Single Technology Appraisal (STA) of rivaroxaban (Xarelto®) for the prevention of venous thromboemobolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

Results in response to Evidence Review Group queries

10th November 2008

Please note commercial in confidence data have been removed from this version

Xarelto economic model report: revised results section created in response to NICE ERG queries

All of the results presented below are based on the model *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls.*

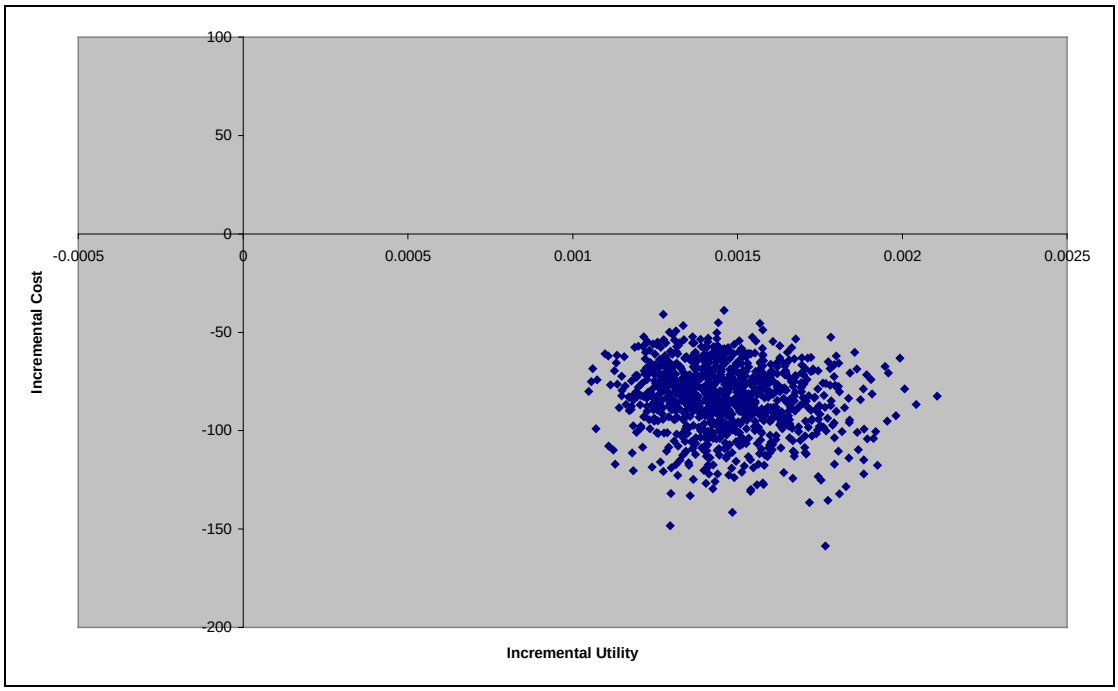
RECORD 1

Table 1 Deterministic Analysis – RECORD 1

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£195.41	£278.92	-£83.51
QALY	10.36717	10.36572	0.0015
Cost /QALY			Rivaroxaban dominates

The results of the PSA are shown in Figure 1.

Figure 1 CUA Plane – Rivaroxaban vs. enoxaparin (RECORD 1)



All of the iterations in Figure 1 appear in the bottom right quadrant indicating that rivaroxaban is associated with lower costs and higher utilities when compared with enxoaparin. Since rivaroxaban dominates in 100% of cases, there is no CEAC. The one way sensitivity analyses are presented in Table 2

Table 2 One way sensitivity analysis – RECORD 1

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£83.51**	**0.0015**	**Rivaroxaban dominates**
1.	Time Period: Acute phase (up to 3 months)	Sullivan et al., 2003(29)	-£67.67	0.0002	Rivaroxaban dominates
2.	Time Period: 5-years	Assumption	-£72.26	0.0006	Rivaroxaban dominates
3.	Extrapolation method: No symptomatic VTE to symptomatic VTE	White et al., 1998(69)	-£70.29	0.0008	Rivaroxaban dominates
4.	Risk of asymptomatic to symptomatic VTE: lower limit (26.3%)	Quinlan et al., 2007(66)	-£83.51	0.0015	Rivaroxaban dominates
5.	Risk of asymptomatic to symptomatic VTE: higher limit (16.3%)	Quinlan et al., 2007(66)	-£83.51	0.0015	Rivaroxaban dominates
6.	Drug costs: excluded	Assumption	-£92.27	0.0015	Rivaroxaban dominates
7.	Discount rates: Costs: 0%, Effects: 0%	Assumption	0.0020	0.0020	Rivaroxaban dominates
8.	Discount rates: Costs: 6%, Effects: 6%	Assumption	-£81.15	0.0012	Rivaroxaban dominates
9.	Duration of hospitalisation: +2 days	Assumption	-£79.67	0.0015	Rivaroxaban dominates
10.	Duration of hospitalisation: -2 days	Assumption	-£87.35	0.0015	Rivaroxaban dominates
11.	Duration of hospitalisation: 1 extra day for enoxaparin (£786)	Assumption	-£869.51	0.0015	Rivaroxaban dominates
12.	Efficacy and Safety data: do not accept non-significant data	Direct comparison	-£82.85	0.0007	Rivaroxaban dominates
13.	Switch to no prophylaxis after discharge: enoxaparin costs and efficacy adjusted	Assumption	£86.52	0.0023	£37,562.38
14.	Switch to no prophylaxis after discharge: enoxaparin costs adjusted only (efficacy remains as per RECORD study)	Assumption	£75.00	0.0015	£51,547.56 per QALY
15.	Utility values following THR: 0.75	Ostendorf et al. (2004)(76;77); Malchau et al. (2005)(78)	-£83.51	0.0015	Rivaroxaban dominates

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£83.51**	**0.0015**	**Rivaroxaban dominates**
16.	Utility values weighted by time: 0.701	Brunenberg et al. (2005)(74)	-£83.51	0.0015	Rivaroxaban dominates
17.	Utility of PTS: upper value (1)	Lenert et al., 1997(73)	-£83.51	0.0008	Rivaroxaban dominates
18.	Utility of PTS: lower value (0.76)	Lenert et al., 1997(73)	-£83.51	0.0206	Rivaroxaban dominates
19.	0% PE patients also have DVT	Assumption	-£84.23	0.0015	Rivaroxaban dominates
20.	100% PE patients also have DVT	Assumption	-£82.39	0.0014	Rivaroxaban dominates
21.	Cost of PTS: £7,072.16 (mean)	MacDougall et al., 2006(85)	-£307.73	0.0015	Rivaroxaban dominates
22.	Cost of PTS: £2,864.75 (median)	MacDougall et al., 2006(85)	-£165.58	0.0015	Rivaroxaban dominates
23.	Cost of PTS: £278.89	NICE, 2007(22)	-£78.21	0.0015	Rivaroxaban dominates
24.	Probability of PTS: upper value (year 1: 0.22)	Prandoni et al., 1997(64)	-£86.41	0.0016	Rivaroxaban dominates
25.	Probability of PTS: lower value (year 1: 0.13)	Prandoni et al., 1997(64)	-£79.70	0.0012	Rivaroxaban dominates
26.	Probability of recurrent VTE: upper value (year 1: 0.16)	Prandoni et al., 1997(64)	-£84.38	0.0015	Rivaroxaban dominates
27.	Probability of recurrent VTE: lower value (year 1: 0.08)	Prandoni et al., 1997(64)	-£83.38	0.0014	Rivaroxaban dominates
28.	Comparison vs LMWHs	BNF, 2008(79); IMS Health(9)	-£65.11	0.0014	Rivaroxaban dominates

RECORD 2

Table 3 Deterministic Analysis – RECORD 2

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£196.63	£196.67	-£0.04
QALY	10.36710	10.35408	0.0130
Cost /QALY			Rivaroxaban dominates

The results of the PSA are shown in Figure 2 and Figure 3.

Figure 2 CUA Plane – Rivaroxaban vs. enoxaparin (RECORD2)

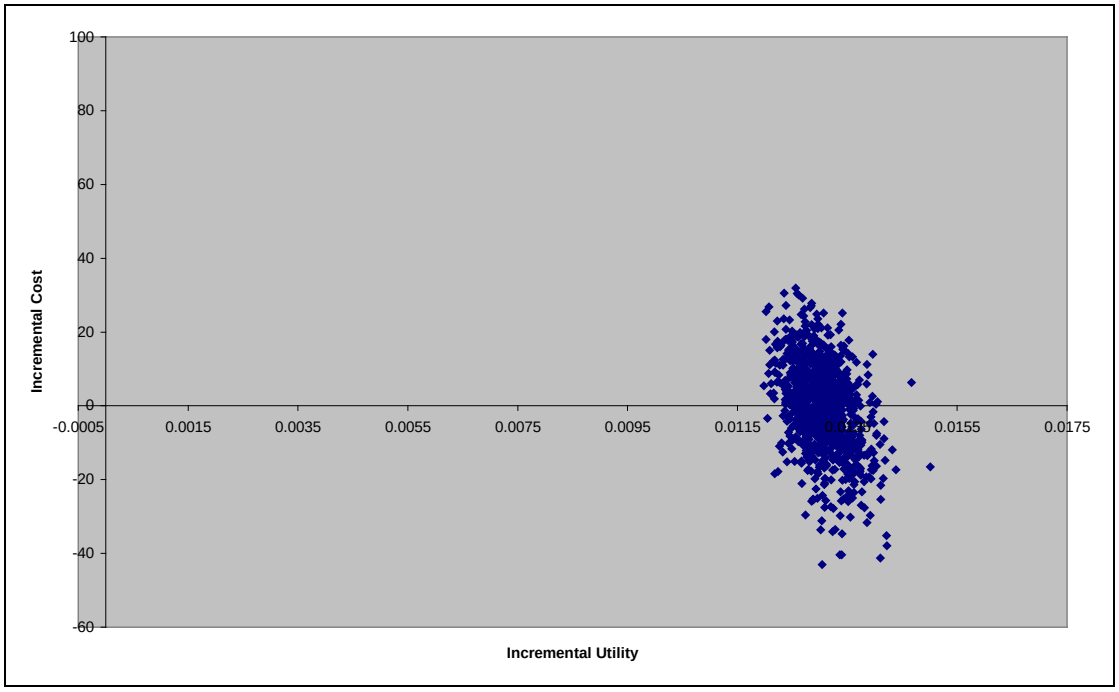


Figure 3 CEAC – Rivaroxaban vs. enoxaparin (RECORD 2)

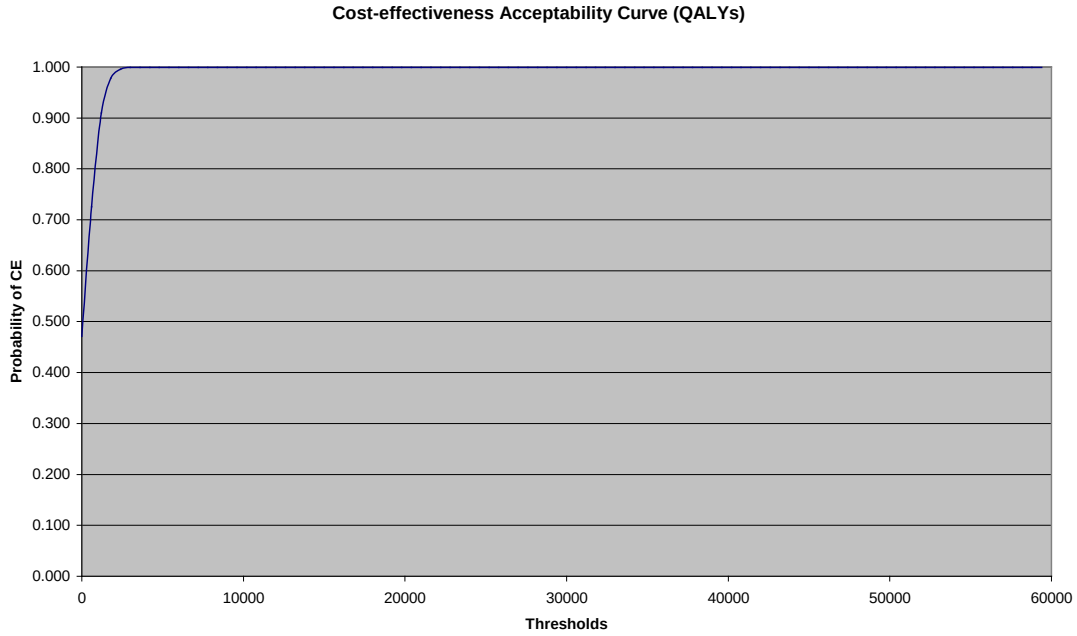


Figure 3 indicates that rivaroxaban is cheaper and more effective than enoxaparin in approximately 50% of iterations (i.e. rivaroxaban dominates). At a threshold of less than £2,500 per QALY, there is a 99% probability that rivaroxaban is cost-effective. The one way sensitivity analyses are presented in Table 4.

Table 4 One way sensitivity analysis – RECORD 2

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£0.04**	**0.0130**	**Rivaroxaban dominates**
1.	Time Period: Acute phase (up to 3 months)	Sullivan et al., 2003(29)	£39.20	£23,720.82	£23,720.82
2.	Time Period: 5-years	Assumption	£5,707.17	0.0048	£5,707.17
3.	Extrapolation method: No symptomatic VTE to symptomatic VTE	White et al., 1998(69)	£35.79	0.0112	£3,192.32
4.	Risk of asymptomatic to symptomatic VTE: lower limit (26.3%)	Quinlan et al., 2007(66)	-£0.04	0.0130	Rivaroxaban dominates
5.	Risk of asymptomatic to symptomatic VTE: higher limit (16.3%)	Quinlan et al., 2007(66)	-£0.04	0.0130	Rivaroxaban dominates
6.	Drug costs: excluded	Assumption	-£98.71	0.0130	Rivaroxaban dominates
7.	Discount rates: Costs: 0%, Effects: 0%	Assumption	-£12.35	0.0185	Rivaroxaban dominates
8.	Discount rates: Costs: 6%, Effects: 6%	Assumption	£5.74	0.0105	£544.55
9.	Duration of hospitalisation: +2 days	Assumption	£3.80	0.0130	£292.07
10.	Duration of hospitalisation: -2 days	Assumption	-£3.88	0.0130	Rivaroxaban dominates
11.	Duration of hospitalisation: 1 extra day for enoxaparin (£786)	Assumption	-£786.04	0.0130	Rivaroxaban dominates
12.	Efficacy and Safety data: do not accept non-significant data	Direct comparison	£2.33	0.0032	£732.68
13.	Switch to no prophylaxis after discharge: enoxaparin costs and efficacy adjusted	Assumption	£21.97	0.0182	£1,207.27
14.	Switch to no prophylaxis after discharge: enoxaparin costs adjusted only (efficacy remains as per RECORD study)	Assumption	0.0130	£2,160.59	£2,160.59
15.	Utility values following THR: 0.75	Ostendorf et al. (2004)(76;77); Malchau et al. (2005)(78)	-£0.04	0.0131	Rivaroxaban dominates
16.	Utility values weighted by time: 0.701	Brunenberg et al. (2005)(74)	-£0.04	0.0130	Rivaroxaban dominates

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£0.04**	**0.0130**	**Rivaroxaban dominates**
17.	Utility of PTS: upper value (1)	Lenert et al., 1997(73)	-£0.04	0.0114	Rivaroxaban dominates
18.	Utility of PTS: lower value (0.76)	Lenert et al., 1997(73)	-£0.04	0.0239	Rivaroxaban dominates
19.	0% PE patients also have DVT	Assumption	£4.39	0.0128	£343 per QALY
20.	100% PE patients also have DVT	Assumption	-£6.92	0.0134	Rivaroxaban dominates
21.	Cost of PTS: £7,072.16 (mean)	MacDougall et al., 2006(85)	-£544.28	0.0130	Rivaroxaban dominates
22.	Cost of PTS: £2864.75 (median)	MacDougall et al., 2006(85)	-£199.24	0.0130	Rivaroxaban dominates
23.	Cost of PTS: £278.89	NICE, 2007(22)	£12.82	0.0130	£985 per QALY
24.	Probability of PTS: upper value (year 1: 0.22)	Prandoni et al., 1997(64)	-£7.18	0.0134	Rivaroxaban dominates
25.	Probability of PTS: lower value (year 1: 0.13)	Prandoni et al., 1997(64)	£9.28	0.0125	£742 per QALY
26.	Probability of recurrent VTE: upper value (year 1: 0.16)	Prandoni et al., 1997(64)	-£2.77	0.0131	Rivaroxaban dominates
27.	Probability of recurrent VTE: lower value (year 1: 0.08)	Prandoni et al., 1997(64)	£0.35	0.0130	£27.11 per QALY
28.	Comparison vs LMWHs	BNF, 2008(79); IMS Health(9)	£3.31	0.0130	£254 per QALY

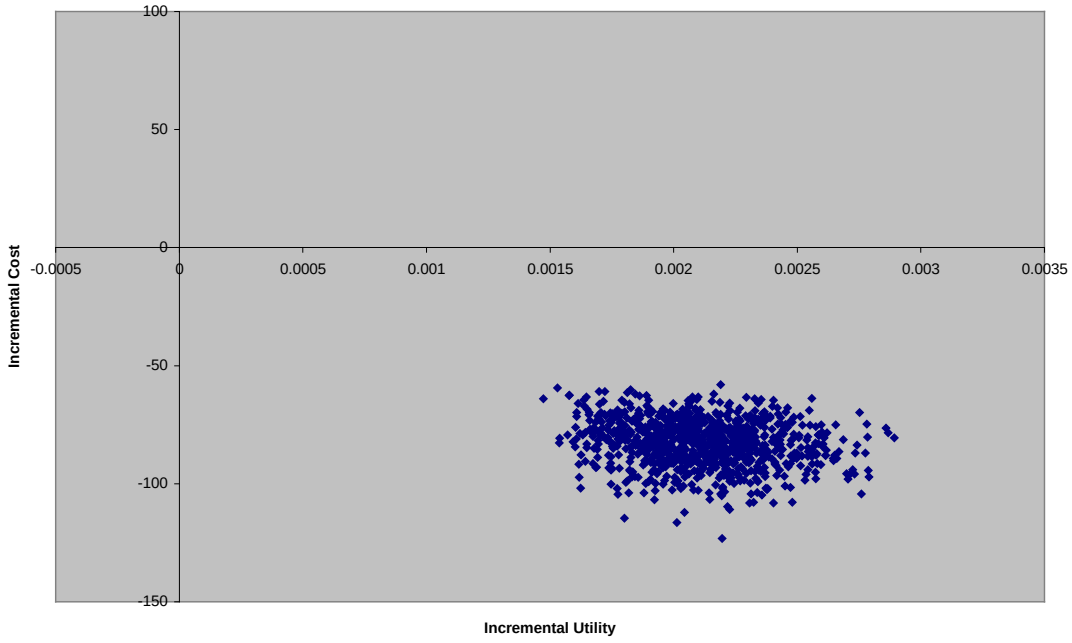
RECORD 3

Table 5 Deterministic Analysis – RECORD 3

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£114.77	£196.95	-£82.17
QALY	10.30315	10.30104	0.0021
Cost /QALY			Rivaroxaban dominates

The results of the PSA are shown in Figure 4.

Figure 4 CUA Plane – Rivaroxaban vs. enoxaparin (RECORD 3)



All of the iterations in Figure 4 appear in the bottom right quadrant indicating that rivaroxaban is associated with lower costs and higher utilities when compared with enxoaparin. Since rivaroxaban dominates in 100% of cases, there is no CEAC. The one way sensitivity analyses are presented in Table 6.

Table 6 One way sensitivity analysis – RECORD 3

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£82.17**	**0.0021**	**Rivaroxaban dominates**
1.	Time Period: Acute phase (up to 3 months)	Sullivan et al., 2003(29)	-£54.60	0.0008	Rivaroxaban dominates
2.	Time Period: 5-years	Assumption	-£62.74	0.0013	Rivaroxaban dominates
3.	Extrapolation method: No symptomatic VTE to symptomatic VTE	White et al., 1998(69)	-£71.37	0.0016	Rivaroxaban dominates
4.	Risk of asymptomatic to symptomatic VTE: lower limit (7.1%)	Quinlan et al., 2007(66)	-£82.17	0.0021	Rivaroxaban dominates
5.	Risk of asymptomatic to symptomatic VTE: higher limit (2.3%)	Quinlan et al., 2007(66)	-£82.17	0.0021	Rivaroxaban dominates
6.	Drug costs: excluded	Assumption	-£83.22	0.0021	Rivaroxaban dominates
7.	Discount rates: Costs: 0%, Effects: 0%	Assumption	-£90.78	0.0027	Rivaroxaban dominates
8.	Discount rates: Costs: 6%, Effects: 6%	Assumption	-£78.13	0.0018	Rivaroxaban dominates
9.	Duration of hospitalisation: +2 days	Assumption	-£78.3	0.0021	Rivaroxaban dominates
10.	Duration of hospitalisation: -2 days	Assumption	-£86.01	0.0021	Rivaroxaban dominates
11.	Duration of hospitalisation: 1 extra day for enoxaparin (£786)	Assumption	-£868.17	0.0021	Rivaroxaban dominates
12.	Efficacy and Safety data: do not accept non-significant data	Direct comparison	-£113.53	0.0023	Rivaroxaban dominates
13.	Switch to no prophylaxis after discharge: enoxaparin costs and efficacy adjusted	Assumption	-£58.70	0.0034	Rivaroxaban dominates
14.	Switch to no prophylaxis after discharge: enoxaparin costs adjusted only (efficacy remains as per RECORD study)	Assumption	-£50.35	0.0021	Rivaroxaban dominates
15.	Utility values weighted by time: 0.701	Brunenberg et al. (2005)(74)	-£82.17	0.0022	Rivaroxaban dominates
16.	Utility of PTS: upper value (1)	Lenert et al., 1997(73)	-£82.17	0.0009	Rivaroxaban dominates

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£82.17**	**0.0021**	**Rivaroxaban dominates**
17.	Utility of PTS: lower value (0.76)	Lenert et al., 1997(73)	-£82.17	0.0097	Rivaroxaban dominates
18.	0% PE patients also have DVT	Assumption	-£77.44	0.0019	Rivaroxaban dominates
19.	100% PE patients also have DVT	Assumption	-£89.53	0.0025	Rivaroxaban dominates
20.	Cost of PTS: £7,072.16 (mean)	MacDougall et al., 2006(85)	-£461.59	0.0021	Rivaroxaban dominates
21.	Cost of PTS: £2,864.75 (median)	MacDougall et al., 2006(85)	-£221.04	0.0021	Rivaroxaban dominates
22.	Cost of PTS: £278.89	NICE, 2007(22)	-£73.21	0.0021	Rivaroxaban dominates
23.	Probability of PTS: upper value (year 1: 0.22)	Prandoni et al., 1997(64)	-£87.18	0.0024	Rivaroxaban dominates
24.	Probability of PTS: lower value (year 1: 0.13)	Prandoni et al., 1997(64)	-£75.66	0.0018	Rivaroxaban dominates
25.	Probability of recurrent VTE: upper value (year 1: 0.16)	Prandoni et al., 1997(64)	-£84.24	0.0022	Rivaroxaban dominates
26.	Probability of recurrent VTE: lower value (year 1: 0.08)	Prandoni et al., 1997(64)	-£79.75	0.0020	Rivaroxaban dominates
27.	Comparison vs LMWHs	BNF, 2008(79); IMS Health(9)	-£78.80	0.0021	Rivaroxaban dominates

Additional Analyses

Additional analyses based on the RECORD 4 clinical trial data and using pooled data from the four RECORD studies and the results are presented in Table 7.

Table 7 Rivaroxaban vs. enoxaparin – additional analyses

Population	Incremental Cost	Incremental QALYs	Results
TKR – RECORD 4	-£50.58	-0.0094	£5,390 per QALY
THR – RECORD 1 & 2 pooled	-£31.48	0.9898	Rivaroxaban dominates
TKR – RECORD 3 & 4 pooled	-£65.56	-0.0086	£7,603 per QALY
THR & TKR (RECORD 1,2,3 & 4 pooled)	-£65.04	0.0037	Rivaroxaban dominates

Indirect comparison – rivaroxaban vs. dabigatran

Using the actual relative risk or risk difference from the indirect comparison regardless of whether or not these values are statistically significant, the probabilities used in the model are as reported in Table 8

Table 8 Rivaroxaban vs. dabigatran - Probability of events during the prophylaxis module

	Rivaroxaban	Dabigatran (submitted base case)	Dabigatran (as per indirect comparison)
RECORD 1			
Prophylaxis related major bleeding	0.0027	0.0027*	[redacted]
Total VTE	0.0113	0.0332	[redacted]
Symptomatic VTE	0.0027	0.0152	[redacted]
Non-fatal PE	0.0025	0.0025*	[redacted]
Fatal PE	[redacted]	[redacted]	[redacted]
RECORD 2			
Prophylaxis related major bleeding	0.0008	0.0008*	[redacted]
Total VTE	0.0197	0.0855	[redacted]
Symptomatic VTE	0.0025	0.0354	[redacted]
Non-fatal PE	0.0012	0.0012*	[redacted]
Fatal PE	[redacted]	[redacted]	[redacted]
RECORD 3			
Prophylaxis related major bleeding	0.0057	0.0057*	[redacted]
Total VTE	0.0959	0.1809	[redacted]
Symptomatic VTE	0.0067	0.0067*	[redacted]
Non-fatal PE	0.0000	0.0000*	[redacted]
Fatal PE	[redacted]	[redacted]	[redacted]

*difference not statistically significant

The results of the cost-effectiveness analysis of rivaroxaban versus dabigatran (220mg) in THR over a lifetime horizon based on data from the RECORD 1 clinical trial and Eriksson et al. (2007a)(26) are shown in Table 9.

Table 9 Rivaroxaban vs. dabigatran – RECORD 1

	RIVAROXABAN	DABIGATRAN	INCREMENTAL
Cost	£195.41	£212.31	-£16.90
QALY	10.36717	10.36529	0.0019
Cost per QALY			**Rivaroxaban dominates**

The results of the cost-effectiveness analysis of rivaroxaban versus dabigatran (220mg) in THR over a lifetime horizon based on data from the RECORD 2 clinical trial and Eriksson et al. (2007a) (26) are shown in Table 12.

Table 10 Rivaroxaban vs. dabigatran – RECORD 2

	RIVAROXABAN	DABIGATRAN	INCREMENTAL
Cost	£196.63	£283.64	-£87.01
QALY	10.36710	10.36163	0.0055
Cost per QALY			**Rivaroxaban dominates**

The results of the cost-effectiveness analysis of rivaroxaban versus dabigatran (220mg) in TKR over a lifetime horizon based on data from the RECORD 3 clinical trial, Eriksson et al. (2007b)(27), and RE-MOBILIZE (2008)(28) are shown in Table 11.

Table 11 Rivaroxaban vs. dabigatran – RECORD 3

	RIVAROXABAN	DABIGATRAN	INCREMENTAL
Cost	£114.77	£105.96	£8.82
QALY	10.30315	10.30322	-0.0001
Cost per QALY			**Dabigatran dominates**

The results in Table 11 suggest that rivaroxaban is more costly and less effective than dabigatran in a TKR population. This result is driven by the high relative risk of symptomatic VTE reported by the indirect comparison. As can be seen in Table 12, the confidence interval around this RR is extremely wide (0.33 to 27.35).

Table 12 Indirect comparison results (based on RECORD 3 and Eriksson et al 2007)

	Relative Risk (95% CI)	Risk Difference (95% CI)
Prophylaxis related major bleeding		
Total VTE		
Symptomatic VTE		
Non-fatal PE		
Fatal PE		

The indirect comparison also indicated that rivaroxaban was associated with fewer total VTE events than dabigatran (RR 0.53). Since asymptomatic VTE is calculated by subtracting the probability of symptomatic VTE from total VTE, it follows that dabigatran is associated with a higher number of asymptomatic VTE events than enoxaparin.

Although the base case analysis assumes that patients with an asymptomatic VTE are not at risk of long-term complications, several studies have reported the incidence of PTS for

patients with asymptomatic (and untreated) DVT to be 23.9% at a follow-up of 2 to 4 years, and 21% at a follow-up of 2 to 10 years. Assuming a cumulative incidence of 22.45% over 5 years (the average of these two studies) gives an annual risk of PTS following asymptomatic VTE of 5%. If we include this risk in the model, the results of the comparison of rivaroxaban versus dabigatran (220mg) over a lifetime horizon are as shown in Table 13, Table 14 and Table 15. See file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_Asymp_PTS.xls*

Table 13 Rivaroxaban vs. dabigatran – RECORD 1 (including risk of PTS following asymptomatic VTE)

	RIVAROXABAN	DABIGATRAN	INCREMENTAL
Cost	£205.22	£234.75	-£29.53
QALY	10.33191	9.61672	0.7152
Cost per QALY			**Rivaroxaban dominates**

Table 14 Rivaroxaban vs. dabigatran – RECORD 2 (including risk of PTS following asymptomatic VTE)

	RIVAROXABAN	DABIGATRAN	INCREMENTAL
Cost	£216.36	£341.20	-£124.84
QALY	10.29614	9.48365	0.8125
Cost per QALY			**Rivaroxaban dominates**

Table 15 Rivaroxaban vs. dabigatran – RECORD 3 (including risk of PTS following asymptomatic VTE)

	RIVAROXABAN	DABIGATRAN	INCREMENTAL
Cost	£237.33	£351.42	-£114.08
QALY	9.86242	8.74787	1.1146
Cost per QALY			**Rivaroxaban dominates**

This analysis was also run versus enxoaparin. The results are presented below.

Table 16 Rivaroxaban vs. enoxaparin – RECORD 1 (including risk of PTS following asymptomatic VTE)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£205.22	£315.91	-£110.69
QALY	10.33191	9.55782	0.7741
Cost per QALY			**Rivaroxaban dominates**

Table 17 Rivaroxaban vs. enoxaparin – RECORD 2 (including risk of PTS following asymptomatic VTE)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£216.36	£289.95	-£73.58
QALY	10.29614	9.34655	0.9496
Cost per QALY			**Rivaroxaban dominates**

Table 18 Rivaroxaban vs. Enoxaparin – RECORD 3 (including risk of PTS following asymptomatic VTE)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£237.33	£428.29	-£190.96
QALY	9.86242	8.79809	1.0643
Cost per QALY			**Rivaroxaban dominates**

Bayer HealthCare
Bayer Schering Pharma

Single Technology Appraisal (STA) of rivaroxaban (Xarelto®) for the prevention of venous thromboemobolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

Clarification on effectiveness and cost effectiveness data in response to Evidence Review Group queries

10th November 2008

Please note commercial in confidence data have been removed from this version

Section A. Clarification on effectiveness data

A1 pages 8 and 82

The submission states that no comparison with fondaparinux has been presented on the grounds that it is not routinely used in clinical practice. Please provide further reasoning for this, because the relevant comparators in an appraisal may not be limited to routine practice only (see the Guide to the Methods of Technology Appraisal 2008, section 2.2.4). It may be useful to bear in mind the evidence, and considerations of the evidence, set out in NICE Clinical Guideline No.46, and NICE Technology Appraisal Guidance No.157.

Consistent with the recommendations in section 2.2.4 of the Guide to the Methods of Technology Appraisal, which state that relevant comparators are identified with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance), the comparisons presented in the submission include low molecular weight heparin (LMWH) and dabigatran. Of the treatments recommended by NICE, LMWH is the main treatment currently used for the prevention of VTE in patients undergoing major orthopaedic surgery in the UK (>98% of cases).[1] Market research indicated enoxaparin is the most widely used LMWH in orthopaedic departments in the UK.[2] Dabigatran was recently approved by NICE for the prevention of VTE in patients undergoing total hip or total knee replacement.[3] A comparison against dabigatran is therefore also presented as a sensitivity analysis.

The NICE Clinical Guideline on VTE prevention in all surgical patients set out to compare most thromboprophylactic treatments available regardless of their frequency of use in the UK.[4] Although the guidelines recommend the use of LMWH or fondaparinux, fondaparinux is used as thromboprophylaxis in less than 2% of all hip and knee replacements.[1 2] LMWHs are the most commonly used treatments in >98% of cases. [1 2] This was discussed extensively with NICE during the teleconference to discuss the decision problem and it was agreed that fondaparinux should not be considered in the submission as this does not reflect routine clinical practice and since the guideline was introduced in Apr 2007 and use of fondaparinux hasn't increased since then it is unlikely to change in the future.

A2 page 38:

Please specify which location the majority of the participants were drawn from, for RECORD 2 and 4 to be consistent with RECORD 1 and 3 as reported under the critical appraisal of the relevant RCTs section?

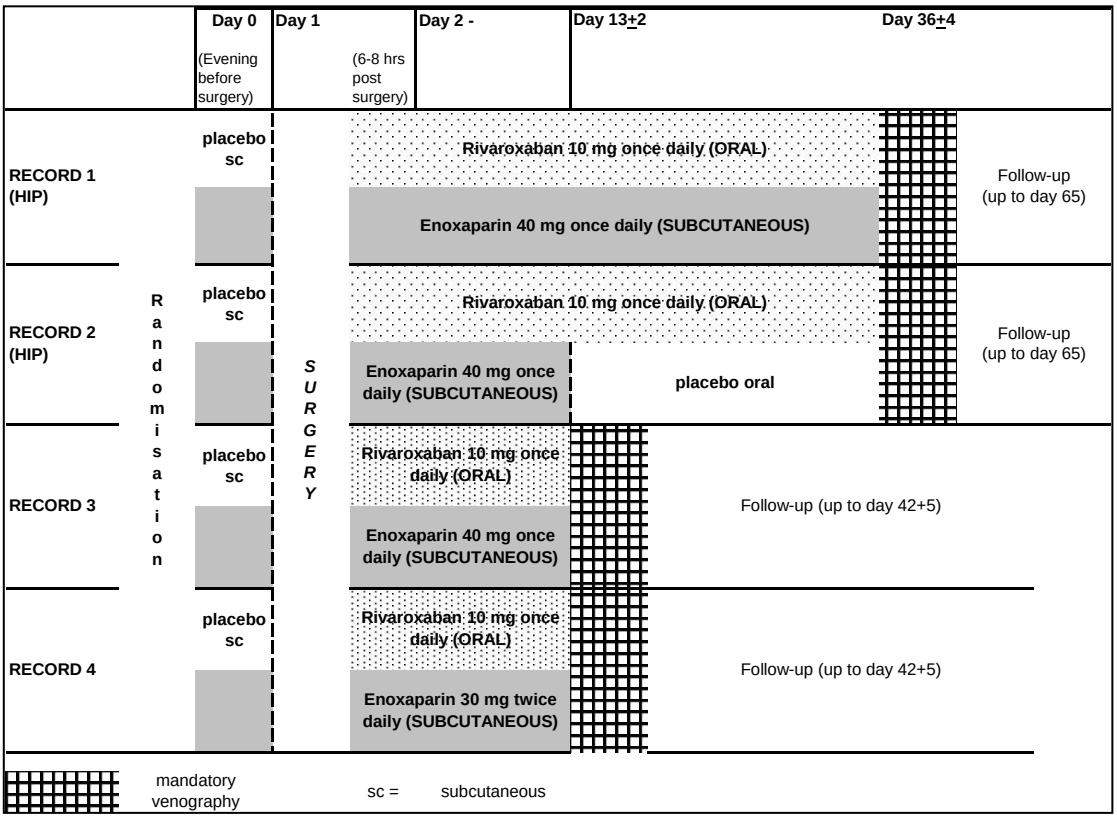
RECORD 2: Majority of subjects were drawn from Europe[5]
RECORD4: Majority of subjects were drawn from the US and Canada[6]

A3 page 44:

Please provide information on when the follow up periods were and which follow up periods are reported in the results of the relevant comparative clinical effectiveness RCTs section and in particular Table 8.

The follow up periods of each RECORD study are detailed in figure 2 of the original submission.

Figure 2: Summary of study design for RECORD 1, 2, 3 and 4



The results of the primary and secondary endpoints are reported for day 36±4 in the RECORD 1 and 2 studies and day 13±2 for the RECORD 3 and 4 studies. The final two rows of table 8 report the results after 30 days of the last intake of study medication, which is up to day 65 for RECORD 1 and 2 and day 42 for RECORD 3 and 4.

A4 page 58:

Please provide an explanation for the higher efficacy event rates for enoxaparin in the dabigatran/enoxaparin studies compared to the rivaroxaban/enoxaparin studies? The submission acknowledges that the enoxaparin efficacy event rates are higher as described above.

The main factor responsible is the different choices of venography assessment centre between these groups of trials. In the RECORD studies, all the independent, blinded venographic assessments (for both treatment arms) were performed in Hamilton, Canada. On the other hand, in the dabigatran studies, all venographic assessments (all three treatment arms) were performed in Gothenberg, Sweden. The Swedish centre is well known to produce greater estimates of event rates than the Canadian centre; this has been documented, for example, in *Quinlan, Eikelboom, et al, J Thromb Haemost 2007.*[7]

Another, minor contributing factor could be the inclusion of symptomatic confirmed (but not necessarily venographically confirmed) events in the composite primary endpoint for the dabigatran studies but not for RECORD, which would again tend to increase the observed event rates.

Importantly, however, within the RECORD programme, the same criteria (same venography assessment centre) were applied across both treatment arms (and across all four studies). The same is true of the three dabigatran studies. Therefore, all of the above centre & criteria differences become irrelevant in the indirect comparison; because the economic model is based on proportional - not numerical - differences in events via the common comparator, and the proportions will be unaffected since the same criteria are applied across all treatment arms in each study.

A5 page 58:
Please provide a reference for the statement 'where extended prophylaxis is now demonstrated to be more effective.'

This is based on evidence that patients have an increased risk of thromboembolism up to 6 weeks following surgery and that VTE rates can be reduced with continued thromboprophylaxis when the patient leaves hospital. [8] [9]

Indeed Guidelines produced by the National Institute for Health and Clinical Excellence (NICE) support the use of extended prophylaxis (4 weeks) in patients undergoing hip replacement surgery with one or more VTE risk factors[4] and updated guidance from the American College of Chest Physicians (ACCP) recommend thromboprophylaxis following elective hip or knee replacement surgery for at least 10 days and continuing up to 35 days.[10] In addition, draft guidelines from the European Agency for the Evaluation of Medicinal Products (EMEA) suggest a duration of post-operative thromboprophylaxis for total hip replacement of 5-6 weeks and, for total knee replacement, a duration of 10-14 days.[11]

A6 page 66:
Please provide a more descriptive explanation of the method of indirect comparison used to compare rivaroxaban with dabigatran and provide a critique of the pros and cons of this approach.

The relative efficacy and safety of two treatments is usually observed by conducting a head-to-head randomised controlled trial of the two agents. However, in the case of rivaroxaban and dabigatran such head-to-head data do not exist. An alternative approach that approximates such results is an indirect comparison of the two treatments.

In the base case analysis, the indirect comparison uses results from two clinical trials in each population;

- THR: RECORD 1 for rivaroxaban and RE-NOVATE for dabigatran[12] [13]
- TKR: RECORD 3 for rivaroxaban and RE-MODEL for dabigatran.[14] [15]

It is important to include in the analysis clinical studies with similar trial settings in order to confidently estimate, indirectly, the differences of both agents. In this analysis, both pairs of clinical trials (for each indication) have similar characteristics, which prevents the introduction of bias. These characteristics include the indication, the comparator (dose regimen and duration of administration), the primary clinical endpoint, and the patient characteristics.

In the THR population the analysis compares RECORD 1 (rivaroxaban vs. enoxaparin) with RE-NOVATE (dabigatran vs. enoxaparin). The demographic and clinical characteristics of the

patient population in these trials are very similar (table 1).

Table 1 THR clinical trials – patient characteristics

	RECORD 1	RE-NOVATE
Mean age	63.2	64.5
% women	55.5%	56%
Weight	78.2	78.5
history*	2.3%	3%

* defined as “history of venous thromboembolism” in RECORD1 and “history of deep vein thrombosis or pulmonary embolism” in RE-NOVATE.

In the TKR population the analysis compares RECORD 3 (rivaroxaban vs. enoxaparin) with RE-MODEL (dabigatran vs. enoxaparin). Again, the demographic and clinical characteristics of the patient population in these trials are very similar (table 2).

Table 2 TKR clinical trials – patient characteristics

	RECORD 3*	RE-MODEL**
Mean age	67.6	67.5
% women	68.2%	66.9%
weight	80.7	82

*safety population

**treated and operated patients

Based on the similarities between the rivaroxaban and dabigatran trials included in the indirect comparison, it is reasonable to conclude that there is no potential bias related to the nature of the population/design in this indirect analysis.

The conducted analysis makes use of the similarities between the clinical trials and the relative efficacy of the each agent versus the common comparator to conclude on the indirect results of rivaroxaban versus dabigatran. This method was introduced by Bucher and colleagues (1997).[16] The analysis derives the indirect estimates by comparing the effects of each treatment versus the common comparator, and therefore retains the benefits of randomisation from the original trial data. In essence, the comparison estimates the differences between rivaroxaban and dabigatran by comparing;

- The result of rivaroxaban vs. enoxaparin
  VS.
- The result of dabigatran vs. enoxaparin

The aim of this method is to ensure that all of the characteristics that make a head-to-head trial statistically sound (in particular, the randomisation) are preserved in the indirect comparison. In order to do this, the key is not to compare the effect of rivaroxaban to the effect of dabigatran in each trial, but to compare the incremental effect of rivaroxaban over enoxaparin to the incremental effect of dabigatran over enoxaparin. The comparison of these incremental effects allows us to estimate the incremental effect of rivaroxaban over dabigatran. Preserving the randomisation is very important. Indeed, if any differences in the populations or designs remained despite the care dedicated to including only comparable trials, the effect of these differences would be minimal since they would affect both arms of each trial equally.

An alternative method for conducting an indirect comparison is the use of meta-regression. While this uses more advanced statistics than the Bucher approach, the underlying concept is the same: the analysis derives the indirect estimates by comparing the effects of each treatment versus the common comparator. Like the Bucher method, meta-regression analysis hence retains the benefits of randomisation from the original trial data. However, meta-regression

analysis requires having data available on more than 2 studies. When this condition was satisfied, meta-regressions were used for the pooled analyses in addition to the Bucher method to support the results.

In conclusion, the indirect comparison methods used in this analysis are widely published and take all the necessary precautions in order to ensure the randomisation is preserved. While this indirect comparison does not replace evidence from a head-to-head trial, this is currently the best evidence available as to the relative efficacy and safety of rivaroxaban versus dabigatran for these populations and these indications.

A7 page 20:
Please clarify the statement in section 5.1 that there are over 25,000 deaths due to VTE in England. Page 15 states that this figure includes all patients admitted for medical care of serious illness, not just those patients undergoing orthopaedic surgery

Each year there are approximately 25,000 deaths due to venous thromboembolism in England.[17] This figure includes both patients admitted for medical care of serious illnesses as well as those admitted for surgery. Patients undergoing major orthopaedic surgery, which includes hip and knee replacement, represent a group that is at particularly high risk for VTE (>40% without prophylaxis).[18]

Section B. Clarification on cost-effectiveness data

Please note. The page numbers are not consecutive as the issues should be addressed in a cumulative manner.

Please note that all of the requested model amendments were implemented in file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*. The results section of the submission has been updated based on this model and is provided in the attached document (See file: *Xarelto VTE Prevention_Results_Response to ERG Queries.doc).*

The following changes have been implemented:

1. The error identified on the outputs worksheet has been corrected
2. The cost of PTS has been amended to reflect the costs used by Caprini et al.
3. The utility of PTS has been amended to reflect the severity of PTS based on the proportions reported by Prandoni et al., and using the utility values reported by Lenert et al.
4. The efficacy and safety data has been amended to reflect the outcomes of the clinical trial regardless of statistical significance

These changes have been made cumulatively in response to the following issues:

B6 page number not applicable:
Please explain whether the following analysis does not constitute double counting? Cell J54 on the 'Outputs sheet' already contains the first 5 years of utility. In cell L31 lifetime and 0-5 years are added together.

This is an error in the model and has been corrected. Since the error applied equally to both arms, the incremental result remains similar.

B8 page 91:
Please note the following PTS costs discrepancies and adjust the cost of PTS in the model accordingly to reflect the proportion of severe and mild to moderate using the costs reported by Caprini et al or other relevant costs. The probability of developing PTS was taken from an Italian study, Prandoni et al. The study reported the cumulative incidence of severe PTS (23.5% of patients) and all PTS. The probabilities used in the model were taken from the 'all PTS' population and therefore includes a proportion of severe PTS. The cost of PTS is taken from an American study, MacDougall et al. and was estimated as £2865. However another American study by Caprini et al[1] reports that the cost of PTS is: mild to moderate $839 in the first year and $341 in subsequent years; severe PTS $3817 in the first year and $1677 in subsequent years. It would appear that the cost of PTS used in the model represents severe PTS whereas the probability of PTS is taken from a population with both mild to moderate and severe PTS. The opinion of the ERG is that the cost of PTS should reflect the severity of PTS.

The treatment protocol on which the costs reported by Caprini et al[19] are based does not take recurrent events such as recurrent ulcers into account, and may therefore be an underestimate of the actual cost. This cost was included as a sensitivity analysis, and in this analysis we did weight the costs for the proportion of patients with severe PTS and mild/moderate PTS based on Prandoni et al.[20] as outlined above.

MacDougall[21] – definition of PTS

In the study by MacDougall et al., PTS was defined as occurring after 90 days or longer following the documented DVT/PE index event, if the patient had both a procedure for extremity venous studies (Doppler waveform analysis, or venous plethysmography) and a clinical evaluation or management claim for one or more of the following: both pain (ICD729.5) and swelling of the limb (ICD 729.81) within seven days of each other; or varicose veins of the lower extremities (ICD 454.xx) or post-phlebetic syndrome (ICD 459.1); or other disorders of the circulatory system (ICD 459.8x).

Prandoni[20] – definition of PTS

The presence of leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and signs (pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness and pain during calf compression) was scored. For each item a score of 0 (= none or minimal) to 3 (= severe) was assigned. The presence of a lower limb venous ulcer was recorded. In patients with bilateral thrombosis the higher score was used. A total score of 15 or more on two consecutive check-ups or the presence of a venous ulcer indicated severe post-thrombotic syndrome, and a total score of 5 to 14 on two consecutive check-ups indicated mild post-thrombotic syndrome.

Caprini[19] – definition of PTS

The definition of PTS used in the model followed the clinical-etiologic-anatomic distribution-patho-physiologic (CEAP) dysfunction system. This system includes six classes:

0. No visible or palpable signs of venous disease
1. Telangiectases, reticular veins, malleolar flare
2. varicose veins
3. edema without skin changes
4. skin changes ascribed to venous disease
5. skin changes as described above with healed ulceration
6. skin changes as described above with active ulceration

Mild to moderate PTS refers to classes 1-4 and severe PTS refers to classes 5 and 6.

Based on the definitions of PTS in each of the studies above, the cost reported by MacDougall et al. doesn't just represent the cost of severe PTS. For example, they include clinical evaluation of varicose veins as PTS which is category 2 in Caprini's system of classification and would therefore be categorised as mild/moderate PTS. It is also worth noting that although the titles relating to the severity of PTS used by Caprini and Prandoni are the same, the definitions are in fact different.

However, the cost of diagnosis and treatment of PTS has been modified in the updated model (see file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*) as requested and now reflects the costs reported by Caprini et al. (inflated to current prices and converted to pounds) and weighted by the proportions reported by Prandoni et al.

B10 page 96:

Please adjust the PTS utility to reflect the severity of the PTS population taken from Prandoni et al. The utility of PTS is taken from Lenert et al and represents severe PTS. Both costs and utilities should reflect the severity of PTS in the population. Lenert et al also report utilities for mild/moderate.

The utility values have been modified as requested.

B15 page 86:
Please provide an updated model with results of the actual outcomes of the trials even if they were not statistically significant. In the base case analysis the following assumption was made 'If the results of the clinical trial or indirect comparison do not show any statistically significant difference between the two arms the model assumes parity between the two comparators'. Even if there is no statistically significant difference in an outcome in the trial, any difference could still make a difference to the cost-effectiveness results, especially if the outcome incurs high costs.

The trial outcomes have been included in the model regardless of whether they are statistically significant.

B17 page number not applicable:
Please provide a model with all the changes outlined above, together with a univariate and PSA analysis. Please provide tables of results including all sensitivity analysis.

Whilst reviewing the evidence and the data presented in the submission for dabigatran it has been noted that there is some evidence to suggest that patients who experience an asymptomatic VTE event are also at risk of PTS.[22] [23] In order to be conservative this assumption has not been included in our base case model. Some analyses including this assumption are included at the end of the revised results section.

Responses to all other issues are provided below. All sensitivity analyses presented in the following section have been run based on the updated model (*Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls)*

B1 page 86:
Please explain why the key assumption: 'All recurrent VTE events are DVTs' is a 'model simplifying assumption'

A VTE is a composite endpoint incorporating both a DVT and a PE. In the acute phase of the model we differentiate between these two conditions, with different costs and utility values assigned to each.

Continuation of this differentiation in the long-term complications model would have required the inclusion of two transitory health states (recurrent DVT and recurrent PE) instead of one (recurrent VTE) each of which would be associated with different costs and utility values. The rate of recurrent VTE was taken from Prandoni et al. (1997)[20] who do not report whether the VTE was a DVT or a PE. No other sources reporting the proportion of recurrent VTE which were a DVT or a PE were identified. In order to include this differentiation in the model we would therefore have had to make an assumption on this proportion.

It is acknowledged that the inclusion of two transitory health states instead of one would not have significantly over-complicated the model. However, since no data was identified with which to populate these health states, the inclusion of the additional state would have required an assumption regarding split between recurrent DVT and recurrent PE. Since rivaroxaban was associated with fewer VTE events, and would therefore be associated with fewer recurrent VTE events, the most conservative assumption in this instance would be to assume that all recurrent VTE events were DVTs since a DVT is associated with lower costs and higher quality of life when compared with a PE. Using this conservative assumption, the transitory health state for recurrent PE would be redundant. Therefore, in order to avoid including redundant health states (and the associated calculations) which would merely serve to complicate the model, only one transitory health state was included – that of recurrent VTE.

B2 page 94:
Please make clear where in the model (which cells) were used to adjust the utility for surgery in the first year.

These cells can be found on Inputs worksheet cell D98 for THR and cell E98 for TKR. The utility of other events occurring during the first year are linked to these cells and will therefore change automatically.

B3 page 94:
Please provide the evidence that all utility estimates have been identified and selected systematically. The NICE reference case requires that 'The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.' Please note that a review of cost-effectiveness literature will fail to find some utility studies.

Please refer to the report of the systematic literature review for utility values (Appendix 7 see file: *Xarelto VTE Prevention_STA form_appendices_confidential.doc)*

B4 page number not applicable:
Please explain the logic behind cell I147 on sheet 'Long term complications'.

The model assumes that patients undergo surgery at the start of year 1. Year 0 therefore represents the period before surgery (the utilities in this period are divided by 2 hence the total utility in this period is a 6 month utility). This is included in order to allow half cycle correction.

Cell I147 calculates the weighted utility of patients who had no long-term complications (i.e. recurrent VTE or PTS) in the first year post-surgery. The label should perhaps have read "utility with no long-term complications" instead of "Utility of no event".

The calculation in year 1 is different from subsequent years because some of those patients will have experienced a DVT or PE during the first three months of that year and would therefore have a lower annual utility.

Please note the utility is weighted by the proportion of the cohort in this health state. As a simple example, if the utility of this health state was 1 and 80% of the cohort was in this health state, the weighted utility would be 0.8. If we had one other health state for which the utility was 0.5, the weighted utility for that health state would be 0.5*(20%) = 0.1. Combining these utilities would give us a total annual utility for the cohort of 0.8*0.1 = 0.9.

The formula in cell I147 is:

=D103*DataFeed!$E$72+E103*DataFeed!$E$74+F103*DataFeed!$E$75

Where:

- D103 is the proportion of the cohort who had no VTE event during the first 3 months
- DataFeed!E72 is the annual utility of no VTE event (adjusted for surgery)

- E103 is the proportion of the cohort who experienced a DVT during the first 3 months post surgery but did not have any long-term complications in the first year
- DataFeed!E74 is the annual utility of having a DVT (adjusted for surgery and for the duration of DVT - as can be seen on the inputs worksheet [cell D100 and E100], the utility for having a DVT is applied for 3 months and the utility of no event for the remainder of the year.)

- F103 is the proportion of the cohort who experienced a PE during the first 3 months post surgery but did not have any long-term complications in the first year
- DataFeed!E75 is the annual utility of having a PE (adjusted for surgery and for the duration of PE treatment- as can be seen on the inputs worksheet [cell D101 and E101], the utility for having a PE is applied for 6 months and the utility of no event for the remainder of the year.)

By combining this utility value with the weighted utility of patients who had a PE (cells D147 and E147) and subtracting the weighted disutility of recurrent VTE (cell H147) we get the total (undiscounted) utility of the cohort in year 1 (cell J147).

B5 page number not applicable:
Please explain the logic behind cell I148-I151 on sheet 'Long term complications'.

These cells calculate the weighted utility of patients who had no long-term complications (i.e. recurrent VTE or PTS) in years 2 to 5.

The formula in cell I148 (which represents year 2) is:
=SUM(D104:F104)*DataFeed!$E$78

Where:
- Cell D104 is the proportion of the cohort still alive in year 2 who did not have an initial VTE event in the first 90 days post-surgery and are not therefore at risk of long-term complications
- Cell E104 is the proportion of the cohort still alive in year 2 who had a DVT in the 3 months post-surgery but did not develop any long-term complications
- Cell F104 is the proportion of the cohort still alive in year 2 who had a PE in the 3 months post-surgery but did not develop any long-term complications

The sum of these three cells gives us the proportion of the cohort still alive in year 2 which has not developed any long-term complications.

- DataFeed!E78 is the long-term utility for patients with no VTE event (i.e. the utility of the general population).

I148 therefore provides us with the weighted utility of patients with no long-term complications in year 2.

The same approach applies to years 3, 4 and 5.

B9 page 83:
Please provide a breakdown of the incremental costs and QALYs gained for every year of the lifetime scenario (base case) for both THR and TKR.

The total cost and utility breakdown for long-term complications rivaroxaban can be found on the long-term complications worksheet, cells N191:O228 while the breakdown for enoxaparin can be found on this worksheet in cells N234:O271. (See file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*)

The breakdown for every year of the lifetime scenario is shown in Table 3, Table 4 and Table 5.

Table 3 Submitted Analysis: Incremental cost and Utility Breakdown – RECORD 1

Year	Incremental cost	Incremental utility
0	£0.00	0
1	-£69.31	0.000334

2	-£1.11	0.000097
3	-£0.74	0.000083
4	-£0.74	0.000082
5	-£0.73	0.000080
6	-£0.57	0.000071
7	-£0.54	0.000067
8	-£0.51	0.000063
9	-£0.48	0.000059
10	-£0.45	0.000056
11	-£0.42	0.000052
12	-£0.39	0.000048
13	-£0.36	0.000045
14	-£0.33	0.000041
15	-£0.30	0.000038
16	-£0.28	0.000034
17	-£0.25	0.000031
18	-£0.22	0.000028
19	-£0.20	0.000025
20	-£0.18	0.000022
21	-£0.15	0.000019
22	-£0.13	0.000016
23	-£0.11	0.000014
24	-£0.09	0.000012
25	-£0.08	0.000010
26	-£0.06	0.000008
27	-£0.05	0.000006
28	-£0.04	0.000005
29	-£0.03	0.000003
30	-£0.02	0.000003
31	-£0.01	0.000002
32	-£0.01	0.000001
33	-£0.01	0.000001
34	£0.00	0.000001
35	£0.00	0.000000
36	£0.00	0.000000
37	£0.00	0.000000

Table 4 Submitted Analysis: Incremental cost and Utility Breakdown – RECORD 2

Year	Incremental cost	Incremental utility
0	£0.00	0
1	£35.11	0.001938
2	-£2.85	0.000904
3	-£1.84	0.000830
4	-£1.83	0.000796
5	-£1.82	0.000762
6	-£1.39	0.000707
7	-£1.31	0.000668
8	-£1.24	0.000630
9	-£1.16	0.000593
10	-£1.09	0.000556
11	-£1.02	0.000519

12	-£0.95	0.000482
13	-£0.88	0.000447
14	-£0.81	0.000411
15	-£0.74	0.000377
16	-£0.67	0.000343
17	-£0.61	0.000310
18	-£0.55	0.000278
19	-£0.49	0.000247
20	-£0.43	0.000218
21	-£0.37	0.000190
22	-£0.32	0.000164
23	-£0.27	0.000140
24	-£0.23	0.000116
25	-£0.19	0.000095
26	-£0.15	0.000076
27	-£0.12	0.000060
28	-£0.09	0.000046
29	-£0.07	0.000035
30	-£0.05	0.000025
31	-£0.04	0.000018
32	-£0.02	0.000012
33	-£0.02	0.000008
34	-£0.01	0.000005
35	-£0.01	0.000003
36	£0.00	0.000002
37	£0.00	0.000000

Table 5 Submitted Analysis: Incremental cost and Utility Breakdown – RECORD 3

Year	Incremental cost	Incremental utility
0	£0.00	0
1	-£57.49	0.000966
2	-£2.02	0.000114
3	-£1.29	0.000085
4	-£1.29	0.000086
5	-£1.28	0.000086
6	-£0.97	0.000070
7	-£0.92	0.000066
8	-£0.86	0.000062
9	-£0.81	0.000058
10	-£0.76	0.000055
11	-£0.71	0.000051
12	-£0.66	0.000047
13	-£0.61	0.000044
14	-£0.56	0.000040
15	-£0.52	0.000037
16	-£0.47	0.000034
17	-£0.42	0.000030
18	-£0.38	0.000027
19	-£0.34	0.000024
20	-£0.30	0.000021

21	-£0.26	0.000019
22	-£0.22	0.000016
23	-£0.19	0.000014
24	-£0.16	0.000011
25	-£0.13	0.000009
26	-£0.10	0.000007
27	-£0.08	0.000006
28	-£0.06	0.000005
29	-£0.05	0.000003
30	-£0.03	0.000002
31	-£0.02	0.000002
32	-£0.02	0.000001
33	-£0.01	0.000001
34	-£0.01	0.000000
35	£0.00	0.000000
36	£0.00	0.000000
37	£0.00	0.000000

B11 page 91:
Please could you explain how the assumption that 'the occurrence of new PTS or recurrent VTE is assumed to last for the first 5 years post-surgery' was made given that the ERG are aware of a number of studies that report rates of PTS and recurrent VTE, for patients that had experienced a DVT, over a period of 13 years.

The model structure was based on a literature review, and closely followed recommendations by Sullivan et al. (2003).[24] Sullivan et al. recommend that the timeframe of the chronic phase should be 90 days to 5 years, and in the conclusions section they state that:

"The outcomes and costs of VTE-related care should be conducted over a timeframe that extends over several years, taking into account both the acute (from surgery up to 3 months) and chronic (from month 4 up to 5 years) phases of the disease."

This is a conservative assumption since rivaroxaban has fewer VTE events than comparators, hence is associated with fewer long-term complications. Extending the risk of long-term complications up to 13 years would therefore be expected to improve the results for rivaroxaban.

The updated model (see file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*) gives the following results:

Table 6 Base case results (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£195.41	£278.92	-£83.51
QALY	10.36717	10.36572	0.0015

Table 7 Base case results RECORD 2

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£196.63	£196.67	-£0.04
QALY	10.36710	10.35408	0.0130

Table 8 Base case results RECORD 3

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£114.77	£196.95	-£82.17
QALY	10.30315	10.30104	0.0021

Prandoni et al. (1997) report the cumulative risk of PTS and recurrent VTE up to 8 years after a VTE. This information was combined with the 5 year risk to calculate the annual risk of an event in years 6, 7 and 8. It was then assumed that this risk continued up to year 13. To modify this assumption, please change the probability in cells E14:E21 and G14:G21 on the long-term complications worksheet. These cells have been coloured yellow.

Assuming the risk of long-term complications extends up to 13 years, the results areas follows (see file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_extended.xls*):

Table 9 Risk of long-term complications extended (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£195.63	£279.52	-£83.89
QALY	10.36715	10.36566	0.0015

Table 10 Risk of long-term complications extended (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£196.94	£198.10	-£1.17
QALY	10.36707	10.35396	0.0131

Table 11 Risk of long-term complications extended (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£115.34	£198.36	-£83.01
QALY	10.30310	10.30092	0.0022

As expected, increasing the risk of long-term complications up to 13 years increases the incremental cost and QALYs in favour of rivaroxaban. This increase is however relatively small.

B12 page 100:
Please explain how the Hull et al study was identified and provide a justification for its use. This study was used to estimate the proportion of post-discharge events.

The study by Hull et al. [25] was identified by means of a pragmatic literature review and has been used in other economic analyses including Sullivan et al (2004). This proportion is expected to have a minimal impact on the results since it only affects the cost of diagnosing a DVT or PE. Using updated model (see file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*) the base case results are:

Table 12 Base case results (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£195.41	£278.92	-£83.51
QALY	10.36717	10.36572	0.0015

Table 13 Base case results (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£196.63	£196.67	-£0.04
QALY	10.36710	10.35408	0.0130

Table 14 Base case results (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£114.77	£196.95	-£82.17
QALY	10.30315	10.30104	0.0021

If we assume that 0% of events occur post-discharge, the results are:

Table 15 Proportion of events occurring post-discharge: 0% (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£192.51	£275.92	-£83.41
QALY	10.36717	10.36572	0.0015

Table 16 Proportion of events occurring post-discharge: 0% (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£193.71	£193.45	£0.27
QALY	10.36710	10.35408	0.0130

Table 17 Proportion of events occurring post-discharge: 0% (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£111.96	£194.00	-£82.04
QALY	10.30315	10.30104	0.0021

And assuming that 100% events occur post-discharge, the results are:

Table 18 Proportion of events occurring post-discharge: 100% (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£204.61	£288.41	-£83.80
QALY	10.36717	10.36572	0.0015

Table 19 Proportion of events occurring post-discharge: 100% (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£205.87	£206.89	-£1.02
QALY	10.36710	10.35408	0.0130

Table 20 Proportion of events occurring post-discharge: 100% (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£123.69	£206.29	-£82.59
QALY	10.30315	10.30104	0.0021

As expected, the proportion of events occurring post-discharge has a minimal impact on the results.

B13 page 100:
Please explain how the studies used to inform the false positive rate of suspected DVT were identified and provide a justification for their use.

The false positive rate was obtained from previously published models which were identified in a systematic literature review. A significant proportion of the models identified included a false positive rate for DVT and PE, and of these the majority used a rate of 10% for DVT and 2% for PE.

These rates were used in several publications including Annemans et al. (2004); Botteman et al. (2002); Bjorvatn et al (2005); Drummond et al. (1994); Hawkins et al. (1998); Oster et al. (1987); Sullivan et al. (2004); and Sullivan et al. (2006).

This rate has been altered in a sensitivity analysis from 0 to 100%, and has minimal impact on the results. Using the updated model (see file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*) the base case results are:

Table 21 Base case results (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£195.41	£278.92	-£83.51
QALY	10.36717	10.36572	0.0015

Table 22 Base case results (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£196.63	£196.67	-£0.04
QALY	10.36710	10.35408	0.0130

Table 23 Base case results (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£114.77	£196.95	-£82.17
QALY	10.30315	10.30104	0.0021

Assuming a 0% probability of false positive diagnosis in either DVT or PE, the results are:

Table 24 Probability of false positive diagnosis: 0% (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£182.75	£266.59	-£83.84
QALY	10.36717	10.36572	0.0015

Table 25 Probability of false positive diagnosis: 0% (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£184.07	£185.06	-£0.99
QALY	10.36710	10.35408	0.0130

Table 26 Probability of false positive diagnosis: 0% (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£103.19	£186.55	-£83.35
QALY	10.30315	10.30104	0.0021

Assuming a false positive rate of 100% for both DVT and PE, the results are:

Table 27 Probability of false positive diagnosis: 100% (RECORD 1)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£469.47	£545.78	-£76.32
QALY	10.36717	10.36572	0.0015

Table 28 Probability of false positive diagnosis: 100% (RECORD 2)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£468.36	£447.88	£20.48
QALY	10.36710	10.35408	0.0130

Table 29 Probability of false positive diagnosis: 100% (RECORD 3)

	Rivaroxaban	Enoxaparin (Clexane)	Incremental
Cost	£365.37	£422.02	-£56.64
QALY	10.30315	10.30104	0.0021

A false positive diagnosis only applies to patients without a VTE event. Since rivaroxaban is associated with fewer VTE events, more rivaroxaban patients would be at risk of a false positive diagnosis. An increase in the probability of false positive diagnosis therefore has a larger impact on the rivaroxaban costs than on the enoxaparin costs.

B14 page 101
Please explain how the MacDougall et al study that was used to obtain the cost of treating PTS was identified and provide a justification for its use.

The cost of treating PTS was identified based on a pragmatic literature review which identified several estimates of the annual cost of treating PTS. The base case analysis was based on the median cost reported by MacDougall et al. (2006)[21]. This was used as this was the most recently published source. The authors of this study also reported that the mean annual cost of PTS was $11,667. As a conservative assumption this was not used in the base case analysis, however this value was used in sensitivity analysis in order to asses the impact on the results.

The cost of PTS used in the NICE analysis was based on a study by Bergqvist et al. (1997)[26] who conducted an observational study of patients who were diagnosed with a DVT or PE between 1970 and 1985 in a Swedish hospital. Patients were followed up for 10 to 15 years, and data on the use of health care resources due to complications or events related to VTE over this time was recorded. NICE use a cost of £4,000 for PTS based on this analysis, although it is not clear exactly how this value was calculated. A sensitivity analysis was run using an annual cost of PTS of £278.89 (£4000 inflated to current prices and divided by 15).

Caprini et al. (2003)[19] estimated the costs of diagnosis and treatment of PTS based on patient care protocols defined by the literature and applying US-specific costs. The authors estimated a cost per year for treating mild/moderate PTS of $839 in the first year and $341 in subsequent years, while the cost per year for treating severe PTS is $3817 in the first year and $933 in subsequent years. The difference between the first and subsequent years was assumed to be the cost of diagnosis. These costs were inflated to current prices, converted to pounds and used in the sensitivity analysis. These costs were not used in the base case analysis since the treatment protocol on which these costs are based does not take recurrent events such as recurrent ulcers into account, and may therefore be an underestimate of the actual cost.

In response to comment B8, the cost of PTS from McDougall has been replaced with the cost of diagnosis and treatment from Caprini et al (2003) in the updated model (see file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*).

B16 page 86:
Please provide a list of all outcome event rates used in this sensitivity analysis and to provide an updated model with these rates in use. Please could you also repeat the PSA with trial data for all trial outcomes included in the model with the trial reported uncertainty? The submission states that the sensitivity analysis included a scenario where actual rates were used regardless of the trial findings and it is not clear which outcomes this applied to.

This applies to all of the outcomes obtained from the clinical trial – i.e. prophylaxis related major bleeding, total VTE, symptomatic VTE, non-fatal PE and fatal PE. In the base case analysis if the direct comparison did not identify any statistically significant difference in any of these outcomes, we assumed no difference and so the rivaroxaban probability was used in both arms.

In the sensitivity analysis referred to above, the probabilities used were exactly as observed in the relevant RECORD trial. A version of the model has been provided with these in use. See file: *Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA.xls*

Table 30 Probability of events during prophylaxis period

	Rivaroxaban	Enoxaparin (submitted base case)	Enoxaparin (as per trial)
RECORD 1			
Prophylaxis related major bleeding	0.0027	0.0027*	0.0009
Total VTE	0.0113	0.0372	0.0372
Symptomatic VTE	0.0027	0.0027*	0.0050
Non-fatal PE	0.0025	0.0025*	0.0005
Fatal PE	[redacted]	[redacted]	[redacted]
RECORD 2			
Prophylaxis related major bleeding	0.0008	0.0008*	0.0008
Total VTE	0.0197	0.0197	0.0937
Symptomatic VTE	0.0025	0.0124	0.0124
Non-fatal PE	0.0012	0.0012*	0.0042
Fatal PE	[redacted]	[redacted]	[redacted]
RECORD 3			
Prophylaxis related major bleeding	0.0057	0.0057	0.0049
Total VTE	0.0959	0.1880*	0.1880
Symptomatic VTE	0.0067	0.0067*	0.0196
Non-fatal PE	0.0000	0.0000*	0.0050
Fatal PE	[redacted]	[redacted]	[redacted]

*difference between rivaroxaban and enoxaparin is not statistically significant

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