Response to NICE
Appraisal Consultation Document

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

Bayer plc

April 2012

1. Executive summary

Bayer plc welcomes the opportunity to respond to the NICE Appraisal Consultation Document (ACD) for rivaroxaban in the treatment of deep vein thrombosis (DVT), and to provide further evidence.

We recognise that the Committee concluded that rivaroxaban was `more effective than enoxaparin followed by a vitamin K antagonist for preventing recurrent venous thromboembolism', and that the ICERs calculated for the appraisal under `reasonable and relevant' assumptions `for 6 and 12 months were within the range that is normally considered a cost-effective use of NHS resources'. We note further that `the Committee heard from the clinical specialists that they were not aware of any clinical reasons why rivaroxaban would be less effective in patients who received 3 months of treatment'. However, we appreciate that further information is required of Bayer.

In response to the request for further consideration as to differences in populations within the EINSTEIN-DVT trial according to treatment duration assigned, we provide additional data and new commentary describing differences in the characteristics of patients in each subgroup. This is given in section 2. We believe biological, clinical and statistical plausibility for differential relative effectiveness is absent. The relative efficacy and safety of rivaroxaban is therefore better characterised by the whole trial measures of treatment effect described in the New England Journal of Medicine publication.

We answer the request for the data on the cost-effectiveness of rivaroxaban in patients in whom long-term anticoagulation is intended in section 3. The economic model has required some adaptation to produce this analysis, and our methods and assumptions are explained and justified by supporting evidence appropriate for this subgroup. The INR monitoring intensity assumptions in the MS were evidence-based, and we consider it unfair if the judgement of one clinical expert should unreasonably override evidence from guidelines, a published study and the view of another clinical expert advising the ERG.

We conclude that rivaroxaban is cost-effective as a lifelong treatment, a group with a greater prevalence of older patients and male patients than others. Furthermore we conclude that rivaroxaban is cost-effective across the whole indication, based on a weighted averaging across the durations of treatment considered. An overview is provided in Table 1 with further detail in Tables 7 and 8 in section 3.5.2.

Table 1: Overview of ICERs (with probability % of cost-effectiveness at a willingness to pay of £20,000 per QALY)

	Evidence-based INR monitoring intensity (from MS)		Reduced INR monitoring intensity (as requested in ACD)	
Patients requiring 3 months treatment	RIV dominant	(99%)	RIV dominant	(99%)
Patients requiring 6 months treatment	RIV dominant	(99%)	£85	(98%)
Patients requiring 12 months treatment	RIV dominant	(99%)	£6,583	(92%)
Patients requiring lifelong treatment	£6,037	(85%)	£15,847	(58%)
Whole indication (weighted average)	**£2,057**	**-**	**£10,269**	**-**

Finally, we comment on the text of the ACD is also given, where certain issues were noted. We believe rivaroxaban should be recommended by NICE as a safe, effective and highly cost-effective option in the treatment of DVT with built-in simplicity.

2. Differences within trial populations by assigned duration

The Appraisal Committee requested in the ACD that Bayer provide the following:

`*Comments on the differences between the populations that were assigned treatment durations of 3, 6 and 12 months, and further details of any clinical criteria or algorithm used by the treating physician for assigning patients to the three groups.'*

2.1. Summary of response

- There were no clinical criteria or algorithms mandated for use in the EINSTEIN-DVT trial. Treatment periods were at trial investigator's discretion, on consideration of individual patient risk-profile and local guidelines.
- Resulting populations, described below, were similar in their risk profiles. A greater prevalence of risk factors tended to exist in the longer duration groups. This is consistent with application of UK guidelines.
- There was no evidence of differences in the relative efficacy or safety of rivaroxaban between duration groups. The hazard ratio for VTE recurrence in the 3 month group should be considered in light of: the small number of patients in that duration group, the shorter follow-up for that group, the few events occurring in that group (5 vs 3), the [redacted] This is consistent with the view stated in EPAR, and views stated by clinical specialists advising this appraisal.

2.2. Trial protocol and procedures

The protocol for EINSTEIN-DVT provided that assignment to an intended treatment duration of 3, 6 or 12 months was at the discretion of trial investigators, as referred to in paragraph 4.6 of the ACD. No particular clinical algorithm was required to be used. The trial protocol (reference 54 of the MS) states:

`The decision to treat for 3, 6 or 12 months will be based on the risk profile of the patient, and local preferences, and will be made by the investigator at the time of randomization.'

2.3. Differences in the patient characteristics of each strata

We previously provided a descriptive analysis of the underlying risk characteristics of patients within each assigned treatment duration. This suggested similarities between patients in each group, with a greater prevalence of risk factors tending to exist in the longer duration groups. Please see Table 12 in section 5.3.4 of the MS, reproduced as Table 1 below.

Patients with `recent surgery or trauma', a transient risk factor for DVT, were mainly treated for 3 or 6 rather than 12 months. Relatively few patients presenting with `idiopathic DVT' were treated for only 3 months, the majority receiving treatment for 6 or 12 months. This is consistent with application of British Committee for Standards in Haematology (BCSH), Scottish Intercollegiate Guidelines Network (SIGN) and a draft NICE guideline which are relevant in the UK (references 9, 11, 12, and 31 of MS).

Table 2: Characteristics of patients in EINSTEIN-DVT, by intended duration group

Patients and characteristics	**Intended treatment duration**			
	3 months	**6 months**	**12 months**	**Whole study**
Number of patients	411	2166	872	3449
Mean (SD) age	51.4 (16.8)	56.9 (16.4)	56.3 (15.8)	56.1 (16.4)
Proportion male	49.1%	56.8%	60.4%	57.5%
Risk factors				
Idiopathic DVT/PE	25.1%	53.9%	45.6%	48.4%
Recent surgery or trauma	50.1%	17.7%	9.6%	19.5%
Immobilisation	30.4%	15.2%	8.0%	15.2%
Use of oestrogen containing drugs	11.2%	8.3%	3.4%	7.4%
Active cancer	3.6%	6.7%	5.3%	6.0%
Previous episodes of DVT/PE	4.9%	12.8%	42.3%	19.3%

2.4. Data relating to any treatment interaction with duration

There was no evidence of differences in the relative efficacy or safety of rivaroxaban between groups of patients treated for 3, 6 or 12 months.

In terms of VTE recurrence, it has been observed that there was a negative direction of effect in the 3 month group compared with a positive effect in the 6 and 12 month groups. However, the treatment effect for 3 months duration was observed in a relatively small subgroup (12% of ITT population). Table 3 provides the results of interaction analyses for four major outcomes.

Table 3: Summary of treatment effects (hazard ratio, 95% CI) observed for major outcomes in EINSTEIN-DVT, by intended treatment duration group

	Intended treatment duration			Wald interaction test
	3 months	6 months	12 months	
Proportion of ITT population	11.9%	62.8%	25.3%	
VTE recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Major or clinically-relevant non-major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Net clinical benefit*	[redacted]	[redacted]	[redacted]	[redacted]

* defined as composite of VTE recurrence and major bleeding

The period of follow-up was related to the treatment duration that had been assigned. Patients in the 3 month treatment duration group were followed-up for less than half of the average treatment follow-up (mean of 2.9 in 3 month group vs 6.7 in other groups vs 6.3 months across trial).

The treatment effect for recurrent VTE was calculated based on 8 (9%) of the 87 patients experiencing such events which occurred in EINSTEIN-DVT. The hazard ratio of 1.555 [redacted] arises from an analysis of the frequency of outcomes (5 with rivaroxaban vs 3 with dual LMWH/VKA therapy) and their timing.

The Gail-Simon test of qualitative interaction assesses whether differences in directions of effect are statistically significant and [redacted] The Wald test assesses whether the degree/size of effect varies between groups, and [redacted]. However, a change in direction of effect would be more clinically important than a change in degree of effect, and a change in direction of effect is particularly implausible. Interaction tests for other outcomes suggested no difference in degree/size of effect between groups.

The EPAR states: `The relative efficacy for rivaroxaban as compared to enoxaparin/VKA was consistent in different subgroups and in subgroups at different baseline risk. The relative difference between the treatment groups also appears consistent in different geographical regions. However the overall VTE rates differ in different geographical regions, which may be due to differences between the populations recruited.'

The ACD notes in paragraph 4.7 that clinical specialists have advised the Committee that they `were not aware of any clinical reasons why rivaroxaban would be less effective in patients who received 3 months treatment'.

2.5. Conclusion

We trust that the information above sufficiently describes trial procedures and clinical differences between the three duration groups. We conclude that the whole trial measures of treatment effect provide the most robust basis for decision-making, and that the direction of the VTE recurrence point estimate in the 3 month duration group is an anomaly, given:

- The small numbers of patients in the 3 month duration group
- The short follow-up period over which the treatment effect is measured in the 3 month duration group
- The sparseness of recurrent VTE events (5 patients with rivaroxaban vs 3 patients with dual LMWH/VKA)
- The lack of any statistically significant interaction in other important outcomes (Table 2, Wald tests)
- The lack of statistically significant qualitative interaction between duration and treatment effect in recurrence of VTE (Gail-Simon test)
- The view of NICE's expert clinical advisors stated in the ACD (paragraph 4.7)
- The view expressed in the EPAR

3. Cost-effectiveness of lifelong anticoagulation

The Appraisal Committee requested in the ACD that Bayer provide the following:

`*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.'*

3.1. Summary of response

- Various adaptations have been made to the economic model in order to accommodate the request to conduct the evaluation. See below `methods in developing lifelong model'.

- The INR monitoring intensity assumptions in the MS were evidence-based, and we consider it unfair if the judgement of one clinical expert should unreasonably override evidence from guidelines, a published study and the view of another clinical expert advising the ERG.

- We conclude that rivaroxaban is cost-effective as a lifelong treatment.

    - Under the evidence-based monitoring intensity of the MS, the ICER for lifelong rivaroxaban vs dual LMWH/VKA was £6,037 per QALY gained, with a 85% probability of cost-effectiveness at a threshold of £20,000 per QALY.

    - Under the reduced intensity assumptions requested in the ACD, the corresponding ICER is £15,847, with a 58% probability of cost-effectiveness.

- Furthermore we conclude that rivaroxaban is cost-effective across the whole indication, based on a weighted averaging across the durations of treatment considered

    - Under the evidence-based monitoring intensity of the MS, the weighted average ICER across all patient groups/durations was £2,057.

    - Under the reduced intensity assumptions requested in the ACD, the weighted average ICER across all patient groups/durations was £10,269.

- Additionally, there are further factors that it has not been possible to capture in the economic model which suggest that the cost-effectiveness of rivaroxaban above may be underestimated. See section 3.5.1.

3.2. Intensity of INR monitoring

The Appraisal Committee requests that the cost-effectiveness of lifelong treatment be conducted on assumptions of less intensity.

The base case assumptions in the MS was that there would be 9 INR monitoring visits in the first 3 months of anticoagulation and five visits each quarter thereafter. This assumption was made on the basis of BCSH guidelines, SIGN guidelines, information in the BNF and, importantly, an observational research study of UK anticoagulation services (references 9, 11, 12, 75, 136 to the MS). The observational research study involved the collection of retrospective data from a secondary care anticoagulation service between March and June 2010. Among the 119 patients with VTE evaluated in the initiation phase, the mean (SD) frequency of INR visits per month was 3.3 (1.12); and among the 117 patients evaluated in the maintenance phase, the respective mean (SD) values were 1.9 (0.87). This equates to a mean of 9.9 visits in the first 3 months and 5.7 visits each quarter thereafter. The ERG report states that one of the ERG's two clinical experts agreed that this frequency was `plausible'.

We understand that the suggestion that a reduced intensity of monitoring may be appropriate is based on advice from the second clinical expert, whose advice was that they `believed that six visits in the first 3 months and 2-3 thereafter would be a more accurate estimate'. It would be unfair if the judgement of a single expert should unreasonably override evidence from guidelines, a published study and the view of another clinical expert advising the ERG.

Later in this response we comment on the lack of clarity of `2 or 3 visits' stated in paragraph 4.14, which is then mirrored in the information request made in paragraph 1.2. It is very clear from the ERG report (Table 36 in section 5.2.1.8 for example) that further analyses in relation to frequency of INR monitoring adopted an assumption that there were 3 visits every 3 months after the first 3 months.

We have therefore conducted analyses on two sets of assumptions:

- The original evidence-based assumptions of 9 visits in the first quarter followed by 5 visits per quarter thereafter
- The reduced intensity of 6 visits in the first quarter followed by 3 visits per quarter thereafter

3.3. Methods in developing lifelong model

The model developed to support the MS was designed to examine differential risks of bleeding and recurrent VTE in patients requiring and receiving 3 to 12 months of treatment, and the long-term consequences of this. Following the 3 to 12 months of treatment, all

patients were assumed to discontinue anticoagulation. A recurrent VTE triggered cost and QALY payoffs reflective of further dual LMWH/VKA treatment.

We have reviewed the structure and assumptions contained in the model in order to evaluate lifelong treatment with rivaroxaban vs dual LMWH/VKA in a group of patients requiring such duration of treatment. It has not been appropriate to use data from the EINSTEIN-Ext trial due to the clinical equipoise entry criteria.

We present deterministic results in some detail on three sets of assumptions relating to INR monitoring costs. Univariate and probabilistic sensitivity analysis are presented in addition. The ICERs quoted here are from deterministic analyses.

3.3.1. First year event rates with dual LMWH/VKA

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. These data are shown in Table 4 below, and were previously provided in Table 12 in Bayer's response to clarification questions from NICE/ERG. It may be of debate whether first year event rates could be even higher in patients requiring lifelong (ie more than 12 months) treatment.

Table 4: Incidence of clinical events and ranges for sensitivity analyses for the 12 month treatment duration group, LMWH/VKA therapy

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]

3.3.2. Long-term risk of VTE recurrence and major bleeding

The economic model developed for the MS incorporates assumptions regarding the long-term incidence of outcomes relevant to the model. Particularly important are the assumptions in relation to incidence of bleeding and recurrent VTE.

In the model presented with the MS for the economic evaluation of rivaroxaban in patients who required 3/6/12 months of treatment, the incidence of bleeding and recurrent VTE with dual LMWH/VKA was assumed to follow EINSTEIN-DVT experience whilst on treatment. Long-term VTE recurrence following the cessation of treatment was taken from a cohort study of 1626 VTE patients who had received initial anticoagulation only and were then followed-up for a mean of 50 months (Prandoni et al, 2007, reference 28 from MS). There was assumed to be no clinically relevant bleeding once treatment had stopped at 3/6/12 months.

In adapting the model to evaluate lifelong treatment, it was important to estimate long-term outcomes from a group of patients who also received long-term treatment. A recent systematic review and meta-analysis by Streiff et al that satisfied this purpose was identified in a brief literature search.[1]

The objective of the Streiff review was to evaluate the evidence on the optimal duration of VKA therapy for venous thromboembolism by identifying randomized controlled trials and summarizing event rates.[1] The review found that the ongoing risk of recurrent VTE after 4-12 months of anticoagulation was 7.9 (95% CI 5.2-10) events per 100 patient-year and that this may reduce to 0.7 (95% CI 0.3-1.1) events with ongoing warfarin treatment targeting INR 2-3. In contrast, the risk of major bleeding is 0.3 (95% CI 0-0.5) per 100 patient years without further anticoagulation but 1.6 (95% CI 0.5-2.7) per 100 patient years with continuous warfarin. It should be recognised that these are average rates observed in patients across the sample of trials with extended follow-up identified in this review, and may not represent the risks of any particular individual.

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.

Limited outcomes were measured and reported in the Streiff review.[1] Other assumptions in the original model were retained (see Table 43 of MS). The long-term rate of clinically relevant non-major bleeding on treatment was assumed to be that experienced in the final six months of EINSTEIN-DVT (2.7% over this period). The case fatality for PE beyond one year was taken from long-term observational data reported in Prandoni (33%, 43 of 130 PEs) as with the original model submitted.

3.3.3. Discontinuation

The value of any treatment intended for lifelong usage depends critically on the persistence and adherence of patients to such a regime. As highlighted in the SmPC, experience with rivaroxaban for DVT treatment beyond 12 months is limited and, as discussed later, Bayer has agreed with the EMA a Risk Management Plan which includes conducting a non-interventional study to monitor the risk-benefit of rivaroxaban in patients treated over the longer term (XALIA). To address the Appraisal Committee's request to evaluate the cost-effectiveness of lifelong treatment, an assumption is required in relation to their longer-term persistence with rivaroxaban.

We considered that such an assumption would be better informed by real-life, longer term observational data rather than trial data, as trial data may be biased towards reflecting the short-term experience of patients motivated to participate in a trial. As there was known to be limited data in relation to rivaroxaban, an analogue approach was taken to capture evidence from long-term observational studies of discontinuation and persistence in other preventive cardiovascular medication. From a brief review of potentially relevant literature, two UK database linkage studies were identified of particular relevance to this appraisal.

Boggon et al[2] was a UK database linkage study of the Myocardial Ischaemia National Audit Project (MINIP) registry, General Practice Research Database (GPRD), Hospital Episode Statistics (HES) and death certificates. Its focus was to examine the levels of prescribing of clopidogrel in patients discharged from hospital after acute myocardial infarction (MI). It also compared discontinuation in clopidogrel and statin use over time between ST elevation MI (STEMI) and non-ST elevation MI (nSTEMI) patients. There were 7543 linked patients included in the study. It found that, despite guideline recommendations for continued use for at least 12 months, the proportion of patients still prescribed clopidogrel at 12 months was 53% in nSTEMI patients and 54% in STEMI patients. Statin prescribing was 84% in nSTEMI and 89% in STEMI patients.

Carey et al[3] was an analysis of predictors of initiation and continuation of the use of statins in 9367 patients having a first MI from the UK primary care database DIN-LINK. Among patients who were prescribed a statin within 6 months of the MI, the point prevalence (patient has a valid prescription on the day) was 85% at 3 months, 80% at one year and 76% by year five onwards. Good coverage (indicating that >=80% of the previous 365 days were covered by a statin prescription) was generally about five percentage points lower. At one year, 70% had good coverage.

There are various limitations in using this data to populate the lifelong DVT treatment model due to the different disease areas and treatments considered, and various outcome measures employed. The data are valuable in that they reflect real-life persistence. The follow-up is not as long as would be ideal, but is greater than the mean time on treatment in EINSTEIN-DVT (6.3 months). However we judge that there are sufficient similarities to rivaroxaban in DVT treatment for these studies to provide reasonable analogues.

The statin persistence levels in Boggon et al were approximately equivalent to a 3 month discontinuation probability of 3.6%. The one year prevalence and good coverage statistics in Carey et al were approximately equivalent to a 3 month discontinuation probability of approximately 6.9%. The MS adopted a 3 month discontinuation probability of 1.9%, reflecting EINSTEIN-DVT data.

Consequently, beyond the 12 month initial treatment period, the economic model for lifelong treatment adopted the conservative assumption of 3.6% discontinuation per 3 month timestep from Boggon et al. Sensitivity analyses on this parameter were conducted on the basis that the 95% CI was 1.9% to 6.9%. 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.

3.3.4. Treatment effect

As requested in the ACD, the assumptions in relation to treatment effects (rivaroxaban vs dual LMWH/VKA) use data from the whole population of EINSTEIN-DVT, specifically:

- 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.

These assumptions were detailed in section 6.3.1 of the MS.

3.3.5. Disutility with warfarin

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 fear and anxiety in patients treated with warfarin on HRQoL have been previously described (section 6.4.1 of MS), several aspects of this have been further highlighted in submission statements of clinical and patient group experts, and some are noted in the ACD (paragraph 4.2). In previous appraisals involving warfarin, NICE Appraisal Committees have recognised this effect.

A systematic literature review was conducted for relevant HRQoL data described in depth in the MS (see also review report provided as reference 17 to the MS). As described in section 6.4.5 of the MS, the systematic review had the broad objective of finding evidence on utility associated with VTEs, including events such as DVT, PE, bleeding, CTEPH and PTS, in patient populations with index DVTs, PEs or VTEs generally. The review also set out to identify evidence that might suggest moderation of utilities according to the nature of treatment received. The review yielded six included studies, of which only one considered treatment related utility (reference 85 of MS). This study, by Marchetti et al, was a modified

time trade-off study in a sample of patients attending an anticoagulation clinic (n=48). Patients read the description of two hypothetical patients who were receiving warfarin or LMWH, and were asked to trade 1 year of life on warfarin or LMWH therapy for 1 year of life reduced by a certain amount of time. A mean utility of 0.988 (SD=0.016) was reported for warfarin, ie: a disutility of 0.012. We noted in the MS that, whilst it may be reasonable to assume that LMWH/VKA treatment is associated with a disutility, no such assumption was made in the MS model, whose purpose was to evaluate up to 12 months of treatment.

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.

In summary, the model presented with this response includes a disutility of 0.012 associated with treatment with dual LMWH/VKA and no disutility associated with rivaroxaban. This is supported by a systematic review of HRQoL evidence, clinical validity, and face validity in relation to the greater treatment satisfaction reported with rivaroxaban (reference 18 of MS).

3.3.6. Transition matrices

In light of the changes in approach outlined above a number of amendments were made to the transition matrices:

- Treatment termination at the end of 12 months was removed. Patients now remain within the on treatment state for the entire time horizon 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).

3.4. Cost-effectiveness results from lifelong model

As described previously, we present the results of cost-effectiveness analyses according to two sets of assumptions:

- The original evidence-based assumptions of 9 visits in the first quarter followed by 5 visits per quarter thereafter
- The reduced intensity of 6 visits in the first quarter followed by 3 visits per quarter thereafter

3.4.1. Results under original evidence-based intensity assumptions

The results of the cost-effectiveness analysis under the original evidence-based assumptions of INR monitoring intensity are that 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. Further results are given in Table 5.

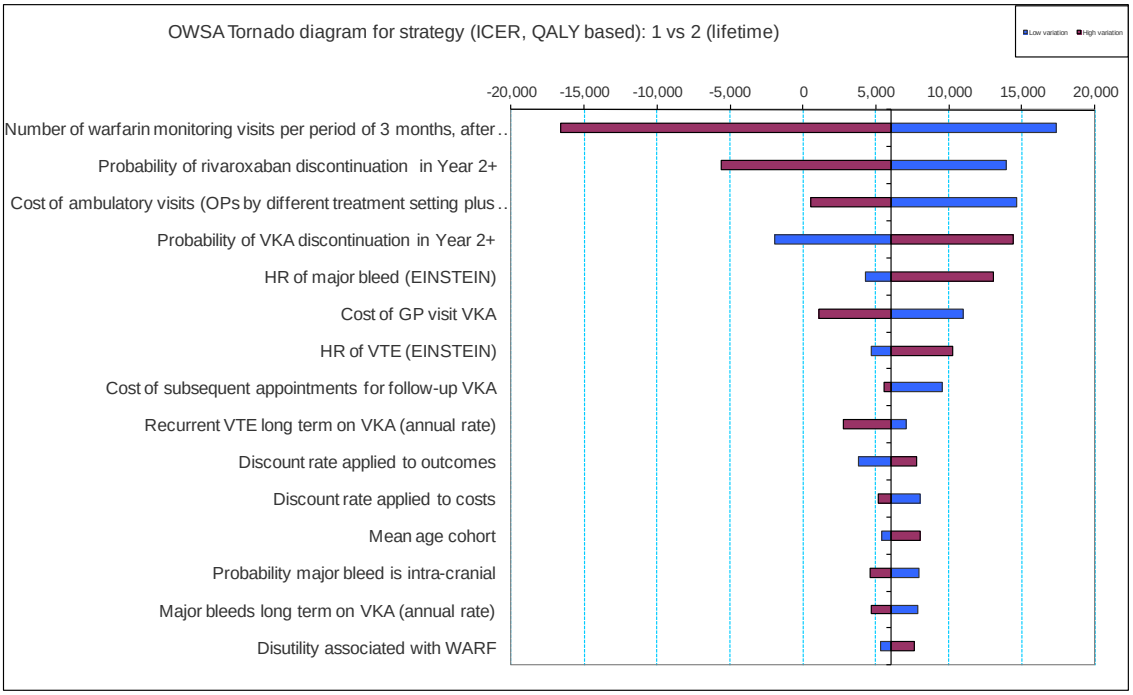
Table 5: Cost-effectiveness results for lifelong treatment, original evidence-based INR monitoring intensity assumptions

		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.

A set of one-way sensitivity analyses (OWSA) was conducted as per the MS. A tornado plot is presented in Figure 1 which identifies the effect of the 15 parameters of greatest sensitivity on the ICER. No analysis produces an ICER in excess of £20,000 per QALY.

Figure 1: Tornado plot for cost-effectiveness analysis of lifelong treatment, original evidence-based INR monitoring intensity assumptions



Probabilistic Sensitivity Analysis (PSA) was also conducted as with the MS, but with 5,000 simulations. A cost-effectiveness plane is presented in Figure 2 and cost-effectiveness acceptability curve in Figure 3. There was a 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

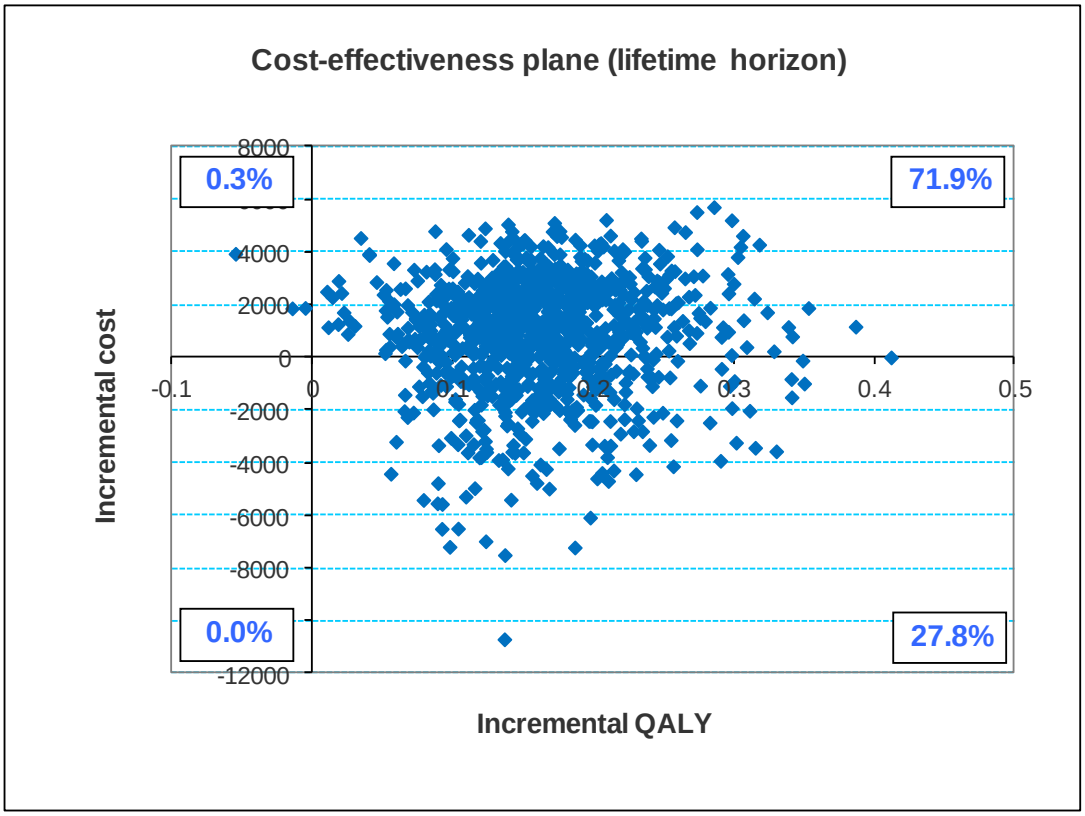
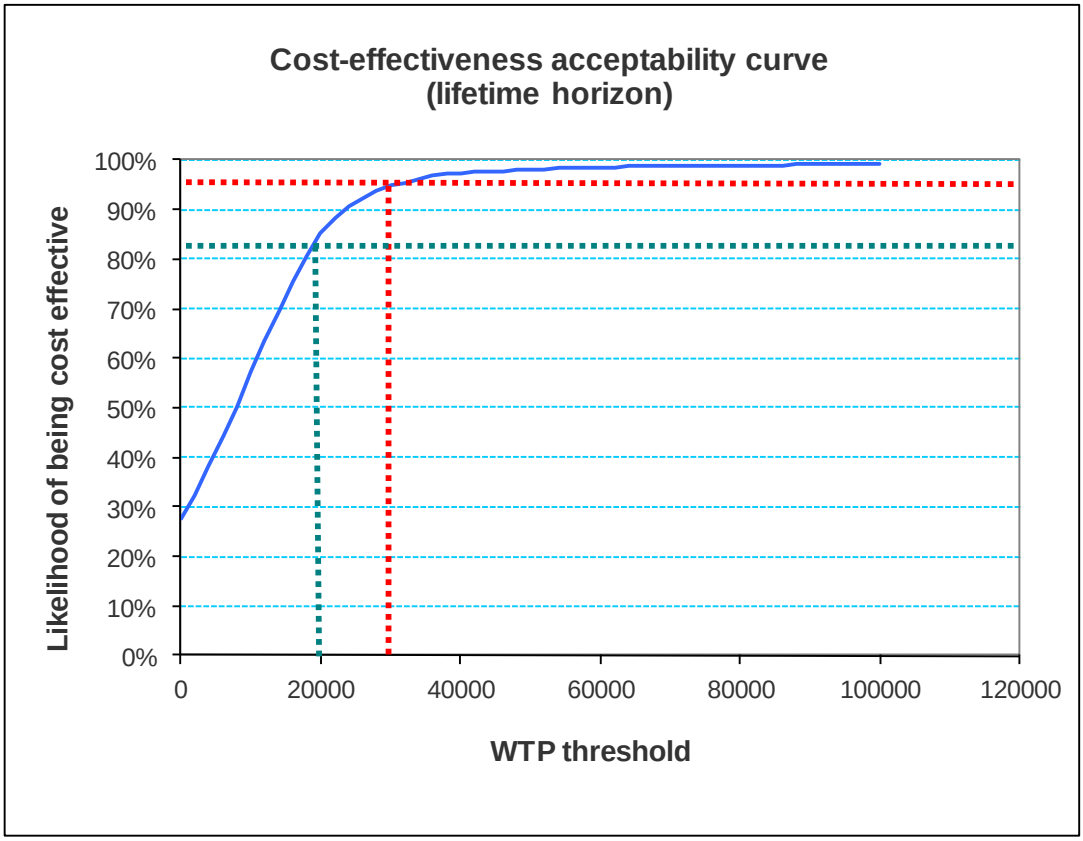


Figure 3: Cost-effectiveness acceptability curve, original intensity assumptions



3.4.2. Results under reduced intensity assumptions

The results of the cost-effectiveness analysis under the reduced intensity assumptions of INR monitoring intensity are that 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 an incremental cost-effectiveness ratio (ICER) of £15,847 per QALY gained. Further results are given in Table 6.

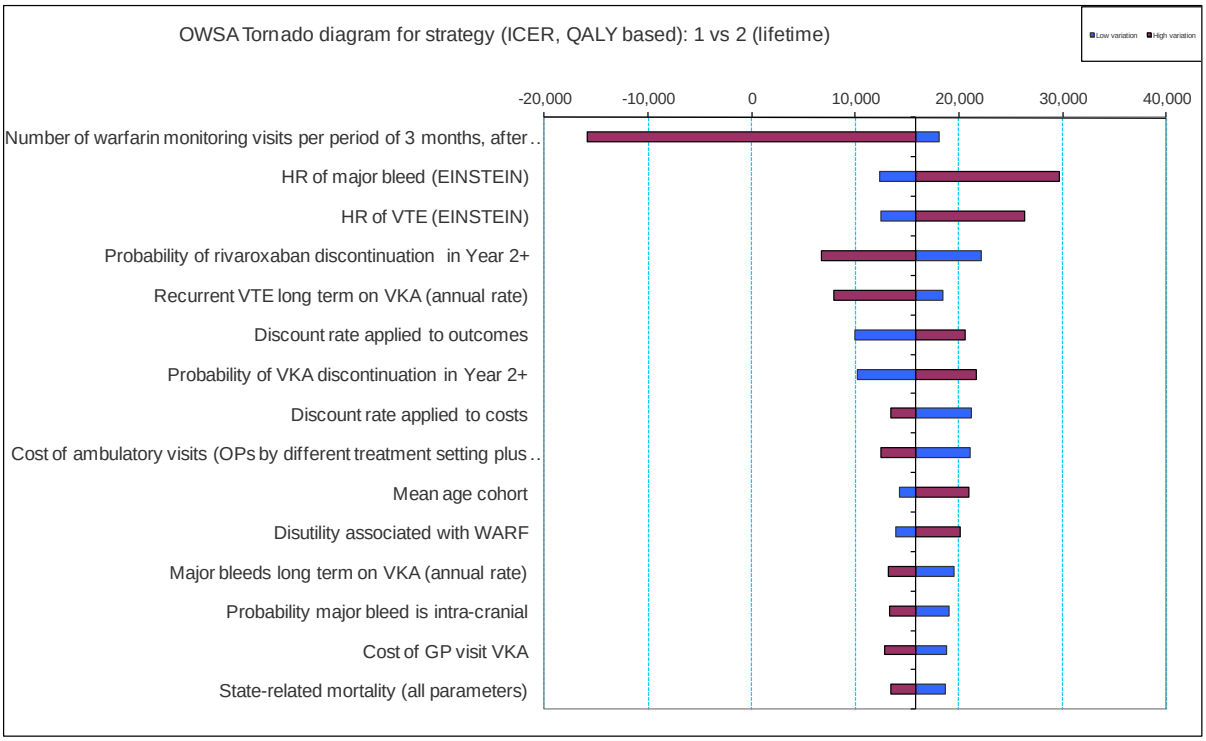
Table 6: Cost-effectiveness results for lifelong treatment, reduced intensity assumptions

		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.

A set of one-way sensitivity analyses (OWSA) was conducted as per the MS. A tornado plot is presented in Figure 4, which identifies the effect of the 15 parameters of greatest sensitivity on the ICER. No analysis produces an ICER in excess of £30,000 per QALY.

Figure 4: Tornado plot for cost-effectiveness analysis of lifelong treatment, reduced intensity assumptions



Probabilistic Sensitivity Analysis (PSA) was also conducted as in the MS, but with 5,000 simulations. A cost-effectiveness plane is presented in Figure 5 and cost-effectiveness acceptability curve in Figure 6. 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

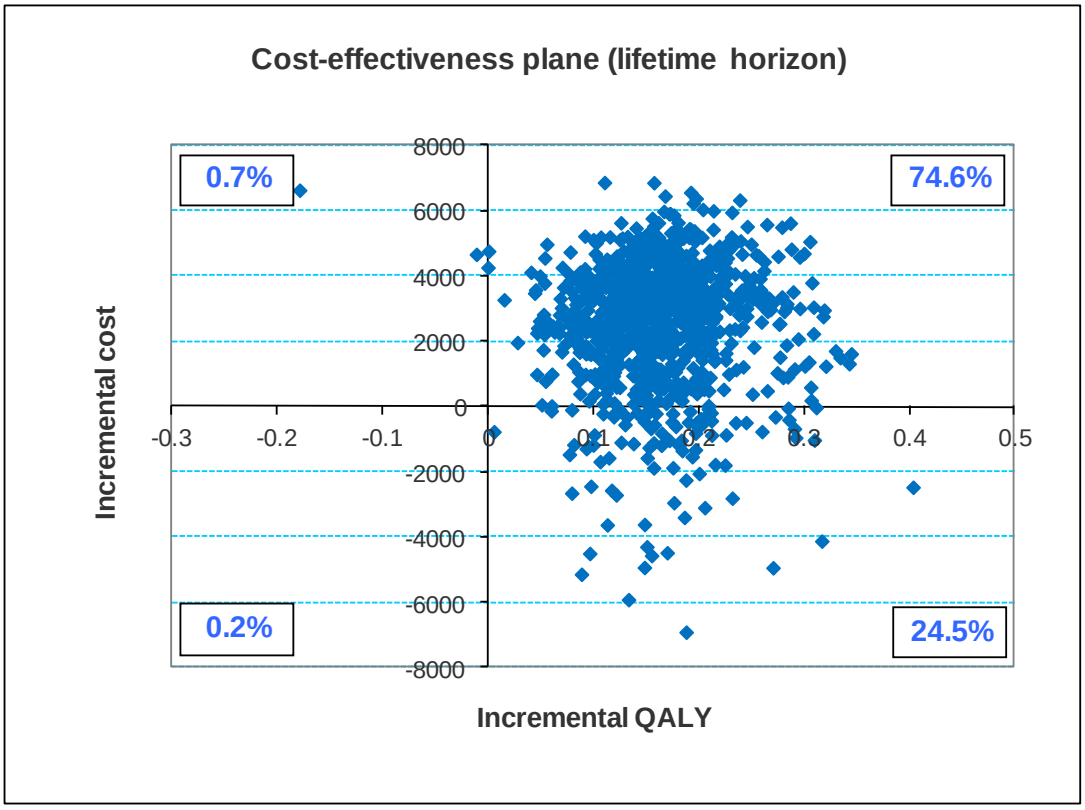
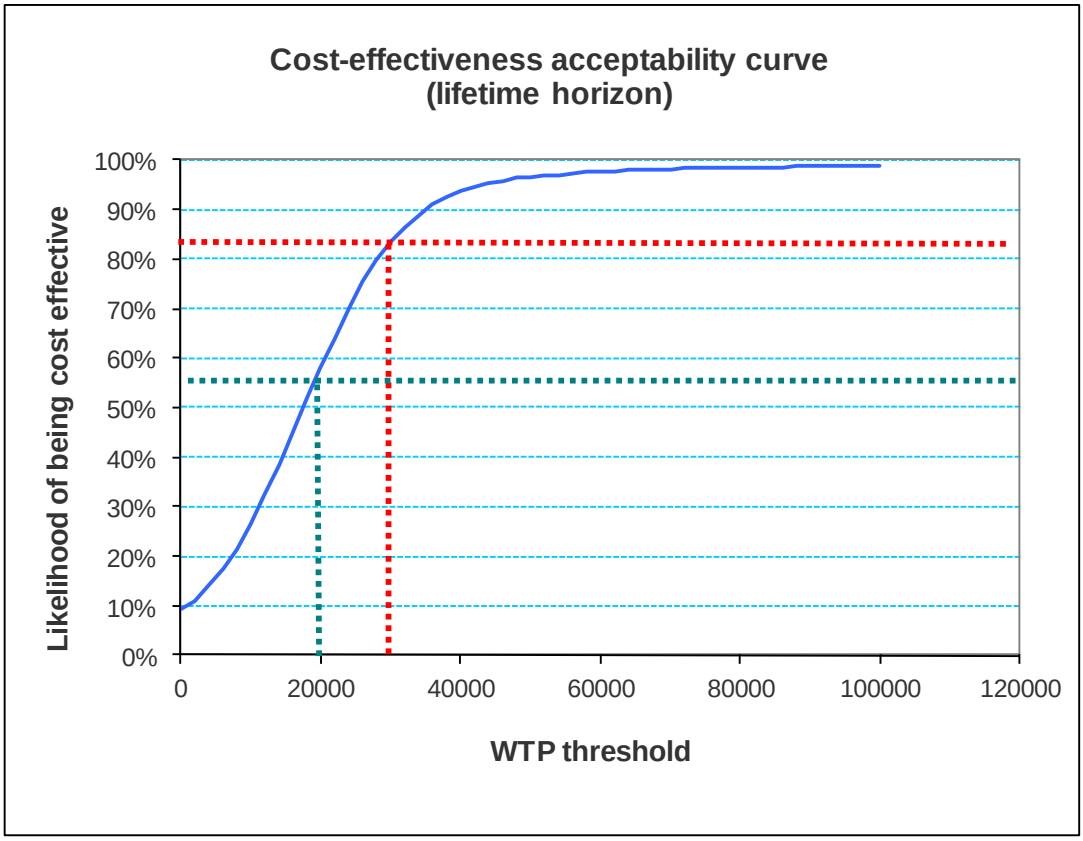


Figure 6: Cost-effectiveness acceptability curve, original intensity assumptions



3.5. Discussion and conclusions

3.5.1. Other uncaptured factors relevant to cost-effectiveness

The strengths and weaknesses of the economic evaluation of 3/6/12 months of treatment have been previously discussed in section 6.10.3 of the MS. The lifelong analysis presented here is limited by the availability of certain long-term data relevant to DVT and rivaroxaban.

As with the evaluation submitted in the MS, it was not possible for all factors potentially relevant to the cost-effectiveness of rivaroxaban to be included in the economic model. The length of hospital stay in patients assigned to rivaroxaban was 3.0 days fewer than in those assigned to dual LMWH/VKA (median of 8 vs 5 days, P<0.0001). Potential additional costs or negative health outcomes associated with medical errors / drug interactions with warfarin or LMWH (see references 7, 10 and 13 of MS) have also not been accounted for due to difficulty capturing these costs and outcomes. It is therefore likely that the potential cost-effectiveness of rivaroxaban have been underestimated.

3.5.2. Cost-effectiveness across whole indication

The cost-effectiveness in each of the four durations of treatment relevant to this indication are summarised in Table 7, having been calculated using a consistent set of assumptions.

This data is summarised as a whole indication ICER – the average incremental cost relative to the average incremental QALY, weighted according to the proportion of patients in each of the treatment duration groups.

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.

We have followed the Appraisal Committee's assumption that 20% of patients requiring more than one year of anticoagulation. The remaining 80% of patients requiring less than one year have been split according to the EINSTEIN-DVT population, which ERG's clinical advisors indicated was representative of UK clinical practice.

The results of the whole indication cost-effectiveness analysis under the original evidence-based assumptions of INR monitoring intensity are that 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 incremental cost-effectiveness ratio (ICER) of £2,057 per QALY gained. Further detail is presented in Table 7.

Table 7: Cost-effectiveness results across all treatment durations considered, INR monitoring costed as per MS

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

The results of the whole indication cost-effectiveness analysis under the reduced intensity assumptions of INR monitoring intensity are 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 incremental cost-effectiveness ratio (ICER) of £10,269 per QALY gained. Further detail is presented in Table 8.

Table 8: Cost-effectiveness results across all treatment durations considered, INR monitoring costed with ERG unit costs and 6/3 frequency

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

4. Additional comments

4.1. Bayer's commitment to obtaining additional long-term data

Bayer agreed with the EMA a Risk Management Plan which includes the conduct of the phase IV non-interventional study, XALIA (Xarelto® for Long-term and Initial Anticoagulation in venous thromboembolism). This study will provide additional evidence as to the long-term effectiveness and safety of rivaroxaban. The main objectives of XALIA are to study recurrence of VTE, incidence of major bleeding and mortality, with additional objectives covering other cardiac and symptomatic thromboemboic events, treatment satisfaction and adherence. Adult patients with a diagnosis of acute DVT and who have an indication for anticoagulation for at least 12 weeks will be eligible for inclusion in the study. It is planned to enrol 4800 patients from Europe into the study. The study ends 12 months after end of enrolment.

4.2. Comments on wording of the ACD

Paragraph 2.2. It is recognised in the MS and SmPC that although over 16,000 patients have been exposed to rivaroxaban in the course of eight RCTs, experience with rivaroxaban beyond 12 months in this indication is limited. The latter point, but not the former, is reflected in paragraph 2.2 of the ACD.

Paragraph 3.1. The final sentence is unclear as to the inclusion criteria of EINSTEIN-Ext. It may instead be said that patients were recruited to this study based on the risk-benefit of further anticoagulation.

Paragraph 3.2. It is not true that 53% of patients had necessarily participated in EINSTEIN-DVT; this proportion also includes patients who had participated in EINSTEIN-Ext. Please see response to ERG clarification question D4. Later in this paragraph, it is slightly misleading to say `some people were excluded from the EINSTEIN-DVT and EINSTEIN-Ext trials' – as with other clinical trials, these two trials had inclusion/exclusion criteria.

Paragraphs 3.7-3.8. There are several errors in connection with the description of the cancer subgroup and mixed treatment comparison analyses presented by Bayer.

- The first sentence should note that the analysis was conducted for the subgroup of patients with cancer. To omit this point suggests that the analysis reflected the full indication, which is quite misleading. This is compounded by an erroneous description later of a secondary analysis.

- We presented three analyses not two. There was a primary analysis and two secondary analyses. These were described in the MS and in response to ERG clarification question D13.

- The following sentence is incorrect: `Following a request from the ERG, the manufacturer also presented an additional analysis for the subgroup of patients with active cancer'. The mixed treatment comparison was included in the original MS and related to the cancer subgroup. The original MS also included a cost-minimisation analysis for the cancer subgroup. The ERG requested in their clarification questions an `indicative cost-effectiveness analysis' for the cancer subgroup based on the results of the mixed treatment comparison, and Bayer provided this.

- The results quoted as being Bayer's mixed treatment comparison results are not Bayer's primary analysis, but instead appear to be one of the two secondary analyses.

Paragraph 3.11. NHS Reference Costs for 2009-10 were used, as noted in the MS.

Paragraph 3.12. Utility values were all sourced from literature. It may be important to recognise that the Kind study measured health preference via EQ-5D, which is NICE's preferred instrument. Utility estimates were additionally made for patients experiencing CTEPH using a disease-specific utility index (reference 120 of MS). It may also be important to recognise that treatment satisfaction has been reported from EINSTEIN-DVT as being significantly higher with rivaroxaban than dual LMWH/VKA (reference 18 of MS).

Paragraph 3.20. It should be made clear that this paragraph relates to an analysis specific to the subgroup of patients with cancer.

Paragraph 3.21. The ACD mixes two distinct issues on which the ERG have provided advice. The concerns about validity described in sentence one appear to refer to the use of composite endpoints in assessing relative clinical effectiveness, not cost-effectiveness. Differential impacts of constituent outcomes of a composite endpoint on cost and quality of life are not particularly relevant in considering relative clinical effectiveness, but the aggregation of constituent health states into a composite health state in an economic model, would not be advisable. DVT and PE are manifestations of the same underlying condition and so rivaroxaban is expected to affect incidence/recurrence of each similarly, which explains why a composite endpoint in the trial was appropriate and is valid. The economic model Bayer presented in its MS distinguishes clearly between DVT and PE states, treating each outcome distinctly, an appropriate and valid approach.

Paragraph 3.23. The first sentence recognises only two of the three principle differences between the basis for the MS economic model outcomes and those given later in the paragraph. The ERG's analyses took into account duration-specific effectiveness data and corrected errors the ERG perceived to exist. A crucial additional difference is that the ERG have chosen to present mean probabilistic outcomes rather than deterministic outcomes.

Paragraph 3.24. The manufacturer's analysis should be referred to as our `illustrative analysis', as we and the ERG were well-aware of its limitations and had only provided such illustrative results at the explicit request of the ERG. It may be helpful to use the terminology

`mixed treatment comparison' here rather than `network meta-analysis' for consistency with the rest of the ACD (eg paras 3.7-8) so as to avoid confusion that there exists an additional analysis.

Paragraph 4.14. It is clear from the ERG report (Table 36 in section 5.2.1.8 for example) that further analyses in relation to frequency of INR monitoring adopted an assumption that there were 3 visits every 3 months after the first 3 months. This paragraph refers to an evaluation of `2 or 3' visits, as if there was some doubt as to the model assumption, yet the model assumption is clearly stated. We note that this has been reflected in the manufacturer comments requested in paragraph 1.2.

Related NICE guidance. We suggest two additions to this list:

- Published. Atrial fibrillation – dabigatran etexilate. NICE technology appraisal guidance 249.
- Under development. Atrial fibrillation (stroke prevention) – rivaroxaban. NICE technology appraisal. ID420.

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