ERG's response to Bayer's document

"Response to NICE Appraisal Consultation Document" (April 2012)

Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent venous thromboembolic events.

ScHARR

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1 Introduction

This document outlines the ERG's response to the document entitled "Response to NICE Appraisal Consultation Document" from Bayer. Included are critiques of both the response to clinical questions and the revised model provided by the manufacturer. A summary is provided of illustrative ICERs when key assumptions are changed.

2 Clinical evidence

2.1 Protocol for allocation to treatment duration

The manufacturer was asked to comment "*on the differences between the populations that were assigned treatment durations of 3, 6 and 12 months, and* [provide] *further details of any clinical criteria or algorithm used by the treating physician for assigning patients to the three groups.*"

The manufacturer's answer concurs with the study protocol and manufacturers submission, that patients were allocated to treatment duration groups by clinical opinion, taking into consideration *"individual patient risk-profile and local guidelines".*

2.2 Differences in the risk characteristics of each treatment duration group

The manufacturer presents a reproduction of Table 12 from the MS which shows the proportion of patients with given risk factors in each group, and a narrative which highlights that [redacted]

Table 2 of Bayer's response (Table 12 in the original manufacturer's submission) presents data as the percentages of patients with a risk factor within each group. Below, in Table 1, we have presented these data as numbers of patients and as the percentages of patients with a given risk factor. Data shown this way reveals much the same trends, [redacted]

Table 1 Number of patients with risk factors in each treatment duration group, and as a proportion of total number with the risk factor

	3 months	6 months	12 months	Total with risk
	411	2166	872	
	n (%)	n (%)	n (%)	n
Idiopathic DVT/PE	[redacted]	[redacted]	[redacted]	[redacted]
Recent surgery or trauma	[redacted]	[redacted]	[redacted]	[redacted]
Immobilisation	[redacted]	[redacted]	[redacted]	[redacted]
Use of oestrogen containing drugs	[redacted]	[redacted]	[redacted]	[redacted]
Active cancer	[redacted]	[redacted]	[redacted]	[redacted]
Previous DVT/PE	[redacted]	[redacted]	[redacted]	[redacted]

A chi-squared analysis was performed to ascertain whether it was likely that the intended treatment duration was independent of the identified risk factors. The p-value was less than 0.00001 indicating that the intended treatment duration was very likely to be influenced by risk factor.

Additionally the age of the patients in the 3 and 6 month intended duration groups were analysed to ascertain whether patient age and intended duration of treatment were independent. This analysis produced a p-value less than 0.00001 indicating that the intended duration of treatment was very likely to be influenced by the age of the patient.

Finally, the proportions of patients who were male in the 3 and 6 month intended duration groups were analysed to ascertain whether gender and intended duration of treatment were independent. This analysis produced a p-value less than 0.002 indicating that the intended duration of treatment was very likely to be influenced by the gender of the patient.

These analyses confirm that the groups are heterogeneous in terms of risk factors. However, the question still remains as to whether these heterogeneous groups would have a differential response to rivaroxaban compared with warfarin, which the manufacturer has addressed within section 2.4.

2.3 Data relating to any treatment interaction with duration

The manufacturer has argued that there is "no evidence" of differences in relative efficacy or safety of rivaroxaban between the intended duration of treatment groups.

The manufacturer dismisses the available evidence on the basis that:

- The results are based on a small underpowered subgroup and a small number of events
- The EPAR reports "consistent" results across subgroups
- The clinical experts at the first Appraisal Committee were "not aware" of any reasons why patients in the different treatment duration groups would have a differential response to rivaroxaban.

The ERG, however, does not believe that the lack of evidence is as clear as the manufacturer states and suggests that a randomised controlled trial (RCT) for patients with intended treatment duration of 3 months would be useful to provide further evidence. However, there remain a number of points that the appraisal committee may wish to discuss within the deliberation process, which suggest that the efficacy of rivaroxaban compared with warfarin for patients with an intended treatment duration of 3 months is unproven. These are

4) Current clinical familiarity with rivaroxaban when used for 3 months for the prevention of VTE may be sub-optimal and there may be characteristics that are currently unanticipated.
5) Time in INR target range was lower than the UK recommended target of 60%.[1] The failure to reach recommended UK targets for those treated with warfarin is likely to make the comparative efficacy of rivaroxaban better, although the magnitude of any bias is not known.

3. Economic evaluation

The manufacturer of rivaroxaban (Bayer) has been requested to provide the following analysis in the appraisal consultation document (ACD):
"*Consideration of the cost effectiveness of rivaroxaban compared with low molecular weight heparin (LMWH) and a vitamin K antagonist in patients in whom long-term anticoagulation is intended. Ideally this should be supported by a cost-effectiveness analysis of rivaroxaban as a lifelong treatment after the index event. This analysis should use data from the whole population of the EINSTEIN-DVT trial for estimating clinical effectiveness and should include sensitivity analyses that assume a less intensive INR monitoring program of 6 visits in the first 3 months, followed by 2 or 3 visits every 3 months thereafter in the comparator arm.*"

In response to this request, the manufacturer submitted a revised economic model accommodating the economic evaluation of long-term anticoagulation treatment and amended some of the assumptions used in the original manufacturer submission (MS).

3.1 Description of the revisions made by the manufacturer to the economic model in response to the ACD's request for the additional analysis for patients requiring long-term anticoagulation treatment

The MS economic model was initially designed to examine anticogulation treatment up to 12 months (with patients discontinuing treatment after the intended treatment durations of 3, 6 or 12 months) and the associated long-term consequences. Following the request in the ACD, the manufacturer revised the mathematical model to accommodate the economic evaluation of longer term anticogulation treatment. The following changes have been made to the mathematical model (taken from the manufacturer's response to the ACD):

- *"Treatment termination at the end of 12 months was removed. Patients now remain within the on treatment state for the entire time horizon* (40 years) *unless an event occurs or the patient discontinues for reasons of non-compliance*
- *The discontinuation rate for beyond 12 months of treatment was included so as to allow differentiation of the likelihood of discontinuation in months 0-3, 4-12 and 13 onwards*
- *Patients in the VTE states are re-exposed to the risk of recurrent VTE and bleeding observed in the first 3 months of EINSTEIN-DVT (12 month treatment subgroup). This was intended to reflect risks associated with more intense treatment in the immediate weeks following VTE and the likely higher risk of further VTE recurrence during this period*
- *Patients who have discontinued from long term treatment re-initiate on their original therapy if they experience a recurrent VTE. This is consistent with the modelling approach adopted for an*

economic model in the draft NICE guideline on management of venous thromboembolic diseases (appendix I of full draft guideline, reference 31 of MS)."

In addition to the structural changes and changes to the transition matrices, assumptions were made by the manufacturer to evaluate the cost-effectiveness of long-term anticoagulation treatments. For transparency, each of these assumptions is described in turn.

a) Event rates (VTE recurrence, bleeding) in the first year in patients treated with dual therapy LMWH/VKA requiring long-term anticoagulation treatment

In the updated analysis evaluating the cost-effectiveness of long-term anticoagulation treatment, the manufacturer assumed that the event rates (VTE recurrence, bleeding) in the first year (first 12 months) in patients treated with dual therapy LMWH/VKA was similar to the event rates observed in the 12 months EINSTEIN-DVT subgroup recognising that a greater prevalence of risk factors existed in the longer treatment duration groups in the EINSTEIN-DVT trial.

The manufacturer stated in its response to the ACD that *"It was noted previously that the 3/6/12 month duration patient populations of EINSTEIN-DVT were similar in their risk profiles, though a greater prevalence of risk factors tended to exist in the longer duration groups. Consequently, in evaluating the cost-effectiveness of rivaroxaban in patients who require more than 12 months duration of treatment, we used event rates for the first year of the model from the trial experience of the 12 month duration group, the group of longest duration."*

The event rates used for the first year in patients treated with dual therapy LMWH/VKA (taken from the event rates for the 12 months subgroup population of the EINSTEIN-DVT trial) are presented in Table 2 (these event rates were also presented in the clarification letter in response to the ERG's comments).

Table 2 Incidence of clinical events and ranges for sensitivity analyses for the 12 month treatment duration group, LMWH/VKA therapy (reproduction of Table 4 of the manufacturer response to the ACD)

Period and outcome	Point estimate	Lower	Upper	Alpha	Beta
0-3 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-6 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-12 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Event rates (VTE recurrence, bleeding) in the long-term (after the first year) in patients treated with dual therapy LMWH/VKA requiring long-term anticoagulation treatment

The long-term risk of VTE recurrence and major bleeding (after the first year) was taken from a recent systematic review and meta-analysis conducted by Streiff et al. (2006). The manufacturer assumed that the continuous risk of VTE recurrence (targeting INR 2-3) was 0.7 (95% CI 0.3 – 1.1) per 100 patient-years and the risk of major bleeding was 1.6 (95% CI 0.5 – 2.7) per 100 patient-years. The manufacturer also states that *"this approach produces rates of VTE recurrence similar to those which may be derived from assumptions adopted for an economic model in the draft NICE guideline on management of venous thromboembolic diseases (appendix I of full draft guideline, reference 31 of MS). This model assumes an ongoing rate of 6.0 VTEs per 100 patient-years without anticoagulation and a relative risk of anticoagulation vs no treatment of 0.09. This equates to a rate on treatment of 0.5 events per 100 patient-years, similar to the rate of 0.7 (95% CI 0.3-1.1) events per 100 patient-years identified in the Streiff review.1 We note that the VTE guideline model considers assumptions of*

two or three times ongoing average risk of VTE recurrence or bleeding. This is not an avenue we have explored, but may be a useful tool in exploring cost-effectiveness in differing patient groups."

In addition to event rates for VTE recurrence and major bleeding, the manufacturer stated that in the absence of data for other outcomes in the Streiff review (2006), the long-term rate of clinically relevant non-major bleeding and the fatality rate after a PE was assumed to the same as in the in original MS.

c) long-term discontinuation rate (after the first year) for patients requiring long-term anticoagulation treatment

In the MS, the manufacturer assumed a 3 month discontinuation rate of 1.9% taken from the EINSTEIN-DVT trial for the first 12 months of the economic evaluation.

The manufacturer states that there is a lack of data on the long term adherence/discontinuation rate of patients treated with rivaroxaban for DVT beyond 12 months and that data from the trial may not be appropriate to reflect the long term discontinuation rate as *"trial data may be biased towards reflecting the short-term experience of patients motivated to participate in a trial"* and that assumptions about long term discontinuation rate *"would be better informed by real-life, longer term observational data rather than trial data."*

As no long-term data were found for rivaroxaban, the manufacturer used data from two observational studies in patients treated with statins (Boggon et al.2011; Carey et al.2010) as a proxy for the long-term discontinuation rate of anticoagulation treatments. A short description of these studies is provided by the manufacturer in its response to the ACD (page 12). The manufacturer acknowledges the limitations of using data from a different disease area anddifferent intervention, and the short follow-up period of these studies. However, the manufacturer believes that *"there are sufficient similarities to rivaroxaban in DVT treatment for these studies to provide reasonable analogues."*

The manufacturer calculated that the 3 month discontinuation rate was 3.6% in Boggon et al. (2011) and 6.9% in Carey et al. (2010) in patients treated with statins. The manufacturer used in the basecase a 3 month discontinuation rate of 3.6% based on Boggon et al. (2011) but conducted a sensitivity analysis varying the discontinuation from 1.9% to 6.9%.

The manufacturer also assumed that the long-term discontinuation rate was the same in patients treated with rivaroxaban or dual therapy LMWH/VKA, but stated that "*assuming no differential effect between treatments provides a conservative estimate of incremental QALYs"* as *"the persistence with rivaroxaban may be higher than with warfarin due to its convenience, as reflected in greater treatment satisfaction".*

d) treatment effect (HR/RR) of rivaroxaban compared with dual therapy LMWH/VKA in patients requiring long-term anticoagulation treatment

The manufacturer used the treatment effect from the whole trial EINSTEIN-DVT population as requested in the ACD, i.e.

- a hazard ratio of 0.68 (95% CI 0.44 to 1.04) for recurrent VTE;
- a hazard ratio of 0.65 (95% CI 0.33 to 1.28) for major bleeding; and
- a risk ratio of 1.05 (95% CI 0.83 to 1.34) for clinically relevant non-major bleeding.

e) a decrement in utility associated with anticoagulation treatment

Compared with the original MS, the manufacturer included a decrement in utility associated with treatment with warfarin in its revised analysis and justified this change with the following statement: "*the value of any treatment intended for lifelong usage also depends critically on any differential in health-related quality of life (HRQoL) whilst being treated".*

The decrement in utility was taken from Marchetti et al. (2001) using time trade off, conducted in a relatively small sample of patients (n = 48) attending an anticoagulation clinic. Patients were asked to read the description of two hypothetical patients who were receiving warfarin and LMWH respectively and were asked to trade a reduction in life to remove the requirement of needing to take warfarin or LMWH for 1 year. The study reported a mean utility of 0.988 (range 0.92 – 1.00) for warfarin, equating to a disutility of 0.012. As suggested by the range (0.92 – 1.00), the ERG notes that most patients would not trade life to avoid taking warfarin. Indeed, Marchetti et al. (2001) reported that only 10 patients would have accepted trade some days of life to avoid warfarin (average of 4 days).

The manufacturer did not include a disutility in patients treated with rivaroxaban and made the argument that no decrement in utility would apply to rivaroxaban given the high level of treatment satisfaction in comparison with dual LMWH/VKA. The following statement has been made by the manufacturer: *"there is also the question of whether a disutility should apply whilst treated with rivaroxaban. In the case of the STA of dabigatran in atrial fibrilation, it appears from published documentation that a disutility may have been applied to account in some way for dyspepsia and observations from a quality of life substudy of the RE-LY trial (but as yet not fully published to our knowledge). No such disutility for rivaroxaban would be appropriate, for three reasons. Firstly, the economic model accounts for incidence of relevant clinical events, VTE and bleeding as separate model states. Secondly, no other clinically important adverse events are significantly raised with rivaroxaban in comparison with warfarin, such as dyspepsia with dabigatran (see section 4.8 of the*

SmPC and New England Journal of Medicine publication of EINSTEIN-DVT and EINSTEIN-Ext). Finally, treatment with rivaroxaban has been associated with raised levels of treatment satisfaction in comparison with dual LMWH/VKA therapy (reference 18 of MS). Therefore we have assumed no disutility to be associated with rivaroxaban treatment of DVT."

f) intensity of INR monitoring, using the MS assumptions or less intensive INR monitoring as recommended in the ACD

Finally, the manufacturer presented results of the cost-effectiveness analyses according to two sets of assumptions on INR monitoring as requested in the ACD:

- a scenario using the MS base case assumptions on INR monitoring, i.e. nine INR monitoring visits in the first 3 months and five visits each quarter thereafter,
- a scenario assuming a less intensive INR monitoring assuming six visits in the first 3 months, and three visits each quarter thereafter as used in the ERG report.

3.2 Summary of results presented by the manufacturer in its response to the ACD

The manufacturer presented results of the cost-effectiveness analyses according to two sets of assumptions on INR monitoring as requested in the ACD:

3.2.1 Cost effectiveness results of long-term anticoagulation treatment using the MS base case assumptions on INR monitoring, i.e. nine INR monitoring visits in the first 3 months and five visits each quarter thereafter,

The manufacturer estimated that under the MS assumptions on INR monitoring, rivaroxaban had an incremental cost over dual LMWH/VKA of £953 and was associated with an incremental gain of 0.158 QALYs, resulting in an incremental cost-effectiveness ratio (ICER) of £6,037 per QALY gained in the deterministic analysis (Table 3).

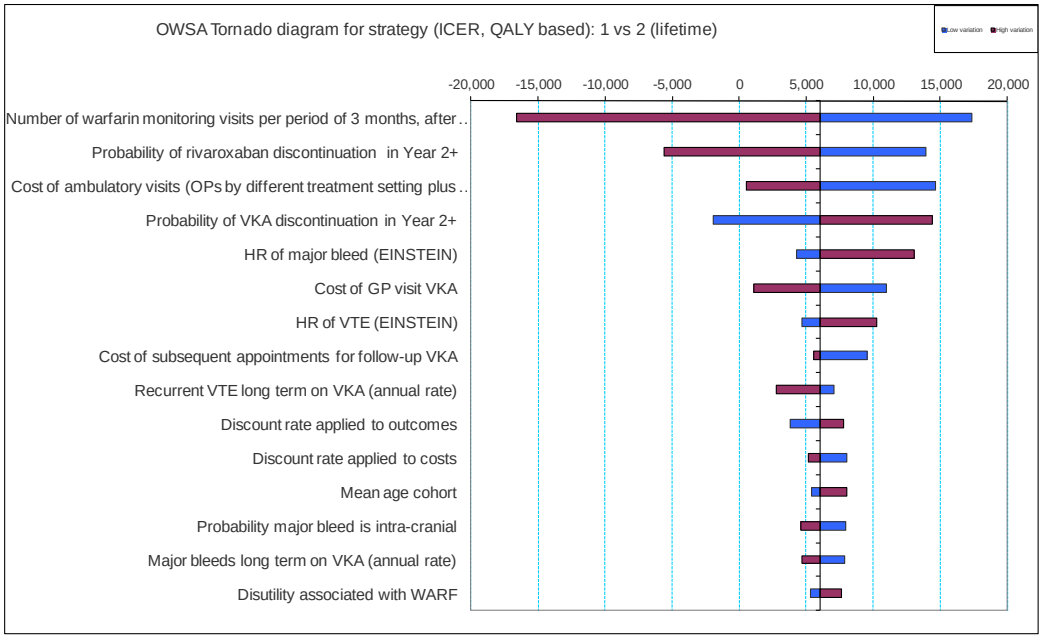
Table 3 Cost-effectiveness results for lifelong treatment, original evidence-based INR monitoring intensity assumptions (reproduction of Table 5 of the manufacturer response to the ACD)

		Rivaroxaban	LMWH/VKA	Increment
Costs (£)				
	Drug cost	5,320	266	5,054
	Monitoring	0	3,783	-3,783
	Event costs	434	543	-109
	Bleeding costs	515	704	-189
	PTS/CTEPH	245	266	-20
	Total	6,514	5,561	953
Outcomes				
	Deaths	0.941	0.942	-0.001
	VTEs	0.826	0.864	-0.038
	Major bleeds	0.091	0.138	-0.047
	QALYs	13.114	12.956	0.158
ICER				6,037

Note: All results quoted relate to a lifetime horizon, with discounting applied.

The manufacturer also conducted a set of one-way sensitivity analyses (OWSA) and indicated that rivaroxaban remained cost-effective at a WTP threshold of £20,000 per QALY gained in all the scenarios analysed (Figure 1).

Figure 1 Tornado plot for cost-effectiveness analysis of lifelong treatment, original evidence-based INR monitoring intensity assumptions (reproduction of Figure 1 of the manufacturer response to the ACD)



The manufacturer also conducted a probabilistic Sensitivity Analysis (PSA) using 5,000 simulations (instead of 1,000 simulations used in the MS). The cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are presented in Figure 2 and Figure 3. The manufacturer indicated that there was an 85% probability that rivaroxaban was cost-effective at a willingness to pay of £20,000 per incremental QALY, and a 28% probability that rivaroxaban was dominant (more effective and less costly).

Figure 2 Cost-effectiveness plane, original intensity assumptions (reproduction of Figure 2 of the manufacturer response to the ACD)

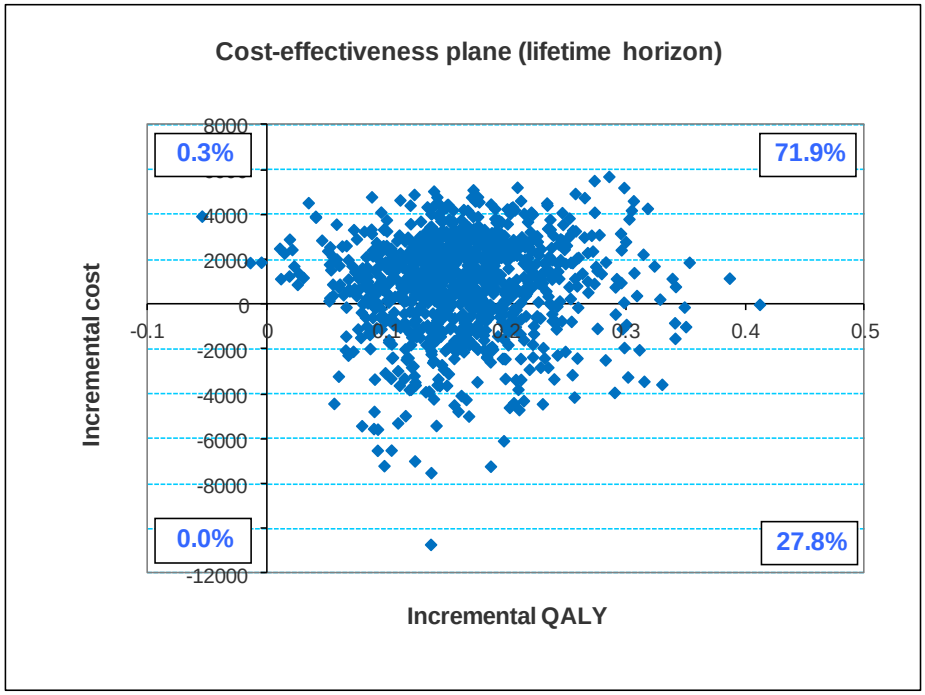
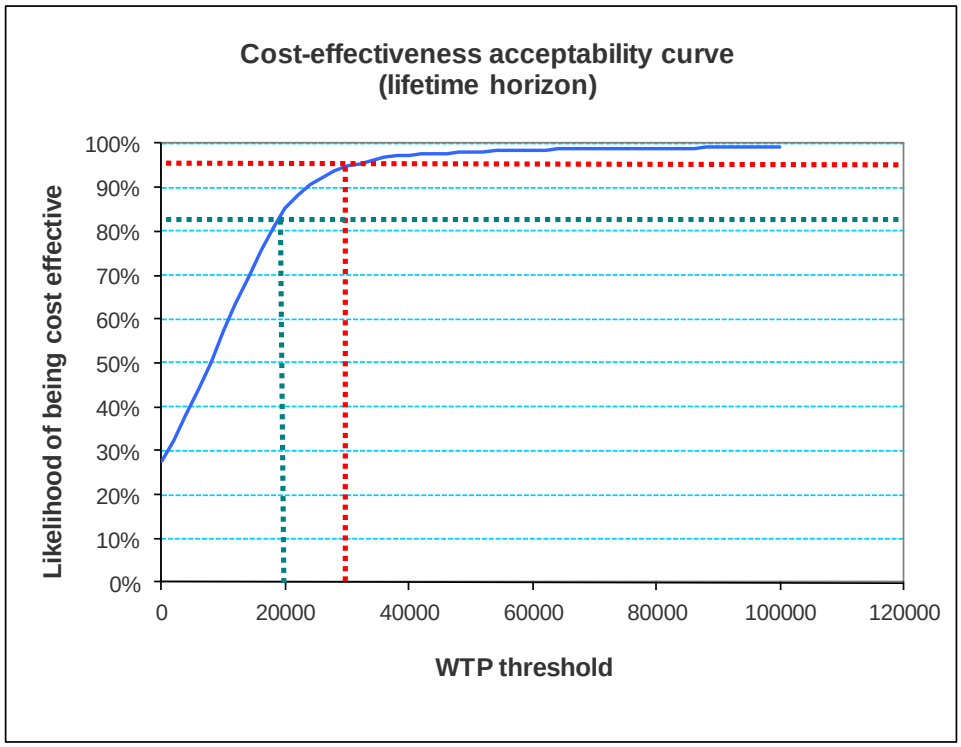


Figure 3 Cost-effectiveness acceptability curve, original intensity assumptions (reproduction of Figure 3 of the manufacturer response to the ACD)



3.2.2 Cost effectiveness results of long-term anticoagulation treatment using a less intensive INR monitoring assuming six visits in the first 3 months, and three visits each quarter thereafter.

The manufacturer estimated that assuming less intensive INR monitoring, rivaroxaban had an incremental cost over dual LMWH/VKA of £2,502 and was associated with an incremental gain of 0.158 QALYs, resulting in ICER of £15,847 per QALY gained in the deterministic analysis (Table 4).

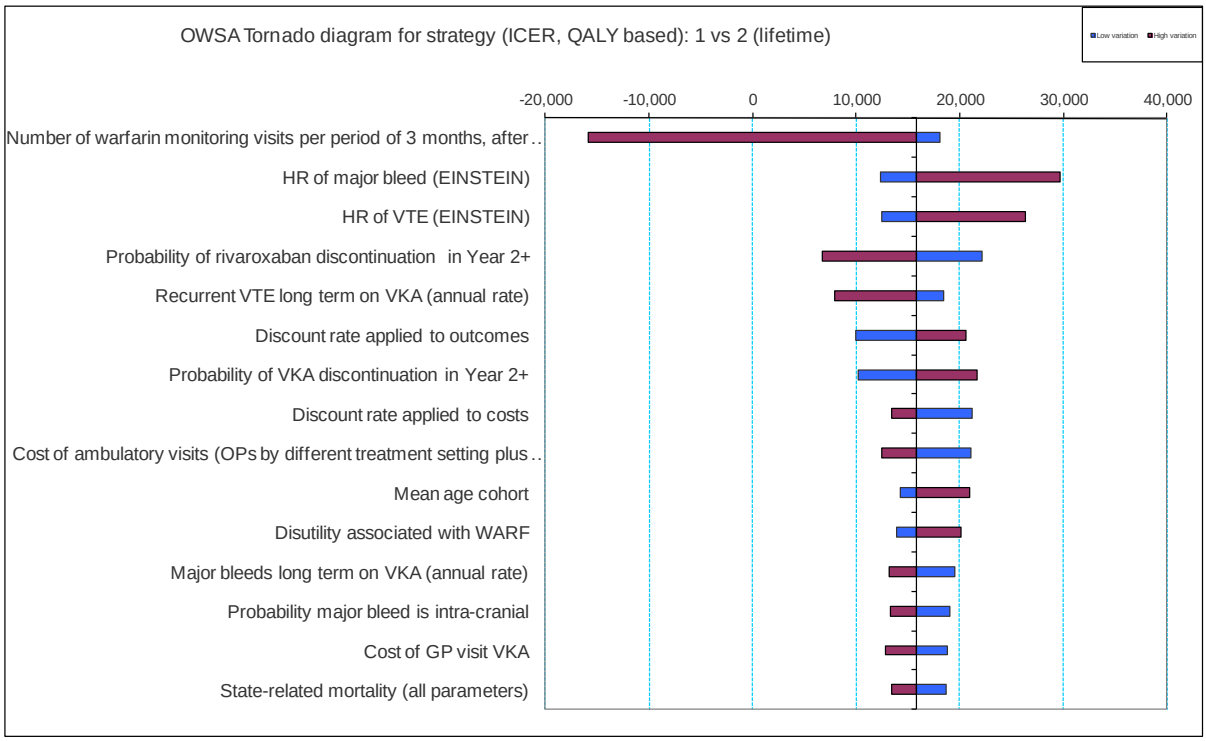
Table 4 Cost-effectiveness results for lifelong treatment, reduced intensity assumptions (reproduction of Table 6 of the manufacturer response to the ACD)

		Rivaroxaban	LMWH/VKA	Increment
Costs (£)				
	Drug cost	5,320	266	5,054
	Monitoring	0	2,295	-2,295
	Event costs	434	499	-65
	Bleeding costs	515	687	-172
	PTS/CTEPH	245	266	-20
	Total	6,514	4,012	2,502
Outcomes				
	Deaths	0.941	0.942	-0.001
	VTEs	0.826	0.864	-0.038
	Major bleeds	0.091	0.138	-0.047
	QALYs	13.114	12.956	0.158
ICER				15,847

Note: All results quoted relate to a lifetime horizon, with discounting applied.

OWSA showed that rivaroxaban remained cost-effective at a WTP threshold of £30,000 per QALY gained in all the scenarios analysed (Figure 4). The ICER was above £20,000 per QALY gained when the treatment effect and long-term discontinuation for patients treated with rivaroxaban was varied.

Figure 4 Tornado plot for cost-effectiveness analysis of lifelong treatment, reduced intensity assumptions (reproduction of Figure 4 of the manufacturer response to the ACD)



The manufacturer also conducted a PSA using 5,000 simulations (instead of 1,000 simulations used in the MS). The cost-effectiveness plane and CEAC are presented in Figure 5 and Figure 6. The manufacturer indicated that there was a 58% probability that rivaroxaban was cost-effective at a willingness to pay of £20,000 per incremental QALY, and a 25% probability that rivaroxaban was dominant (more effective and less costly).

Figure 5 Cost-effectiveness plane, reduced intensity assumptions (reproduction of Figure 5 of the manufacturer response to the ACD)

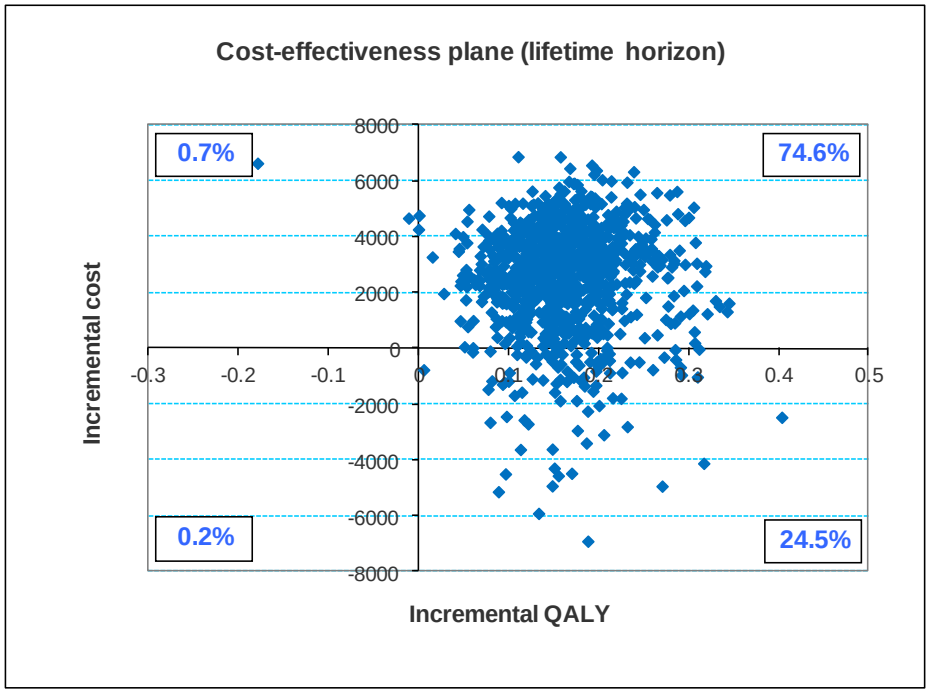
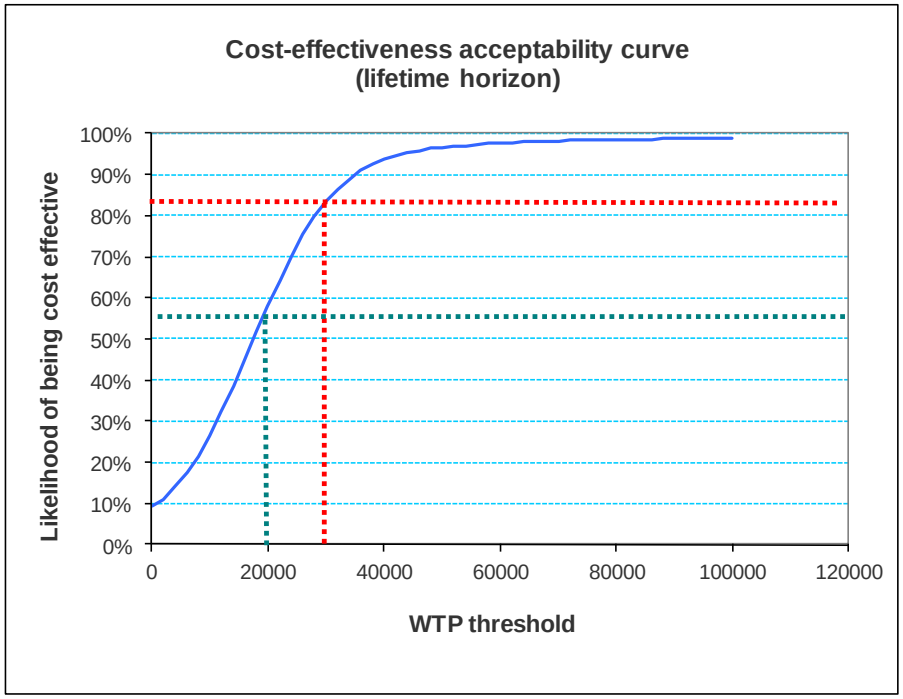


Figure 6 Cost-effectiveness acceptability curve, reduced intensity assumptions (reproduction of Figure 6 of the manufacturer response to the ACD)



3.2.3 Cost effectiveness results across the whole indication

Furthermore, the manufacturer presented an analysis across the whole indication, calculated using the average incremental costs and average incremental QALYs, weighted according to the proportion of patients in each of the treatment duration groups.

The manufacturer stated that *"It has been noted previously that there is little evidence describing the proportion of patients who would be indicated for lifelong treatment, or their characteristics. A brief literature review identified evidence from the PROLONG trial[4-6], patient-level meta-analyses[7;8], and observational studies and risk models[9;10] which have highlighted gender and age as among the relevant factors in the assessment of the risk-benefit of continued treatment for an individual. This in turn would be expected to lead to a greater prevalence of older patients and male patients in the group requiring lifelong treatment than in groups requiring shorter term treatment"*.

For the calculation of the ICER for the whole indication, the manufacturer assumed that 20% of patients required long term anticoagulation treatment as suggested in the ACD. The manufacturer assumed the same split according to the EINSTEIN-DVT population for the remaining 80% of patients requiring less than one year treatment.

The manufacturer indicated that under the MS assumptions on INR monitoring, rivaroxaban had an incremental cost over dual LMWH/VKA of £106 and was associated with an incremental gain of 0.0517 QALYs, resulting in an ICER of £2,057 per QALY gained (Table 5).

Table 5 Cost-effectiveness results across all treatment durations considered, INR monitoring costed as per MS (reproduction of Table 7 of the manufacturer response to the ACD)

Treatment duration	Proportion of patients	Economic model results			
		ΔCost	ΔQALY	ICER	Prob CE
3 months	10%	-162	0.0245	Dominant	99%
6 months	50%	-124	0.0239	Dominant	99%
12 months	20%	-32	0.0287	Dominant	99%
Lifelong	20%	953	0.1579	6,037	85%
Overall	100%	106	0.0517	2,057	

Prob CE: probability of rivaroxaban being cost-effective at a willingness to pay threshold of £20,000 per QALY

Assuming a less intensive INR monitoring, the manufacturer indicated that rivaroxaban had an incremental cost over dual LMWH/VKA of £531 and was associated with an incremental gain of 0.0517 QALYs, resulting in an ICER of £10,269 per QALY gained (Table 6).

Table 6 Cost-effectiveness results across all treatment durations considered, INR monitoring costed with ERG unit costs and 6/3 frequency (reproduction of Table 8 of the manufacturer response to the ACD)

Treatment duration	Proportion of patients	Economic model results			
		ΔCost	ΔQALY	ICER	Prob CE
3 months	10%	-86	0.0245	Dominant	99%
6 months	50%	2	0.0239	85	98%
12 months	20%	189	0.0287	6,583	92%
Lifelong	20%	2502	0.1579	15,847	58%
Overall	100%	531	0.0517	10,269	

Prob CE: probability of rivaroxaban being cost-effective at a willingness to pay threshold of £20,000 per QALY

3.3 ERG comments on the manufacturer response to the ACD

The ERG acknowledges the efforts made by the manufacturer to provide an analysis for patients requiring long-term anticoagulation treatment. However, there remain uncertainties in some of the assumptions used to assess the long term cost-effectiveness of patients requiring long term anticoagulation treatment.

3.3.1 ERG comments on the method and assumptions used by the manufacturer to assess the cost-effectiveness of long term anticoagulation treatment

Due to time constraints [the model arriving 4 working days before the report was required], the ERG was not able to conduct a full check and validation of the economic model and has assumed that no further changes were made than those identified by the manufacturer in its response to the ACD. Overall, the ERG is satisfied with the changes made to the economic model and no computational errors have been identified. Whilst some new functionality were added for the PSA compared with the MS, some inconsistencies remain. For instance, the values used in the PSA for the Beta distribution (alpha, beta) use the raw values where few events were observed, whereas the ERG would recommend an uninformative prior to be used (for example adding 0.5 to both the alpha and beta value). However, this has a very minimal impact.

The ERG is generally satisfied with the assumptions made by the manufacturer when evaluating the cost-effectiveness of long-term anticoagulation treatment, however the ERG highlights that there may be considerable uncertainty in the assumption that the chosen treatment effect would last/continue over lifetime. Ideally, a scenario should be conducted assuming a possible reduction in the treatment effect with time. The ERG is satisfied with the assumptions made by the manufacturer on the long-term event rates for patients treated with dual therapy LWMH/VKA and the treatment effect for patients treated with rivaroxaban compared with dual therapy LMWH/VKA (using the HR for the whole trial population as suggested in the ACD). For completeness, a scenario was evaluated by the ERG extrapolating the treatment effect for the 12 month population subgroup over lifetime for patients requiring long-term anticoagulation to provide the committee an indication of the ICER under such assumption, if they were minded to assume a subgroup effect.

In the basecase, the manufacturer calculated the discontinuation rate from a study conducted in patients treated with statins. The ERG acknowledges the lack of long-term evidence for the long term adherence of patients treated with rivaroxaban for VTEs. However, the ERG is unclear whether long-term data for patients treated with warfarin were sought by the manufacturer. Furthermore, data used

by the manufacturer only provided information on the discontinuation at 12 months. The manufacturer assumed in the basecase a 3 month discontinuation rate of 3.6% and assumed the discontinuation rate to be the same in patients treated with rivaroxaban and dual therapy LMWH/VKA. However, the ERG explored the impact of this assumption on the ICER and found that a change in the discontinuation rate had a limited impact on the ICER assuming the same discontinuation rate between the two treatments.

In its response to the ACD, the manufacturer stated that *"although persistence with rivaroxaban may be higher than with warfarin due to its convenience, as reflected in greater treatment satisfaction, we assumed no differential effect between treatment arms in the model so as to provide a conservative estimate of incremental QALYs."* The validity of this assumption has been explored by the ERG in a scenario assuming a lower long-term discontinuation rate for patients treated with rivaroxaban (1.9%) compared with patients treated with dual therapy LMWH/VKA (3.6%) as suggested by the manufacturer. Only a reduction in the discontinuation rate for rivaroxaban compared with warfarin was explored, as the manufacturer hypothesised that rivaroxaban was more convenient and if warfarin was associated with a greater disutility than rivaroxaban this could also be manifested in a greater discontinuation rate for warfarin. Of note, in the trial evidence, compliance was marginally lower in the rivaroxaban arm than in the VKA arm; whilst patient satisfaction may have been higher, this has not resulted in higher compliance

Furthermore, in the updated analysis evaluating the cost-effectiveness of long-term anticoagulation treatment, the manufacturer included a decrement in utility associated with treatment with warfarin (this was not included in the original MS), but not with rivaroxaban. It is uncertain whether a similar or reduced decrement in utility should be applied to rivaroxaban.

The decrement in utility for patients treated with warfarin was taken from Marchetti et al. (2001) using time trade off in a small sample of patients (n = 48). Patients were asked to read the description of an hypothetical patient receiving warfarin. Of note, it is unclear from the paper if the description given to the patients described the probability of developing adverse events or only related to the monitoring associated with the drug.

Furthermore, as suggested by the range of utility values (0.92 – 1.00), the ERG notes that most patients would not trade life to avoid taking warfarin. Indeed, Marchetti et al. (2001) reported that only 10 patients would have accepted trade some days of life to avoid warfarin (average of 4 days).
To explore the potential impact of this assumption on the ICER, the ERG conducted three scenarios:

- a scenario assuming a decrement in utility of 0.012 for warfarin only (no decrement for patients treated with rivaroxaban),

- a scenario assuming a decrement in utility of 0.012 for warfarin and a decrement in utility of 0.006 for rivaroxaban (half of the disutility for warfarin)
- a scenario assuming no decrement in utility for either rivaroxaban or dual therapy LMWH/VKA (the manufacturer's basecase).

Finally, as requested in the ACD the manufacturer explored two set of assumptions on INR monitoring using the MS base case assumptions on INR monitoring and a scenario assuming a less intensive INR monitoring using the assumptions detailed in a sensitivity analysis conducted in the ERG report. However for the scenario using assumptions used in the ERG report, only part of the assumptions were used. The manufacturer correctly assumed 6 INR monitoring visits for the first 3 months and 3 INR visits thereafter, but did not change the assumptions on the proportion of patients treated by GPs and nurses for primary care visits, and regarding the type of consultants who conduct follow-up visits in secondary care. Further details are available in the ERG report in page 144.

In the economic model submitted in response to the ACD, the manufacturer used an annual cost of £656 (for the first year) using the MS assumptions on INR monitoring (i.e. 9 INR monitoring visits the first 3 months and 5 INR visits thereafter). For the scenario, replicating the assumptions used in the ERG report (i.e. 6 INR monitoring visits the first 3 months and 3 INR visits thereafter) the manufacturer estimated the INR monitoring cost for the first year to be £413. However, the manufacturer did not change the assumptions on the proportion of patients treated by GPs and nurses for primary care visits, and the type of consultants who conduct follow-up visits in secondary care as suggested in the ERG report. For the scenario using the assumptions used in the ERG report, the INR monitoring cost for the first year should be £320 instead of £413 used by the manufacturer. This error has been corrected by the ERG in the calculation of the ICERs presented hereafter.

3.3.2 Additional work undertaken by the ERG

Additional work was undertaken by the ERG to provide the appraisal committee an indication of the ICER using combinations of plausible assumptions. The ERG also corrected the error in the estimation of INR monitoring for the scenario assuming a less intensive INR monitoring to reflect the assumptions used in the ERG report. Overall, 24 ICERs are presented, which explored combinations of the following assumptions;

- assumptions on treatment effect
    - using the treatment effect from the whole trial population over lifetime,
    - extrapolating the treatment effect from the 12 months subgroup over lifetime
- assumptions on INR monitoring
    - using the MS assumptions (£656 for the first year; £540 annually thereafter)
    - using assumptions used in the ERG report (£320 in the first year; £248 annually thereafter)
- the long-term discontinuation rate
    - assuming the same discontinuation rate (3.6% over 3 months) independent of whether patients were treated with dual therapy LMWH/VKA or rivaroxaban,
    - assuming a lower discontinuation rate for patients treated with rivaroxaban (1.9%) compared with patients treated with dual therapy LMWH/VKA (3.6%) as detailed by the manufacturer in its response to the ACD.
- decrement in utility for patients treated with rivaroxaban and warfarin
    - assuming a decrement in utility for patients treated with warfarin (0.012) only,
    - assuming a decrement in utility for patients treated with warfarin (0.012) and a decrement in utility for patients treated with rivaroxaban (0.006),
    - assuming no decrement in utility.

Due to time constraints, results are presented for the deterministic analyses only as the model was found to be relatively linear when comparing the basecase deterministic results and results from the PSA for the analysis in patients requiring long term anticoagulation treatment.. The ICERs calculated by the ERG for the different set of assumptions are presented in Figure 7.

It is commented that these ICERs will be subject due to uncertainty due to uncertainties in the assumptions, for example it may not be the case that the treatment effect observed at 12 months (whether for the entire population or the 12 month subgroup) would continue for the remainder of the patient's lifetime.

3.3.2.1 Using the treatment effect calculated from the whole trial population

Using the treatment effect calculated from the whole trial population and using the MS assumptions on INR monitoring, the ICER was above £20,000 per QALY gained only for the scenario assuming no decrement in utility and a lower discontinuation rate for patients treated with rivaroxaban (£21,600 per QALY gained). The ICER remained below £30,000 per QALY in all the scenarios examined (ranging from £6,037 to £21,600) using the MS assumptions on INR monitoring.

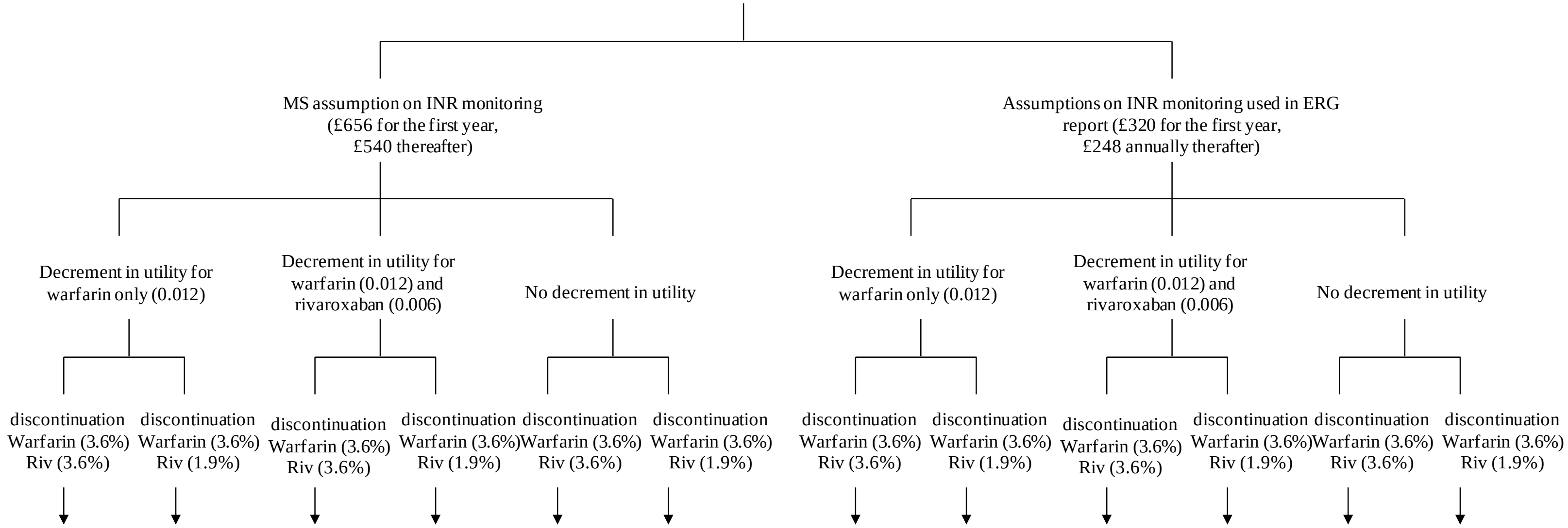
Using the treatment effect calculated from the whole trial population and using the ERG assumptions on INR monitoring, the ICER was above £20,000 per QALY gained in 5 out of 6 scenarios (ranging from £19,381 to £38,837 per QALY gained), and was above £30,000 per QALY gained in 3 out of the 6 scenarios examined (Figure 7).

3.3.2.2 Extrapolating the treatment effect from the 12 month subgroup over lifetime to patients requiring long-term anticoagulation treatment

Extrapolating the treatment effect from the 12 month subgroup over lifetime to patients requiring long-term anticoagulation treatment and using the MS assumptions on INR monitoring, the ICER was below £20,000 per QALY gained in all of the scenarios considered and ranged from £5,357 to £17,419 per QALY gained (Figure 7).

Using the ERG assumptions on INR monitoring, the ICER was above £20,000 per QALY gained in 4 out of 6 scenarios examined (ranging from £16,105 to £30,596 per QALY gained), and above £30,000 per QALY gained in only one scenario when no decrement in utility and a differential discontinuation rate was assumed (£30,596 per QALY gained).

Figure 7 Deterministic ICERs calculated by the ERG using different set of assumptions for patients requiring long term anticoagulation treatment



Analysis assuming the HR for the whole trial population	£6,037	£13,946	£7,697	£18,246	£10,496	£21,600	£19,381	£25,076	£24,710	£32,806	£33,697	£38,837
Analysis assuming the HR for 12 month subgroup population	£5,357	£12,271	£6,495	£15,309	£8,143	£17,419	£16,105	£21,554	£19,529	£26,889	£24,483	£30,596

3.4 Comments on the analysis for the cost effectiveness results across the whole indication

The manufacturer also presented an analysis across the whole indication, calculated using the average incremental cost relative to the average incremental QALY, weighted according to the proportion of patients in each of the treatment duration groups.

The ERG believes that the individual ICERs for each of the intended treatment duration are more pertinent than a composite ICER which could potentially result in cost-ineffective prescribing being recommended. A precedent for this is the NICE evaluations of osteoporosis medications where different age subgroups were analysed separately rather than being combined into an all osteoporotic population.

Furthermore, discussion with clinical experts previously indicated that the 12 month group does not exist in clinical practice, and that patients randomised to this group in the EINSTEIN-DVT trial would be considered to be patients that required long-term anticoagulation treatment. This view is supported by current clinical guidelines, as outlined in Table 3 of the MS, which do not indicate that 12 months treatment is a usual prescription period, but rather than patients would be considered for ongoing treatment.

3.5 Summary of ICERs previously presented in the ERG report for patients treated for 3, 6 and 12 months assuming the treatment effect to be different by intended treatment duration.

Finally for completeness, a summary of the different ICERs reported in the ERG report for the 3, 6 and 12 months population using different assumptions about INR monitoring and assuming that the treatment effect is different by intended duration subgroup are presented. The results presented in Table 7 use a lifetime horizon and are estimated probabilistically using 1,000 parameter configurations.

Table 7 ICERs presented in the ERG report for the 3, 6 and 12 month subgroups using treatment effect specific to the subgroup

	3 month population subgroup	**6 months population subgroup**	**12 months population subgroup**
MS assumptions on INR monitoring (£656 for the first year, £540 thereafter)	11,792 per QALY yielded	Dominant	Dominant
Assumption on INR monitoring used in the ERG report (£320 for the first year, £248 annually thereafter)	6,358 per QALY yielded	8,341 per QALY gained	8,089 per QALY gained

4 References

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