	This section should be reworded to make it clear that SE is clearly a more relevant endpoint than PE with regards to the decision problem. We concede that PE was excluded as a modelling simplification that was deemed	Fundamentally, patients with AF are at major risk of "firing" thrombotic material from the left atrium of the heart, and thus are predisposed to atrial complications/embolic events. SE is such an atrial event, whereas	The manufacturer has not presented a factual inaccuracy. This justification was provided by the manufacturer in response to the ERG's points for clarification. However, in their response, the manufacturer also stated that variation in rates of SE

in the model whilst presenting similar rates as PE." (page 86). With this statement the ERG implies that SE and PE should carry equal weighting in our economic evaluation but this is factually inaccurate.	to have a low impact on the overall conclusions. However despite low event rates, SE was imperative to be included in the economic model for a host of reasons.	PE is a venous event. Further, the ERG fails to contextualise this issue by considering that: 1) SE was a component of the primary endpoint of the RE-LY trial. 2) The prevention of SE is one of the goals of treatment. 3) SE was mentioned by name in both the indication and outcomes section of the final scope. PE was not. 4) PE was a secondary endpoint in RE-LY. SE is therefore clearly a more relevant endpoint than PE with respect to the decision problem.	showed little impact on overall cost-effectiveness, and similar results would be expected for PE due to similar costs and outcomes for this event, and prevention of stroke and systemic embolism refers to arterial embolism, and PE is a venous event. The manufacturer therefore excluded PE from the model for pragmatic reasons. Therefore, we have changed the statement to eliminate the manufacturer's suggested implication to, "PE, however, was not included in the model. The manufacturer justified this decision in part by stating that PE was a rare event that occurred at similar rates across the treatment arms. SE, however, was included in the model whilst presenting similar rates as PE. Further justification given for the exclusion of PE from the model were: 1. that PE had similar costs and outcomes to SE, and variation in rates of SE showed little impact of on overall cost-effectiveness, and 2. stroke and systemic embolism are arterial events and PE is a venous event. ."

Issue 8 The intended use of the DBG 110mg bid regimen

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The final scope states that DBG is to be appraised within its licensed indication. Throughout the report	Unfortunately the ERG report does not seem to fully account for the sequence analysis and its purpose. Our expectation is that DBG 150mg	The ERG report should properly reflect the intended use of the 110mg dose. The purpose of the	The manufacturer has not presented a factual inaccuracy.

the ERG's own analyses repeatedly compare DBG 110mg bid directly with DBG 150mg bid. It is inappropriate to continually make this comparison without providing the context that the proposed licensed indication for DBG is for the two doses to be used in different patient groups.	bid will be indicated in patients under the age of 80, and DBG 110mg bid will be indicated in patients aged 80 and over (as per the proposed label). This dosing regimen has been proposed to the EMA and is based on risk-benefit assessments of each dose versus warfarin, and taking into account the increased bleeding risk of an elderly population. This proposed posology has been approved in Canada. Therefore each of the ERG's analyses that directly compare the two doses has not been adequately contextualised. This should be corrected.	availability of two doses is to allow flexibility of dosing. As it stands, the report could mislead the reader because the analyses repeatedly apply and compare both doses to the whole AF cohort without accounting for the sequence. The two doses are intended to be complementary rather than substitutes for one another. Therefore the ERG's analyses, and emphasis of the report, do not properly inform the decision problem.	The ERG has undertaken a full incremental analysis by comparing all available treatments for each sub-group. The manufacturer's proposed licensed indication is not a treatment option in the RE-LY trial but a post-hoc subgroup analysis and has not been recommended by the FDA. However, it was included to determine whether it was a cost-effective option.

Issue 9 The manufacturer failed to include analyses on additional treatment sequences in the ERG clarification response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 104 it states: "In the response to the points for clarification, the manufacturer failed to include these treatment sequences in the economic model." This is an inaccurate criticism.	This statement should be removed.	The ERG implies that we did not comply with the request. In actual fact, this was an impossible demand. The ERG was well aware that the economic model could not perform these analyses. In its clarification letter, the ERG requested that we provide a revised model with the additional functionality of a third line of treatment and the flexibility to choose any sequence. This is no simple task and would be a significant project involving several	The manufacturer has not presented a factual inaccuracy. The request made by the ERG for a model that allowed the evaluation of all relevant treatment sequences was a reasonable one; the fact that the manufacturer was unable to provide such a model within the timeframe permitted does not make this statement

		weeks of dedicated work. However as we are given only 10 working days in which to respond to the entire letter, the ERG must appreciate that this is not a reasonable request.	inaccurate.

Issue 10 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 111, 2nd paragraph. Word/phrase missing after “more”.			Have added in "cost-effective" after more.

Issue 11 Linking discontinuation to GI adverse effects

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states: “…the discontinuation rates for the two dabigatran doses are higher in the early stages of the trial compared to warfarin, possibly due to the higher rate of GI adverse effects with dabigatran.” (page 7) This is not factually accurate.	It should be made clear that this is not evidence-based and is only a hypothesis.	There is no evidence yet to prove this causal link.	Have deleted ", possibly due to the higher rate of GI adverse effects with dabigatran.”

Issue 12 Table 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG misquotes the INR control in the “real-world prescription” scenario (page 77).	Remove fourth column of Table 32.	These numbers refer to the % of cohort on different treatments and not the % with different levels of INR control. This column appears to have been mistakenly included.	Corrected numbers.