Response to Venous thromboembolism (knees and hips) - apixaban (clarification letter)

24th August 2011

Section A: Clarification on effectiveness data

A1 **Priority request:** Please provide a complete set of data for all comparisons of all outcomes estimated using Winbugs. This should be in a format that can be run immediately (i.e. without any editing) in WinBUGs. It also should be accompanied by a complete set of comments showing the study from which the data was obtained. This will enable the ERG to check the results of the mixed treatment comparison (MTC).

Response:
This dataset was not available by the deadline of the 24th August but will be provided by the 31st August.

A2 **Priority request:** Please provide, for THR and TKR, an overview of the studies used in the indirect comparison and, separately, in the MTC for group 2. Please provide justification if any studies are excluded from these analyses.

Response:
Adjusted indirect comparison
For the adjusted indirect comparison, 11 studies (ADVANCE-3, Lassen 2002, Turpie 2002, ADVANCE-2, RECORD 3, RE-MODEL, APROPOS, ADVANCE 1, RECORD 4, RE-MOBILIZE, Bauer 2001) were included in the group 2 (pooling of enoxaparin 40 mg od + 30mg dose trials) analyses. For inclusion in this analysis, studies within each orthopaedic surgery population had to compare against **either** enoxaparin 40mg od **or** enoxaparin 30 mg bd. For the THR population there were two fondaparinux 2.5mg od studies eligible for pooling:

- Lassen 2002 vs. enoxaparin 40 mg od and Turpie 2002 comparing against enoxaparin 30 mg bd.

However, there were no apixaban, dabigatran or rivaroxaban studies comparing against enoxaparin 30 mg bd in the THR population. The data allowed for an indirect comparison between apixaban (ADVANCE-3: vs. enoxaparin 40 mg) and the two fondaparinux studies, with the pooled enoxaparin dose group being the common comparator.
For the TKR population there were seven studies eligible for pooling of enoxaparin doses:

- Three apixaban 2.5 mg od studies (APROPOS vs. enoxaparin 30 mg bd, ADVANCE 1 vs. enoxaparin 30 mg bd, ADVANCE-2 vs. enoxaparin 40 mg od)
- Two rivaroxaban 10 mg od studies (RECORD 3 vs. enoxaparin 40 mg od, RECORD 4 vs. enoxaparin 30 mg bd)
- Two dabigatran 220 mg od studies (RE-MODEL vs. enoxaprin 40 mg od and RE-MOBILIZE vs. enoxaparin 30 mg bd)

The data allowed for adjusted indirect comparisons for 1) apixaban vs. rivaroxaban, 2) apixaban vs. dabigatran, and 3) apixaban vs. fondaparinux (the latter made viable by a study of fondaparinux vs. enoxaparin 30 mg bd [Bauer 2001]). A list of the studies included in the group 2 adjusted indirect comparison are presented in the table below (adapted from Table 28 in section 5 of the main submission document), and in the two diagrams below from appendix 15.

Table 1: Studies eligible for inclusion in the group 2 adjusted indirect comparison (pooling of enoxaparin 40 mg od + 30mg dose trials) analyses

Group 2 adjusted indirect comparisons					
Total Hip Replacement (THR)			**Total Knee Replacement (TKR)**		
Study	**Treatment**	**Comparison**	**Study**	**Treatment**	**Comparison**
ADVANCE-3	Apixaban 2.5 mg bd	Enoxaparin 40 mg od	ADVANCE-2	Apixaban 2.5 mg bd	Enoxaparin 40 mg od
			RECORD 3	Rivaroxaban 10 mg od	Enoxaparin 40 mg od
			RE-MODEL	Dabigatran 220 mg od	Enoxaparin 40 mg od
			APROPOS	Apixaban 2.5 mg bd	Enoxaparin 30 mg bd
			ADVANCE 1	Apixaban 2.5 mg bd	Enoxaparin 30 mg bd
Lassen 2002	Fondaparinux 2.5 mg od	Enoxaparin 40 mg od	RECORD 4	Rivaroxaban 10 mg od	Enoxaparin 30 mg bd
Turpie 2002	Fondaparinux 2.5 mg od	Enoxaparin 30 mg bd	RE-MOBILIZE	Dabigatran 220 mg od	Enoxaparin 30 mg bd
			Bauer 2001	Fondaparinux 2.5 mg od	Enoxaparin 30 mg bd

Diagram 1: THR RCTs included in the combined enoxaparin 30 mg bd + 40 mg od adjusted indirect comparison

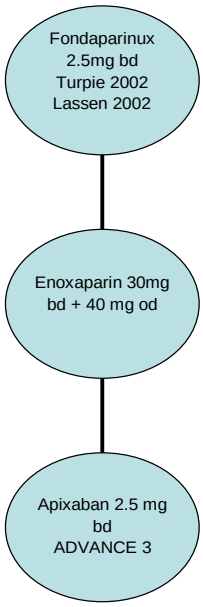
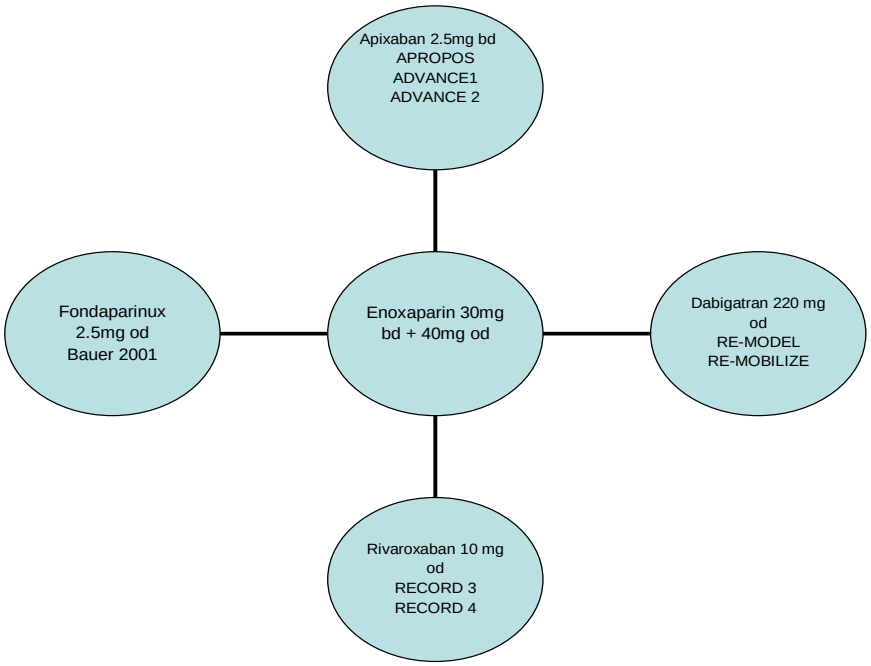


Diagram 2: TKR RCTs included in the combined enoxaparin 30 mg bd + 40 mg od adjusted indirect comparison



Mixed treatment comparison (MTC)
For the MTC group 2 analysis (pooling of enoxaparin 40 mg od + 30mg dose trials), Table 2 below displays the trials eligible for the THR and TKR populations.

THR population
Twenty-seven studies in Table 2, section A were potentially eligible for the THR group 2 analysis (24 studies were finally included), and of these, 22 included a comparison to enoxaparin 40 mg od or 30 mg bd, or both doses of enoxaparin. Of the remaining 5 studies, none included an enoxaparin comparator arm. Studies with treatment doses in **bold** (Table 2) are directly relevant to the group 2 MTC analyses. Although 13/27 studies (BISTRO II, Eriksson 1997, Eriksson 2006, Fuji 2008a (Hip trial), Levine 1991, Mouret 2010, Pentathlon 2001, Planes 1990 trial 2, Planes 1990 trial 3, Planes 1998, Samama 1997, Spiro 1994, Turpie 1990) did not investigate UK or US license doses of apixaban, rivaroxaban, dabigatran and fondaparinux, they were included in the MTC for the enoxaparin treatment arms (40 mg od or 30 mg bd). Note that for trials of relevant treatments (e.g. enoxaparin 40 mg od) vs. other comparator treatments outside the NICE scope for apixaban (e.g. semuloparin), the latter were entered into the network, but played no further part in the generation of results. Placebo comparisons were also included in the MTC. The 13 studies without UK or US license doses of apixaban, rivaroxaban, dabigatran and fondaparinux were excluded from the THR adjusted indirect comparisons since they did not include head-to-head comparisons of treatments relevant to the NICE scope for apixaban.

Although included in the MTC, one study of rivaroxaban 10mg od (ODIXa-HIP Study [1]) in the THR population was excluded from the adjusted indirect comparison analyses, since the duration of treatment for both the rivaroxaban and enoxparin 40mg od treatment arms was 5-9 days. This is shorter than the UK licensed dose duration recommended for either therapy in the THR population, and that recommended by NICE, and in particular is likely to result in an underestimate of the treatment effect of rivaroxaban 10mg od in this population. Note that this trial could not be included in the group 2 adjusted indirect comparison anyway since there were no rivaroxaban trials in the THR population that compared against enoxaparin 30 mg bd. Enoxaparin was the only LMWH considered for inclusion in the adjusted indirect comparison analyses, as it is the most widely used LMWH VTE prophylaxis option in the UK for the THR and TKR populations. However, in the MTC group 2 analyses, trials of other LMWHs were included provided they investigated UK license doses. Therefore studies with tinzeparin (Planes 1999 (Equivalence)) and dalteparin (Torholm, 1991) arms were included in the MTC as relevant comparators and results are reported for these where available.

Of the 5 studies that did not include an enoxaparin comparator arm, three (highlighted in red in section A in Table 2 below) were excluded from the MTC. Eriksson 1991 dropped out of the any DVT network as the study was unconnected to any other treatments, and was not used in the major bleeding MTC, since the definition of major/serious bleed was not consistent with the main ISTH major bleed criteria.The study did not report any other outcomes that could be included in an MTC. Hull 2000 dropped out of all networks as the study could not be connected to any other treatments. Kakkar 2000 dropped out of the any DVT network as it was unconnected to any other treatments, and was not used in the major bleeding MTC, since the definition of major/serious bleed was not consistent with the main ISTH major bleed criteria. The study did not report any other outcomes that could be included in an MTC. Fuji 2008b (Fondaparinux trial) included a comparison of fondaparinux 2.5 mg od vs. placebo, and Torholm 1991 compared dalteparin 2500 or

5000 IU od vs. placebo. These were connected in the MTC analyses since they allowed for an indirect comparison with the placebo-controlled enoxaparin trials in the networks (Fuji 2008a Hip trial, Samana 1997, Turpie 1990). Note that for Torholm 1991, the MTC results were not reported as the dose range of dalteparin in this study was not the exact UK licensed dose, i.e. 5000 IU. These 5 studies were excluded from the adjusted indirect comparison since they did not include head-to-head comparisons of treatments relevant to the NICE scope for apixaban.

TKR population

Seventeen studies in Table 2, section B were potentially eligible for the TKR group 2 analysis (all were finally included), and of these, 16 included a comparison to enoxaparin 40 mg od or 30 mg bd, or both doses of enoxaparin. One additional study (Fuji 2008b (Fondaparinux trial)) included a comparison of fondaparinux 2.5mg od to placebo and was included in the MTC analyses since it allowed for an indirect comparison with the other placebo-controlled enoxaparin trials in the TKR networks (Leclerc 1992, Fuji 2008a (Knee trial)).

Studies with treatment doses in **bold** (Table 2) are directly relevant to the group 2 MTC analyses. Although 7/17 studies did not investigate UK or US license doses of apixaban, rivaroxaban, dabigatran and fondaparinux (BISTRO II trial, Fuji 2008a (Knee trial), Lassen 2009b, Lassen 2010b, Leclerc 1992, Leclerc 1996, Turpie 2005), they were included in the MTC for the enoxaparin treatment arms (40 mg od or 30 mg bd). Note that for trials of relevant treatments (e.g. enoxaparin 40 mg od) vs. other comparator treatments outside the NICE scope for apixaban (e.g. semuloparin), the latter were entered into the network, but played no further part in the generation of results. Placebo comparisons were also included in the MTC.

Note that the 7 studies without UK or US license doses of apixaban, rivaroxaban, dabigatran and fondaparinux were excluded from the adjusted indirect comparisons since they did not include head-to-head comparisons of treatments relevant to the NICE scope for apixaban. In addition, Fuji 2008b (Fondaparinux trial) was excluded from the adjusted indirect comparison since it compared against placebo, rather than enoxaparin 40 mg od or 30 mg bd. In the MTC group 2 analyses, trials of other LMWHs besides enoxaparin were included provided they investigated UK license doses. Navarro-Quilis 2003 compared bemiparin 3500 IU vs. enoxaparin 40 mg od and was included in the MTC, but excluded from the adjusted indirect comparison since enoxaparin was the only LMWH considered for inclusion in the latter analyses, as it is the most widely used LMWH VTE prophylaxis option in the UK for the THR and TKR populations.

Table 2: Trials included in the THR and TKR group 2 MTCs

No.	Study	Surgery	Treatment arm
Section A – THR trials included in the group 2 MTC			
1	ADVANCE-3	THR	**Apixaban 2.5 mg bd**
	ADVANCE-3	THR	**Enoxaparin 40 mg od**
2	BISTRO II Trial	THR	Dabigatran etexilate 150 mg bd

	BISTRO II Trial	THR	Dabigatran etexilate 225 mg bd
	BISTRO II Trial	THR	Dabigatran etexilate 300 mg od
	BISTRO II Trial	THR	Dabigatran etexilate 50 mg bd
	BISTRO II Trial	THR	**Enoxaparin 40 mg od**
3	Eriksson 1997	THR	Desirudin 15 mg bd
	Eriksson 1997	THR	**Enoxaparin 40 mg od**
4	Eriksson 2006	THR	**Enoxaparin 40 mg od**
	Eriksson 2006	THR	Rivaroxaban 10 mg bd
	Eriksson 2006	THR	Rivaroxaban 2.5 mg bd
	Eriksson 2006	THR	Rivaroxaban 20 mg bd
	Eriksson 2006	THR	Rivaroxaban 30 mg bd
	Eriksson 2006	THR	Rivaroxaban 5 mg bd
5	Fuji 2008a (Hip trial)	THR	Enoxaparin 20 mg bd
	Fuji 2008a (Hip trial)	THR	Enoxaparin 20 mg od
	Fuji 2008a (Hip trial)	THR	**Enoxaparin 40 mg od**
	Fuji 2008a (Hip trial)	THR	Placebo
6	Huo 2010 (RENOVATE 2)	THR	**Dabigatran etexilate 220 mg od**
	Huo 2010 (RENOVATE 2)	THR	**Enoxaparin 40 mg od**
7	Lassen 2002	THR	**Enoxaparin 40 mg od**
	Lassen 2002	THR	**Fondaparinux 2.5 mg od**
8	Levine 1991	THR	**Enoxaparin 30 mg bd**
	Levine 1991	THR	Heparin 7500 IU bd
9	Mouret 2010	THR	**Enoxaparin 40 mg od**
	Mouret 2010	THR	Semuloparin 20 mg od
10	ODIXa-HIP Study	THR	**Enoxaparin 40 mg od**
	ODIXa-HIP Study	THR	**Rivaroxaban 10 mg od**
	ODIXa-HIP Study	THR	Rivaroxaban 20 mg od
	ODIXa-HIP Study	THR	Rivaroxaban 30 mg od
	ODIXa-HIP Study	THR	Rivaroxaban 40 mg od
	ODIXa-HIP Study	THR	Rivaroxaban 5 mg od
11.	Pentathlon 2001	THR	**Enoxaparin 30 mg bd**
	Pentathlon 2001	THR	Fondaparinux 0.75 mg od
	Pentathlon 2001	THR	Fondaparinux 1.5 mg od
	Pentathlon 2001	THR	Fondaparinux 3 mg od
	Pentathlon 2001	THR	Fondaparinux 6 mg od
	Pentathlon 2001	THR	Fondaparinux 8 mg od
12	Planes 1990 TRIAL 2	THR	Enoxaparin 20 mg bd
	Planes 1990 TRIAL 2	THR	**Enoxaparin 40 mg od**
13	Planes 1990 TRIAL 3	THR	**Enoxaparin 40 mg od**
	Planes 1990 TRIAL 3	THR	Unfractionated heparin 5000 IU od
14	Planes 1998	THR	**Enoxaparin 40 mg od**
	Planes 1998	THR	Reviparin 4200 IU od
15	Planes 1999 (Equivalence)	THR	**Enoxaparin 40 mg od**
	Planes 1999 (Equivalence)	THR	**Tinzaparin 4500 IU od**
16	RECORD 1	THR	**Enoxaparin 40 mg od**

	RECORD 1	THR	**Rivaroxaban 10 mg od**
17	RECORD 2	THR	**Enoxaparin 40 mg od**
	RECORD 2	THR	**Rivaroxaban 10 mg od**
18	RE-NOVATE	THR	Dabigatran etexilate 150 mg od
	RE-NOVATE	THR	**Dabigatran etexilate 220 mg od**
	RE-NOVATE	THR	**Enoxaparin 40 mg od**
19	Samama 1997	THR	**Enoxaparin 40 mg od**
	Samama 1997	THR	Placebo
20	Spiro 1994	THR	Enoxaparin 10 mg od
	Spiro 1994	THR	**Enoxaparin 30 mg bd**
	Spiro 1994	THR	**Enoxaparin 40 mg od**
21	Turpie 1990	THR	**Enoxaparin 30 mg bd**
	Turpie 1990	THR	Placebo
22	Turpie 2002	THR	**Enoxaparin 30 mg bd**
	Turpie 2002	THR	**Fondaparinux 2.5 mg od**
23	Eriksson 1991	THR	Dalteparin 5000 IU
	Eriksson 1991	THR	Unfractionated heparin 5000 IU od
24	Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 0.75 mg od
	Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 1.5 mg od
	Fuji 2008b (Fondaparinux trial)	THR	**Fondaparinux 2.5 mg od**
	Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 3 mg od
	Fuji 2008b (Fondaparinux trial)	THR	Placebo
25	Hull 2000	THR	Dalteparin 5000 IU
	Hull 2000	THR	Preop dalteparin 2500 IU-5000IU od
	Hull 2000	THR	Warfarin 10mg od
26	Kakkar 2000	THR	Bemiparin 3500 IU
	Kakkar 2000	THR	Unfractionated Heparin 5000 IU bd
27	Torholm 1991	THR	**Dalteparin 2500 or 5000 IU od**
	Torholm 1991	THR	Placebo
Section B: TKR trials included in the group 2 MTC			
1	Bauer, 2001 (Pentamks)	TKR	**Fondaparinux 2.5 mg od**
	Bauer, 2001 (Pentamks)	TKR	**Enoxaparin 30 mg bd**
2	BISTRO II Trial	TKR	Dabigatran etexilate 150 mg bd
	BISTRO II Trial	TKR	Dabigatran etexilate 225 mg bd
	BISTRO II Trial	TKR	Dabigatran etexilate 300 mg od
	BISTRO II Trial	TKR	Dabigatran etexilate 50 mg bd
	BISTRO II Trial	TKR	**Enoxaparin 40 mg od**
3	Fuji 2008a (Knee trial)	TKR	Enoxaparin 20 mg bd

	Fuji 2008a (Knee trial)	TKR	Enoxaparin 20 mg od
	Fuji 2008a (Knee trial)	TKR	**Enoxaparin 40 mg od**
	Fuji 2008a (Knee trial)	TKR	Placebo
4	Lassen 2007 (APROPOS)	TKR	Apixaban 10 mg bd
	Lassen 2007 (APROPOS)	TKR	Apixaban 10 mg od
	Lassen 2007 (APROPOS)	TKR	**Apixaban 2.5 mg bd**
	Lassen 2007 (APROPOS)	TKR	Apixaban 20 mg od
	Lassen 2007 (APROPOS)	TKR	Apixaban 5 mg bd
	Lassen 2007 (APROPOS)	TKR	Apixaban 5 mg od
	Lassen 2007 (APROPOS)	TKR	**Enoxaparin 30 mg bd**
	Lassen 2007 (APROPOS)	TKR	Warfarin (adjusted-dose)
5	Lassen 2009a (ADVANCE-1)	TKR	**Apixaban 2.5 mg bd**
	Lassen 2009a (ADVANCE-1)	TKR	**Enoxaparin 30 mg bd**
6	Lassen 2009b	TKR	**Enoxaparin 40 mg od**
	Lassen 2009b	TKR	Semuloparin 10 mg od
	Lassen 2009b	TKR	Semuloparin 20 mg od
	Lassen 2009b	TKR	Semuloparin 40 mg od
	Lassen 2009b	TKR	Semuloparin 5 mg od
	Lassen 2009b	TKR	Semuloparin 60 mg od
7	Lassen 2010 (ADVANCE-2)	TKR	**Apixaban 2.5 mg bd**
	Lassen 2010 (ADVANCE-2)	TKR	**Enoxaparin 40 mg od**
8	Lassen, 2010b	TKR	**Enoxaparin 30 mg bd**
	Lassen, 2010b	TKR	Semuloparin 20 mg od
9	Leclerc 1992	TKR	**Enoxaparin 30 mg bd**
	Leclerc 1992	TKR	Placebo
10	Leclerc 1996	TKR	**Enoxaparin 30 mg bd**
	Leclerc 1996	TKR	Warfarin (adjusted-dose)
11	Navarro-Quilis 2003	TKR	**Bemiparin 3500 IU**
	Navarro-Quilis 2003	TKR	**Enoxaparin 40 mg od**
12	RECORD 3	TKR	**Enoxaparin 40 mg od**
	RECORD 3	TKR	**Rivaroxaban 10 mg od**
13	RECORD 4	TKR	**Enoxaparin 30 mg bd**
	RECORD 4	TKR	**Rivaroxaban 10 mg od**
14	RE-MOBILIZE	TKR	Dabigatran etexilate 150 mg od
	RE-MOBILIZE	TKR	**Dabigatran etexilate 220 mg od**
	RE-MOBILIZE	TKR	**Enoxaparin 30 mg bd**
15	RE-MODEL	TKR	Dabigatran etexilate 150 mg od
	RE-MODEL	TKR	**Dabigatran etexilate 220 mg od**
	RE-MODEL	TKR	**Enoxaparin 40 mg od**
16	Turpie 2005	TKR	**Enoxaparin 30 mg bd**
	Turpie 2005	TKR	Rivaroxaban 10 mg bd
	Turpie 2005	TKR	Rivaroxaban 2.5 mg bd
	Turpie 2005	TKR	Rivaroxaban 20 mg bd
	Turpie 2005	TKR	Rivaroxaban 30 mg bd
	Turpie 2005	TKR	Rivaroxaban 5 mg bd
17	Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 0.75 mg od

	Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 1.5 mg od
	Fuji 2008b (Fondaparinux trial)	TKR	**Fondaparinux 2.5 mg od**
	Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 3 mg od
	Fuji 2008b (Fondaparinux trial)	TKR	Placebo

A3 **Priority request:** It is expected that the MTC and the indirect comparisons should produce the same results given that all three comparisons are estimated via the same common comparator, which is enoxaparin 40mg od i.e. there are no head to head comparisons between these comparators. Please explain why the results for the MTC are different from the results of the indirect comparisons for apixaban 2.5mg bd with the other comparators, dabigatran 220mg od and rivaroxaban 10mg od.

Response:
Table 3 below displays the results from the base case adjusted indirect comparison (vs. enoxaparin 40 mg od) for the THR and THR populations juxtaposed with the MTC group 1 for all outcomes for which it was possible to run an MTC. For the comparison of apixaban vs. rivaroxaban 10 mg od the results of the adjusted indirect comparison and MTC are consistent across all outcomes. For the comparison of apixaban vs. dabigatran 220 mg od the results of the adjusted indirect comparison and MTC were inconsistent across 3 outcomes (VTE composite, Any DVT, and asymptomatic DVT), but were consistent across all others (see Table 3 below - the inconsistencies are highlighted in red). In the case of these 3 outcomes, while the point estimates from the adjusted indirect comparison and the MTC were very similar, the latter displayed wider credibility intervals (i.e. increased uncertainty) which resulted in no statistically significant between-treatment differences. In contrast the adjusted indirect comparison displayed narrower confidence intervals on these 3 outcomes which resulted in statistically significant differences favouring apixaban. Table 3 indicates that in general the MTC results displayed wider credibility intervals for all outcomes and treatments in comparison to the confidence intervals displayed in the adjusted indirect comparisons. The MTC results therefore displayed more uncertainty around the point estimates than the adjusted indirect comparison.

Table 3: Base case adjusted indirect comparison (vs. enoxaparin 40 mg od) and group 1 MTC results

Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd				
	Total hip replacement (THR)		**Total knee replacement (TKR)**	
VTE composite (primary efficacy analysis)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban				
Dabigatran				
Any DVT (primary efficacy analysis)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban	0.709 (0.304-1.652)	0.698 (0.133-3.698)	0.895 (0.621-1.294)	0.857 (0.319-2.773)

Dabigatran	2.63 (1.402-4.931)	2.601 (0.5151-13.1)	1.772 (1.258-2.498)	1.83 (0.513-9.639)
Asymp DVT (primary efficacy analysis)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban	N/A	N/A	N/A	0.808 (0.073-12.35)*
Dabigatran	2.244 (1.172-4.297)	2.25 (0.064-76.4)	1.865 (1.32-2.635)	1.848 (0.103-34.11)
Any bleeding (ITT)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban				
Dabigatran				
Major bleeding (ITT)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban				
Dabigatran				
CRNM bleed (ITT)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban				
Dabigatran				
Minor bleed (ITT)	**IC**	**MTC**	**IC**	**MTC**
Rivaroxaban	1.099 (0.787-1.534)	1.191 (0.061-23.186)	1.064 (0.617-1.834)	1.142 (0.441-2.996)
Dabigatran	1.044 (0.705-1.547)	1.04 (0.034-37.94)	0.915 (0.54-1.549)	0.048 (0.025-0.088)

*derived from RECORD 4 (vs. enoxaparin 30 mg bd)

The explanation for this inconsistency between the indirect comparison and the MTC has already been outlined in section 5.7.9 of the submission document, viz. that the wider credibility intervals in the MTC may be due to the large number of trials contributing to the enoxaparin 40mg od node within the MTC network in addition to the trial sub-set included in the adjusted indirect comparison. The former tended to 1) be older (see Table 5 below), 2) have fewer study quality criteria reported (see Table 5 below), 3) have fewer participants (mean number per arm N=184, see Table 7 below), and 4) compare enoxaparin 40mg od against treatments not within the NICE STA scope for apixaban (see Table 2 above, and response to priority item 2), compared to the adjusted indirect comparison sub-set. These factors could have contributed to a lack of precision and an increase in uncertainty (i.e. wider credibility intervals) in the relative treatment effects for enoxaparin 40 mg od observed in the MTC results, despite the apparent increase in power (i.e. more eligible studies) afforded by the MTC study inclusion criteria.

The adjusted indirect comparison necessarily restricted the number of studies for inclusion to those possessing a common comparator (enoxaparin 40 mg od in the main analysis), which may have allowed for more precision in the relative treatment effect estimates of interest to the submission in this instance. This sub-set of studies tended to report and fulfil more study quality criteria (see Table 4 below), have more participants (mean number per arm N=570, see Table 6 below), and reported similar outcome definitions and measures (see appendices 3 and 5 of the submission), although there was inconsistency across the comparators of interest on some bleeding outcomes (see Table 31 and Table 32**Error! Reference source not found.** of the submission).

Table 4: Quality overview of subset of the 15 studies included in the adjusted indirect comparisons (vs. enoxaparin 40 mg od; vs. enoxaparin 30 mg bd) and MTC

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
ADVANCE-1 Lassen, 2009a	Adequate: independent, blinded adjudication committee	Adequate: interactive telephone system	Double-blind, identical placebo tablets/injections	Adequate: no venography and protocol violations
ADVANCE-2 Lassen, 2010a	Adequate: central system	Adequate: schedule was generated by randomization center using SAS and was stratified by study site with a block size of four	Double-blind, interactive central telephone system	Adequate: no venography
ADVANCE-3 Lassen, 2010 Manuscript	Adequate: central system	Adequate: schedule was generated by randomization center using SAS and was stratified by study site with a block size of four	Double-blind, interactive central telephone system	Adequate: no venography and protocol violations
APROPOS Lassen, 2007	Adequate: central system	Adequate: Computer generated allocation	Double-blind: Mixed; apixaban and enoxaparin administered in double-dummy fashion; Warfarin, open label	Adequate: no venography and protocol violations
Bauer, 2001 (Pentamks)	Adequate: Central system	Adequate: Central computer-generated	Double-blind: double-dummy fashion	Adequate: no venography and protocol violations
Huo Michael, 2010 Abstract (RENOVATE 2)	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Unclear, not reported
Lassen, 2002	Adequate: central independent committee blinded to treatment allocation	Adequate: Computer generated allocation	Double-blind, placebo was matched to volume with enoxaparin and/or fondaparinux were identical	Adequate: no venography and inappropriate surgery

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
RECORD 1 Eriksson, 2008	Adequate: central independent committee blinded to treatment allocation	Adequate: Computer generated allocation	Double-blind, no details on blinding method reported	Adequate: no venography
RECORD 2 Kakkar, 2008	Adequate: central independent committee blinded to treatment allocation	Adequate: Computer generated allocation	Double-blind, no details on blinding method reported	Adequate: no intake of study medication
RECORD 3 Lassen, 2008	Adequate: central independent committee blinded to treatment allocation	Adequate: Central telephone system	Double-blind, double-dummy; no details on blinding method reported	Adequate: no venography
RECORD 4 Turpie, 2009	Adequate: central independent committee masked to treatment allocation	Adequate: Central telephone system	Double-blind, double-dummy; identical placebo formulations were given	Adequate: no intake of study medication
RE-MOBILIZE Ginsberg, 2009	Adequate: independent committee masked to treatment allocation	Adequate: centralised via interactive voice response system	Double-blind, double-dummy; identical placebo formulations were given	Adequate: no intake of study medication, AEs, non-compliance, consent.
RE-MODEL Eriksson, 2007	Adequate: independent committee masked to treatment allocation	Adequate: Computer generated allocation	Double-blind, medications were identical; identical placebo	Adequate: no venography
RE-NOVATE Eriksson, 2007	Adequate: independent central adjudication committee masked to treatment allocation	Adequate: Central computer generated allocation	Double-blind, medications were identical	Adequate: not treated, no surgery, no venography

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
Turpie, 2002	Unclear, not reported	Adequate: Computer generated allocation	Double-blind, no details on blinding method reported	Adequate: consent, AEs and inclusion criteria

Table 5: Quality overview of the 25 additional studies included only in the MTC

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
BISTRO-II Erikson, 2005 (2 studies: hip and knee)	Adequate	Adequate: Computer generated allocation	Double-blind, no details on blinding method reported	Adequate: no venography
Eriksson, 1997	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Adequate: no venography and protocol violations
Eriksson, 2006a	Adequate: blinded independent monitors	Unclear; no description of method of randomisation	Double-blind, medications were identical	Adequate: no venography
Fuji, 2008a	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Adequate; dropouts and missing or defective evaluation of VTE
Fuji, 2008b FONDAPARINUX Trial (2 studies: hip and knee)	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported; but reported Investigators/evaluation was blinded	Unclear
Lassen, 2009b	Adequate: independent, blinded adjudication committee	Adequate: centralised via interactive voice response system	Double-blind, no details on blinding method reported	Adequate: premature discontinuation, study medication
Lassen, 2010b Abstract	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Unclear
Leclerc, 1992	Adequate: independent, blinded adjudication committee	Adequate: Computer generated allocation	Double-blind, medications were identical	Adequate; previous VTE, age, allergy, peptic ulcer, informed consent

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
Leclerc, 1996	Adequate: central independent committee	Adequate: Computer generated allocation	Double-blind, sham treatment, central committee unaware of treatment allocation	Adequate: no venography, refusal, embolism
Levine, 1991	Adequate: central independent committee	Unclear; no description of method of randomisation	Double-blind, confounding factors were not available during study period to maintain blinding	Adequate: allergy, refusal, embolism
Mouret, 2010 Abstract	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Unclear, not reported
Navarro-Quilis, 2003	Adequate: independent statistical center	Adequate: Computer generated allocation	Double-blind, medications were identical	Adequate: no venography
ODIXa-HIP Eriksson, 2006	Adequate: double dummy, central independent committee	Unclear; no description of method of randomisation	Double-blind, double-dummy: matching medication	Adequate: no venography
PENTATHLON Turpie, 2001	Adequate: central independent committee	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Unclear, not reported
Planes, 1990 (Two studies: Trial 2 and Trial 3)	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Adequate: Error (shelf procedures)
Planes, 1998	Adequate: double dummy	Unclear; no description of method of randomisation	Double-blind, double-dummy: matching medication	Adequate: protocol voilation
Planes, 1999 (Equivalence)	Unclear, not reported	Adequate: Computer generated allocation	Double-blind, medications were identical	Adequate: no venography and other reasons
Samama, 1997	Unclear, not reported	Adequate: Computer generated allocation	Double-blind, no details on blinding method reported	Adequate: no venography
Spiro, 1994	Adequate: blinded investigators assessed outcomes	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Adequate: no venography, insufficient therapy

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
Torholm, 1991	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, medications were identical	Adequate: medication error, no surgery, consent and AEs
Turpie, 1990	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Adequate: no venography
Turpie, 2005	Unclear, not reported	Adequate: Computer generated and interactive voice response system allocation	Double-blind, medications were identical; identical placebo	Adequate: no venography

Table 6: Patient numbers in the 15 studies included in both the adjusted indirect comparisons and the MTC

Study	THR/TKR	Treatment arm	Patients in arm
ADVANCE-3	THR	Apixaban 2.5 mg bd	2708
ADVANCE-3	THR	Enoxaparin 40 mg od	2699
Bauer, 2001 Pentamks)	TKR	Fondaparinux 2.5 mg od	526
Bauer, 2001 Pentamks)	TKR	Enoxaparin 30 mg bd	523
Huo 2010 (RENOVATE 2)	THR	Dabigatran etexilate 220 mg od	792
Huo 2010 (RENOVATE 2)	THR	Enoxaparin 40 mg od	785
Lassen 2002	THR	Enoxaparin 40 mg od	1154
Lassen 2002	THR	Fondaparinux 2.5 mg od	1155
Lassen 2007 (APROPOS)	TKR	Apixaban 2.5 mg bd	153
Lassen 2007 (APROPOS)	TKR	Enoxaparin 30 mg bd	152
Lassen 2009a (ADVANCE-1)	TKR	Apixaban 2.5 mg bd	1599
Lassen 2009a (ADVANCE-1)	TKR	Enoxaparin 30 mg bd	1596
Lassen 2010 (ADVANCE-2)	TKR	Apixaban 2.5 mg bd	1528
Lassen 2010 (ADVANCE-2)	TKR	Enoxaparin 40 mg od	1529
RECORD 1	THR	Enoxaparin 40 mg od	2275
RECORD 1	THR	Rivaroxaban 10 mg od	2266
RECORD 2	THR	Enoxaparin 40 mg od	1257
RECORD 2	THR	Rivaroxaban 10 mg od	1252
RECORD 3	TKR	Enoxaparin 40 mg od	1277
RECORD 3	TKR	Rivaroxaban 10 mg od	1254
RECORD 4	TKR	Enoxaparin 30 mg bd	1564
RECORD 4	TKR	Rivaroxaban 10 mg od	1584
RE-MOBILIZE	TKR	Dabigatran etexilate 220 mg od	862
RE-MOBILIZE	TKR	Enoxaparin 30 mg bd	876
RE-MODEL	TKR	Dabigatran etexilate 220 mg od	694
RE-MODEL	TKR	Enoxaparin 40 mg od	699

Study	THR/TKR	Treatment arm	Patients in arm
RE-NOVATE	THR	Dabigatran etexilate 220 mg od	1157
RE-NOVATE	THR	Enoxaparin 40 mg od	1162
Turpie 2002	THR	Enoxaparin 30 mg bd	1137
Turpie 2002	THR	Fondaparinux 2.5 mg od	1138

Table 7: Patient numbers in the additional 25 studies only included in the MTC

Study	THR/TKR	Treatment arm	Patients in arm
BISTRO II Trial (hip)	THR	Dabigatran etexilate 150 mg bd	266
BISTRO II Trial	THR	Dabigatran etexilate 225 mg bd	124
BISTRO II Trial	THR	Dabigatran etexilate 300 mg od	270
BISTRO II Trial	THR	Dabigatran etexilate 50 mg bd	123
BISTRO II Trial	THR	Enoxaparin 40 mg od	258
BISTRO II Trial (knee)	TKR	Dabigatran etexilate 150 mg bd	127
BISTRO II Trial	TKR	Dabigatran etexilate 225 mg bd	265
BISTRO II Trial	TKR	Dabigatran etexilate 300 mg od	124
BISTRO II Trial	TKR	Dabigatran etexilate 50 mg bd	270
BISTRO II Trial	TKR	Enoxaparin 40 mg od	122
Eriksson 1997	THR	Desirudin 15 mg bd	1043
Eriksson 1997	THR	Enoxaparin 40 mg od	1036
Eriksson 2006	THR	Enoxaparin 40 mg od	136
Eriksson 2006	THR	Rivaroxaban 10 mg bd	138
Eriksson 2006	THR	Rivaroxaban 2.5 mg bd	135
Eriksson 2006	THR	Rivaroxaban 20 mg bd	137
Eriksson 2006	THR	Rivaroxaban 30 mg bd	37
Eriksson 2006	THR	Rivaroxaban 5 mg bd	139
Fuji 2008a (Hip trial)	THR	Enoxaparin 20 mg bd	105
Fuji 2008a (Hip trial)	THR	Enoxaparin 20 mg od	104
Fuji 2008a (Hip trial)	THR	Enoxaparin 40 mg od	107
Fuji 2008a (Hip trial)	THR	Placebo	105
Fuji 2008a (Knee trial)	TKR	Enoxaparin 20 mg bd	99
Fuji 2008a (Knee trial)	TKR	Enoxaparin 20 mg od	93
Fuji 2008a (Knee trial)	TKR	Enoxaparin 40 mg od	94
Fuji 2008a (Knee trial)	TKR	Placebo	96
Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 0.75 mg od	80
Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 1.5 mg od	86
Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 2.5 mg od	80
Fuji 2008b (Fondaparinux trial)	THR	Fondaparinux 3 mg od	85
Fuji 2008b (Fondaparinux trial)	THR	Placebo	81
Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 0.75 mg od	84

Study	THR/TKR	Treatment arm	Patients in arm
Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 1.5 mg od	83
Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 2.5 mg od	84
Fuji 2008b (Fondaparinux trial)	TKR	Fondaparinux 3 mg od	82
Fuji 2008b (Fondaparinux trial)	TKR	Placebo	87
Lassen 2009b	TKR	Enoxaparin 40 mg od	120
Lassen 2009b	TKR	Semuloparin 10 mg od	88
Lassen 2009b	TKR	Semuloparin 20 mg od	130
Lassen 2009b	TKR	Semuloparin 40 mg od	137
Lassen 2009b	TKR	Semuloparin 5 mg od	93
Lassen 2009b	TKR	Semuloparin 60 mg od	122
Lassen, 2010b	TKR	Enoxaparin 30 mg bd	427
Lassen, 2010b	TKR	Semuloparin 20 mg od	428
Leclerc 1992	TKR	Enoxaparin 30 mg bd	51
Leclerc 1992	TKR	Placebo	55
Leclerc 1996	TKR	Enoxaparin 30 mg bd	336
Leclerc 1996	TKR	Warfarin (adjusted-dose)	334
Levine 1991	THR	Enoxaparin 30 mg bd	333
Levine 1991	THR	Heparin 7500 IU bd	332
Mouret 2010	THR	Enoxaparin 40 mg od	933
Mouret 2010	THR	Semuloparin 20 mg od	916
Navarro-Quilis 2003	TKR	Bemiparin 3500 IU	190
Navarro-Quilis 2003	TKR	Enoxaparin 40 mg od	191
ODIXa-HIP Study	THR	Enoxaparin 40 mg od	160
ODIXa-HIP Study	THR	Rivaroxaban 10 mg od	147
ODIXa-HIP Study	THR	Rivaroxaban 20 mg od	142
ODIXa-HIP Study	THR	Rivaroxaban 30 mg od	145
ODIXa-HIP Study	THR	Rivaroxaban 40 mg od	146
ODIXa-HIP Study	THR	Rivaroxaban 5 mg od	133
Pentathlon 2001	THR	Enoxaparin 30 mg bd	260
Pentathlon 2001	THR	Fondaparinux 0.75 mg od	184
Pentathlon 2001	THR	Fondaparinux 1.5 mg od	188
Pentathlon 2001	THR	Fondaparinux 3 mg od	177
Pentathlon 2001	THR	Fondaparinux 6 mg od	72
Pentathlon 2001	THR	Fondaparinux 8 mg od	52
Planes 1990 TRIAL 2	THR	Enoxaparin 20 mg bd	60
Planes 1990 TRIAL 2	THR	Enoxaparin 40 mg od	60
Planes 1990 TRIAL 3	THR	Enoxaparin 40 mg od	124
Planes 1990 TRIAL 3	THR	Unfractionated heparin 5000 IU od	113
Planes 1998	THR	Enoxaparin 40 mg od	251
Planes 1998	THR	Reviparin 4200 IU od	247
Planes 1999 (Equivalence)	THR	Enoxaparin 40 mg od	248
Planes 1999 (Equivalence)	THR	Tinzaparin 4500 IU od	251
Samama 1997	THR	Enoxaparin 40 mg od	85
Samama 1997	THR	Placebo	85
Spiro 1994	THR	Enoxaparin 10 mg od	161
Spiro 1994	THR	Enoxaparin 30 mg bd	210

Study	THR/TKR	Treatment arm	Patients in arm
Spiro 1994	THR	Enoxaparin 40 mg od	201
Torholm 1991	THR	Dalteparin 2500 or 5000 IU od	60
Torholm 1991	THR	Placebo	60
Turpie 1990	THR	Enoxaparin 30 mg bd	50
Turpie 1990	THR	Placebo	50
Turpie 2005	TKR	Enoxaparin 30 mg bd	104
Turpie 2005	TKR	Rivaroxaban 10 mg bd	103
Turpie 2005	TKR	Rivaroxaban 2.5 mg bd	100
Turpie 2005	TKR	Rivaroxaban 20 mg bd	98
Turpie 2005	TKR	Rivaroxaban 30 mg bd	106
Turpie 2005	TKR	Rivaroxaban 5 mg bd	102

A4 **Priority request:** A possible typographical error was identified by the ERG for fondaparin* in line #9 of the Medline search strategy for clinical effectiveness where it appears as fonadaparin*. The error appears to have been repeated across all strategies containing comparison drugs. When the ERG repeated the searches using the correct spelling they noticed considerable differences in the number of records identified. Please check that no relevant fondaparinux trials were missed in your search strategy.

Response:
The searches have been re-run with the correct spelling for fondaparinux (accessed August 15th 2011). The relevant search strategies are reported in appendix A, section 1(new correct terms are highlighted in yellow). The following number of additional 'hits' was reported for each database:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, n=19
- Embase 1980 to 2011 Week 32, n=2
- Cochrane Library, n=6
- CINAHL Plus with Full Text, n=2

However, on review of the title and abstract, none of these studies met the criteria for inclusion in the meta-analysis.

A5 Please explain why the abbreviation LMWH was not used in the search strategy for the mixed treatment comparison and all subsequent searches for low molecular weight heparin. Please clarify whether this could have influenced the results.

Response:
The original search strategies contain MeSH terms for Heparin/Low Molecular Weight Heparins (both exploded). In addition, the search strategies included several free text terms for a number of LMWHs. However, for completeness, the searches have been re-run including the free-text terms 'LMWH' and 'low molecular weight

heparin*' (accessed August 15th 2011). The relevant search strategies are reported in Appendix A, section 2 (new terms are highlighted in yellow). The following number of additional 'hits' was reported for each database:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, n=26
- Embase 1980 to 2011 Week 32, n=8
- Cochrane Library, n=52
- CINAHL Plus with Full Text, n=4

However, on review of the title and abstract, none of these studies met the criteria for inclusion in the meta-analysis.

A6 Please explain the rationale behind not including the following LMWH listed on Emtree as free text searches as you have done with other LMWHs: livaraparin-calcium; tafoxiparin; idrabiotaparinux; rd-11885;; idraparinux; semuloparin; cy-222; deligoparin; antixarin. The ERG noted that the scope for the mixed treatment comparison methodology (Appendix 16 in the manufacturer's submission) states that "low molecular weight heparins other than enoxaparin were included in the MTC analyses where these were available at relevant licensed doses". The ERG considers that any issues surrounding licensing would not be a reason for their exclusion. Could you confirm if these LMWHs were also excluded during screening?

Response:
At the initial citation screening stage (on the basis of title and abstract), all LMWH RCTs which met the inclusion criteria for the review were included. However, as stated in appendix 16 of the submission, it was decided a priori that meta-analysis was restricted to licensed doses of LMWHs, since the NICE appraisal is primarily focused on UK licensed doses of apixaban and its relevant comparison treatments. For completeness, the searches have been re-run including the free-text terms (and MeSH terms where appropriate) for the LMWHs listed on Emtree (accessed August 15th 2011). The relevant search strategies are reported in Appendix A, section 3 (new terms are highlighted in yellow). The following number of additional 'hits' was reported for each database:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, n=2
- Embase 1980 to 2011 Week 32, n=0
- Cochrane Library, n=0
- CINAHL Plus with Full Text, n=0

However, on review of the title and abstract, neither of these studies met the criteria for inclusion in the meta-analysis.

A7 On page 85 of the manufacturer's submission, it states: "The adjusted indirect comparison is regarded as the most appropriate analysis for informing the clinical efficacy and safety of apixaban versus relevant treatment comparators in this submission, since the MTC results were inconsistent with some of the head-to-head RCT data." Please explain which results were inconsistent; and provide an explanation for these inconsistencies.

Response:
Table 8 displays the head-to-head comparison data (single trials or pair-wise meta-analysis where feasible) for apixaban vs. enoxaparin 40 mg od , rivaroxaban vs. enoxaparin 40 mg od, and dabigatran 220 mg od vs. enoxaparin 40 mg od, and juxtaposes these with the group 1 MTC results for these comparisons on the available outcomes in the THR population. In the TKR population, the group 1 MTC used enoxaparin 30 mg bd as the reference treatment for all the outcome analyses apart from minor bleeding since there were slightly more arms of this enoxaparin dose in the TKR MTC than there were of enoxaparin 40 mg od. Therefore for TKR, the results from the group 2 (pooled enoxaparin 40 mg od and 30 mg bd doses) MTC are reported in Table 8 since they are more similar to the head-to-head trial comparisons of apixaban, rivaroxaban, and dabigatran vs. enoxaparin 40 mg od. The exception is for the minor bleeding outcome where the group 1 MTC network contained more enoxaparin 40 mg od than 30 mg bd treatment arms, and hence the former was chosen as the reference treatment in this MTC and is reported in Table 8. The juxtaposition of results from the head-to-head comparisons and the MTC below indicates there were no inconsistencies between the direct and MTC evidence for dabigatran 220 mg od. For the comparisons of apixaban and rivaroxaban vs. enoxaparin 40 mg od respectively, there was inconsistency in the direct and MTC evidence on the VTE composite outcome across both THR and TKR populations, and inconsistency between the direct evidence and the MTC on the any DVT outcome in the TKR population only. In addition, for apixaban, the direct and MTC evidence was inconsistent for the asymptomatic DVT outcome across both TKR and THR populations (see Table 8 below, the inconsistencies are highlighted in red). For all other outcomes, the respective direct head-to-head and MTC apixaban and rivaroxaban evidence was consistent.

For all inconsistent outcomes, the MTC displayed wider credibility intervals (i.e. increased uncertainty) which resulted in no statistically significant between-treatment differences. In contrast the head-to head comparisons for apixaban and rivaroxaban displayed narrower confidence intervals on the outcomes affected, which resulted in statistically significant differences favouring apixaban and rivaroxaban respectively vs. enoxaparin 40 mg od. Table 8 indicates that in general the MTC results displayed wider credibility intervals for all outcomes and treatments in comparison to the confidence intervals displayed in the head-to-head comparisons. The MTC results therefore displayed more uncertainty around the point estimates than the head-to-head comparisons.

Table 8: Consistency of head-to-head trial/pair-wise meta-analysis results compared with MTC results vs. enoxaparin

Direct Odds Ratio (95% CI) vs. Enoxaparin				
	Total hip replacement (THR)		Total knee replacement (TKR)	
VTE composite (primary efficacy analysis)	**Direct**	**MTC group 1 (vs. enox 40 mg od)**	**Direct**	**MTC group 2 (vs. enox 40 mg od + 30 mg od)**
Apixaban				
Rivaroxaban				
Dabigatran				
Any DVT (primary efficacy analysis)	**Direct**	**MTC group 1**	**Direct**	**MTC group 2**
Apixaban	0.31 (0.191-0.504)	0.317 (0.09883-0.991)	0.531 (0.423-0.668)	0.681 (0.267-1.697)
Rivaroxaban	0.22 (0.11-0.4)	0.221 (0.0685-0.698)	0.476 (0.357-0.635)	0.566 (0.188-1.741)
Dabigatran	0.816 (0.547-1.217)	0.817 (0.262-2.496)	0.942 (0.73-1.216)	0.959 (0.205-4.392)
Asymp DVT (primary efficacy analysis)	**Direct**	**MTC group 1**	**Direct**	**MTC group 2**
Apixaban	0.32 (0.194-0.526)	0.311 (0.026-3.939)	0.536 (0.425-0.675)	0.69 (0.237-2.023)
Rivaroxaban	N/A	N/A	N/A	0.702 (0.111-4.267)*
Dabigatran	0.718 (0.473-1.089)	0.693 (0.06-8.351)	0.999 (0.773-1.291)	0.999 (0.157-6.252)
Any bleeding (ITT)	**Direct**	**MTC group 1**	**Direct**	**MTC group 2**
Apixaban				
Rivaroxaban				
Dabigatran				
Major bleeding (ITT)	**Direct**	**MTC group 1**	**Direct**	**MTC group 2**
Apixaban				
Rivaroxaban				
Dabigatran				
CRNM bleed (ITT)	**Direct**	**MTC group 1**	**Direct**	**MTC group 2**
Apixaban				
Rivaroxaban				
Dabigatran				
Minor bleed (ITT)	**Direct**	**MTC group 1**	**Direct**	**MTC group 1 (vs. enox 40 mg od)**
Apixaban	0.91 (0.74-1.12)	0.904 (0.079-10.69)	0.94 (0.64-1.39)	0.911 (0.394-2.23)
Rivaroxaban	1 (0.77-1.28)	1.08 (0.19-5.839)	1 (0.68-1.47)	1.036 (0.455-2.547)
Dabigatran	0.95 (0.68-1.33)	0.948 (0.081-11.7)	0.86 (0.6-1.24)	0.87 (0.311-2.333)

*RECORD 4

The explanation for this inconsistency between the direct head-to-head comparisons and the MTC has already been outlined in section 5.7.9 of the submission document, viz. that the wider credibility intervals in the MTC may be due to the large number of trials contributing to the enoxaparin 40mg od node within the MTC network in addition to the trial sub-set reporting head-to-head comparisons of treatments that all fall within the NICE scope for apixaban. The former tended to 1) be older (see Table

5 above), 2) have fewer study quality criteria reported (see Table 5 above), 3) have fewer participants (mean study arm size N=184, see Table 7 above), and 4) compare enoxaparin 40mg od against treatments not within the NICE STA scope for apixaban (see Table 2 above, and response to priority item A2), compared to the within-scope head-to-head comparison trial sub-set. These factors could have contributed to a lack of precision and an increase in uncertainty (i.e. wider credibility intervals) in the relative treatment effects for enoxaparin 40 mg od observed in the MTC results, despite the apparent increase in power (i.e. more eligible studies) afforded by the MTC study inclusion criteria.

The sub-set of head-to-head studies in the main submission analysis tended to report and fulfil more study quality criteria (see Table 9 below), have more participants (mean study arm size N=1446, see Table 10 below), and reported similar outcome definitions and measures (see appendices 3 and 5 of the submission), although there was inconsistency across the comparators of interest on some bleeding outcomes (see Table 31 and Table 32 of the submission).

For the TKR population, an additional factor likely to have contributed to the inconsistent outcomes is that the MTC reference treatment was not enoxaparin 40 mg od. Comparing apixaban and rivaroxaban against the group 2 MTC (pooled doses of enoxaparin 40 mg od and 30 mg bd) has contributed to observed differences in point estimates between the direct trial evidence and MTC results on these outcomes (VTE composite, any DVT, asymptomatic DVT). Note that these differences between the direct head-to-head trials and the MTC evidence would have been exacerbated if the results from the group 1 TKR MTC (where enoxaparin 30 mg bd is the reference treatment) had been used instead.

Table 9: Quality overview of subset of the 8 head-to-head studies informing the main analysis (vs. enoxaparin 40 mg od) in the submission

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
ADVANCE-2 Lassen, 2010a	Adequate: central system	Adequate: schedule was generated by randomization center using SAS and was stratified by study site with a block size of four	Double-blind, interactive central telephone system	Adequate: no venography
ADVANCE-3 Lassen, 2010 Manuscript	Adequate: central system	Adequate: schedule was generated by randomization center using SAS and was stratified by study site with a block size of four	Double-blind, interactive central telephone system	Adequate: no venography and protocol violations

Study	Allocation concealment	Randomisation method	Blinding	Withdrawal
Huo Michael, 2010 (RENOVATE 2) Abstract	Unclear, not reported	Unclear; no description of method of randomisation	Double-blind, no details on blinding method reported	Unclear, not reported
Lassen, 2002	Adequate: central independent committee blinded to treatment allocation	Adequate: Computer generated allocation	Double-blind, placebo was matched to volume with enoxaparin and/or fondaparinux were identical	Adequate: no venography and inappropriate surgery
RECORD 1 Eriksson, 2008	Adequate: central independent committee blinded to treatment allocation	Adequate: Computer generated allocation	Double-blind, no details on blinding method reported	Adequate: no venography
RECORD 3 Lassen, 2008	Adequate: central independent committee blinded to treatment allocation	Adequate: Central telephone system	Double-blind, double-dummy; no details on blinding method reported	Adequate: no venography
RE-MODEL Eriksson, 2007	Adequate: independent committee masked to treatment allocation	Adequate: Computer generated allocation	Double-blind, medications were identical; identical placebo	Adequate: no venography
RE-NOVATE Eriksson, 2007	Adequate: independent central adjudication committee masked to treatment allocation	Adequate: Central computer generated allocation	Double-blind, medications were identical	Adequate: not treated, no surgery, no venography

Table 10: Patient numbers in the 8 head-to-head studies included in the main analysis (vs. enoxaparin 40 mg od) of the submission

Study	THR/TKR	Treatment arm	Patients in arm
ADVANCE-3	THR	Apixaban 2.5 mg bd	2708
ADVANCE-3	THR	Enoxaparin 40 mg od	2699
Huo 2010 (RENOVATE 2)	THR	Dabigatran etexilate 220 mg od	792
Huo 2010 (RENOVATE 2)	THR	Enoxaparin 40 mg od	785
Lassen 2002	THR	Enoxaparin 40 mg od	1154

Study	THR/TKR	Treatment arm	Patients in arm
Lassen 2002	THR	Fondaparinux 2.5 mg od	1155
Lassen 2010 (ADVANCE-2)	TKR	Apixaban 2.5 mg bd	1528
Lassen 2010 (ADVANCE-2)	TKR	Enoxaparin 40 mg od	1529
RECORD 1	THR	Enoxaparin 40 mg od	2275
RECORD 1	THR	Rivaroxaban 10 mg od	2266
RECORD 3	TKR	Enoxaparin 40 mg od	1277
RECORD 3	TKR	Rivaroxaban 10 mg od	1254
RE-MODEL	TKR	Dabigatran etexilate 220 mg od	694
RE-MODEL	TKR	Enoxaparin 40 mg od	699
RE-NOVATE	THR	Dabigatran etexilate 220 mg od	1157
RE-NOVATE	THR	Enoxaparin 40 mg od	1162

A8 On page 132, the manufacturer's submission states "For simplicity a comparison with enoxaparin only is made in the base case, as it is the most widely used LMWH. Therefore, the **indirect** comparison results for apixaban versus enoxaparin are used only. This approach assumes that LMWHs are broadly clinically equivalent, which was an assumption also made in the NICE appraisal of dabigatran for VTE prevention in orthopaedic patients (64) and is consistent with the analyses underpinning the VTE prevention NICE guidelines too" The ERG is unclear why a reference to the indirect comparison has been made here when direct evidence is available. Please clarify this statement.

Response:
This reference to the indirect comparison is incorrect as the ERG points out. As explained in section 6.3.1 of the submission, enoxaparin is the reference treatment in the model, and relative risks from direct evidence for enoxaparin versus apixaban is used along with evidence from the indirect comparison to enable dabigatran and rivaroxaban to be included in the model.

A9 On page 133 (table 58), baseline risks cannot be found in the publications regarding Advance 2 (Lancet 2010) and Advance 3 (NEJM 2010). Please clarify these risks.

Response:
Please find below Table 58 from the submission (Composite VTE and bleed rates) together with the table of numerator and denominator data for the outcomes which were used to calculate the baseline risks. The description of how the baseline risks for enoxaparin 40 mg od were calculated was incorrect in the submission. These risks were not based solely on the Advance 2 and 3 trials but based on all of the trials for the oral anticoagulants, so that the relative risks for each drug could be applied to a common absolute risk.

To calculate the baseline enoxaparin 40 mg od absolute risk for a particular event, the log odds were calculated in Excel for each of the enoxaparin treatment arms using number with event/number without event. A pooled log odds was then calculated in Stata IC version 10.1. The exponential of the pooled log odds was

calculated to give the odds which were then converted to the baseline absolute risk for enoxaparin. The direct odds ratios for the other treatments of interest were applied to the enoxaparin odds to give the odds for each treatment. These odds were then converted into probabilities (absolute risks for each treatment).

Table 58 (from submission): Composite VTE and bleed rates

	THR: All VTE & All cause death (95% CI)	TKR: All VTE & All cause death (95% CI)	THR: Any bleeding (95% CI)	TKR: Any bleeding (95% CI)
	Primary efficacy population analysis		ITT analysis	
Baseline risk (Enoxaparin 40mg OD)	4.58%	26.29%	9.39%	8.75%
Apixaban RR	[redacted]			
Rivaroxaban RR				
Dabigatran RR				

Table 11: Data inputs for composite efficacy and safety endpoints from trials

Data inputs for VTE composite (primary efficacy population)					
THR		**Ns**	**TKR**		**Ns**
ADVANCE-3	Apixaban 2.5 mg bd	27/1949	ADVANCE-2	Apixaban 2.5 mg bd	147/976
	Enoxaparin 40 mg od	74/1917		Enoxaparin 40 mg od	243/997
RECORD 1	Enoxaparin 40 mg od	58/1558	RECORD 3	Enoxaparin 40 mg od	166/878
	Rivaroxaban 10 mg od	18/1595		Rivaroxaban 10 mg od	79/824
RE-NOVATE	Dabigatran etexilate 220 mg od	53/880	RE-MODEL	Dabigatran etexilate 220 mg od	183/503
	Enoxaparin 40 mg od	60/897		Enoxaparin 40 mg od	193/512
Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	61/792			
	Enoxaparin 40 mg od	69/785			
Data inputs for any bleeding (ITT population)					
THR		**Ns**	TKR		**Ns**
ADVANCE-3	Apixaban 2.5 mg bd	313/2708	ADVANCE-2	Apixaban 2.5 mg bd	104/1528
	Enoxaparin 40 mg od	334/2699		Enoxaparin 40 mg od	126/1529
RECORD 1	Enoxaparin 40 mg od	131/2275	RECORD 3	Enoxaparin 40 mg od	142/1277
	Rivaroxaban 10 mg od	133/2266		Rivaroxaban 10 mg od	160/1254
RE-NOVATE	Dabigatran etexilate 220 mg od	141/1157	RE-MODEL	Dabigatran etexilate 220 mg od	110/694
	Enoxaparin 40 mg od	132/1162		Enoxaparin 40 mg od	115/699
Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	NR /792	N/A		
	Enoxaparin 40 mg od	NR /785			

A10 Please explain why Medline, Cinahl & Cochrane searches for clinical effectiveness and the MTC used the term Arthro**scopy** rather than Arthro**plasty** (as in the Embase search for these sections and all other searches) and clarify whether the inclusion of arthroplasty in the search is likely to result in additional relevant publications being identified.

Response:
The relevant MeSH term for Cochrane, Medline and Cinahl is 'Arthroscopy' and for EMBASE is 'knee arthroplasty'. For completeness, the searches have been re-run including the free-text term '(hip or knee) and (replacement* or arthroscop* or arthroplast*)' (accessed August 15th 2011). The relevant search strategies are reported in Appendix A, section 4 (new terms are highlighted in yellow). The following number of additional 'hits' was reported for each database:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, n=45
- Embase 1980 to 2011 Week 32, n=3
- Cochrane Library, n=42
- CINAHL Plus with Full Text, n=2

However, on review of the title and abstract, none of these studies met the criteria for inclusion in the meta-analysis.

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Section B: Clarification on cost-effectiveness data

B1 **Priority request:** The model structure does not seem to allow for transition between mild to moderate post thrombotic syndrome in year 1 to severe post thrombotic syndrome in year 2 and beyond. Please justify this assumption and advise whether it is supported by any evidence.

Response:
The ERG and NICE technical team are correct that the model unfortunately does not allow transition between mild to moderate post thrombotic syndrome (MM PTS) and severe post thrombotic syndrome (Severe PTS) in year two and beyond.

When the model was being developed a systematic literature review of the PubMed and Embase databases was conducted to identify long term risks of PTS and VTE events (full report included in appendix 18 of the submission). The PTS search strategy and results are presented in Appendix B Section 1. The systematic review identified eight relevant sources in total [2-9]. There was no risk information in any of the papers identified that would inform developing the model to allow patients to transition from MM PTS to Severe PTS in subsequent years. Preceding models that we are aware of have dealt with this problem in one of two ways; ignoring the distinction between MM PTS and Severe PTS [10] (rivaroxaban vs. enoxaparin) or by treating MMPTS and Severe PTS as distinct states where transition between them is not possible [11] (dabigatran vs. enoxaparin). In the absence of data to allow transition between MMPTS and Severe PTS we opted to treat MMPTS and Severe PTS as distinct states in the model to facilitate as comprehensive a disease representation of VTE in orthopaedic surgery as we could.

B2 **Priority request:** The model does not distinguish between types of bleed and types of VTE for each comparator individually (they are all the same). However, as an example, apixaban has fewer total bleeds, but more major bleeds compared with enoxaparin in THR. This assumption may favour apixaban, therefore please adjust the model to allow for differences in type of bleed and type of VTE.

Response:
As stated in section 6.3.1 of the submission, the model was based on the composite efficacy and safety trial endpoints as the trials for apixaban, rivaroxaban and dabigatran are only powered to detect differences in these endpoints. In addition, not all of the trials reported all the outcomes required for the model nor were they consistent in the definition of the outcomes either. Basing a cost effectiveness assessment on the components of these composite endpoints would introduce spurious chance findings and potentially bias the results.

However, a scenario analysis was undertaken where trial data from the ADVANCE 2 and ADVANCE 3 [12, 13] for total VTE and all-cause death, PE, Symptomatic DVT, asymptomatic DVT, all bleeding events, major, non major clinically relevant and minor bleeds were used rather than NOAC data to compare enoxaparin with apixaban (see below relevant rows extracted from Tables 100 and 101 in the

submission). Reference should be made to Table 80 in the submission as this shows the probability for each type of VTE and bleeding events used in this scenario analysis. These results show that when type of VTE and bleeding events are assumed to differ across drugs, apixaban remains cost effective in both TKR and THR populations.

As requested, the model was adapted so that types of VTE and bleed could vary across the comparators. Absolute risks for the reference treatment (enoxaparin 40mg od) were generated from the indirect comparison so that they were comparable to each of the NOACs so that relative risks for each comparator could then be applied. Indirect comparisons could not be undertaken to generate relative risks for each drug on the probabilities of All VTE and non-VTE death, and so the model continues to use blended NOAC and Advance trial data. In addition, indirect comparisons for all types of VTE (PE, asymptomatic and symptomatic DVT) and bleed (CRNM, major and minor) could not be undertaken for either fondaparinux nor rivaroxaban, as these data were not available from the trials. The lack of available data for fondaparinux is explained in the submission (see section 5.6.1), however, the reasons for why rivaroxaban data are not available are given below.

Rivaroxaban 10 mg od could not be included in this analysis, since the RECORD1, RECORD2, and RECORD 3 trials do not report symptomatic DVT and asymptomatic DVT as discrete outcomes, and so the data could not be extracted by the systematic review. These three trials report all DVT (proximal and distal DVT) and symptomatic VTE (any symptomatic deep-vein thrombosis [proximal or distal] or symptomatic non-fatal or fatal pulmonary embolism), but fail to report symptomatic DVT on its own. Therefore it is not possible to subtract symptomatic DVT from all DVT to obtain the number of asymptomatic DVT events that occurred in these trials. In addition, RECORD 1 and RECORD 2 only report non-fatal PE as an outcome, but deaths do occur in these trials, so the total number of PEs (i.e. fatal and non-fatal) is unclear. Hence it is not possible to determine the number of symptomatic DVT events by subtracting the number of non-fatal PEs from the number of symptomatic VTE events, since the latter could also include symptomatic fatal PEs. The RECORD 1 and 2 trials report non-fatal PE, while RECORD 3 reports total PE. These trials therefore do not distinguish between the number of symptomatic and asymptomatic PEs that occur. So it is not possible to simply subtract the number of total PE or non-fatal PE events from the number of symptomatic VTE events to obtain the number of symptomatic DVT events, since these PE outcome categories may include asymptomatic PE events which are not part of the symptomatic VTE outcome.

Tables 12 to 19 below outline the results of the revised modelling. In the base case apixaban dominated enoxaparin and dabigatran in both TKR and THR. Table 14 outlines the one way sensitivity analysis of the relative risks used to distinguish between types of bleed and types of VTE for the interventions. In the first analysis apixaban's relative risks were set to their upper 95% confidence interval (more VTE and bleeding) whilst the comparators risk (dabigatran and enoxaparin) were held constant (see table 14 for the values used). In this very conservative analysis dabigatran and enoxaparin were cost-effective compared to apixaban in TKR. Even in this analysis apixaban had the lowest costs. Apixaban dominated enoxaparin and dabigatran in THR. The apixaban relative risks were held constant in the second analysis whilst the dabigatran relative risks were set to their lower confidence intervals. In both TKR and THR apixaban dominated enoxaparin and dabigatran

(tables 15 and 16). When the discount rate, unit costs, utilities and duration of treatment were varied apixaban continued to dominated enoxaparin and dabigatran in both TKR and THR (see tables 17 and 18).

The probabilistic sensitivity analysis presented in Table 19 and Figures 1 and 2 showed that apixaban had a probability of 100% of being the most cost-effective from £20,000 to £30,000 per incremental QALY gained in THR. In TKR apixaban had a 62.5–64.1% probability of being the most cost-effective at £20,000 to £30,000 per QALY. Dabigatran had a probability of 34.15-34.95% of being the most cost-effective (enoxaparin 1.75%- 2.55%). The sensitivity analysis conducted indicates that the base case findings in this analysis are robust.

Table 12: Cost effectiveness results in THR

	Original Results					Revised Results				
Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**
Apixaban	£196.81	9.535	–£238.98	0.015	Dominant	£222.89	9.535	-£240.37	0.014	Dominant
Enoxaparin	£435.79	9.520				£463.26	9.520			
Rivaroxaban	£226.28	9.536	–£209.51	0.016	Dominant	-	-	-	-	-
Dabigatran	£263.89	9.523	–£171.90	0.003	Dominant	£297.64	9.522	-£165.62	0.002	Dominant
Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**					**ICER (£) versus apixaban (QALYs)**
Apixaban	£196.81	9.535				£222.89	9.535			
Rivaroxaban	£226.28	9.536	£29.47	0.001	£21,661.08	-	-	-	-	-
Dabigatran	£263.89	9.523	£67.08	–0.012	Dominated	£297.64	9.522	£74.75	-0.012	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Table 13: Cost effectiveness results in TKR

	Original Results					Revised Results				
Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**
Apixaban	£360.54	9.075	–£273.63	0.052	Dominant	£363.43	9.057	-£266.92	0.02	Dominant
Enoxaparin	£634.17	9.023				£630.35	9.039			
Rivaroxaban	£332.66	9.090	–£301.51	0.068	Dominant	-	-	-	-	-
Dabigatran	£514.80	9.028	–£119.36	0.005	Dominant	£512.87	9.046	-£117.48	0.01	Dominant
Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus rivaroxaban (QALYs)**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**
Apixaban	£360.54	9.075	£27.88	–0.015	Dominated	£363.43	9.057			
Rivaroxaban	£332.66	9.090				-	-	-	-	-
Dabigatran	£514.80	9.028	£182.15	–0.063	Dominated	£512.87	9.046	£149.44	-0.012	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years										

Table 14: Efficacy and bleeding variables subject to one-way sensitivity analysis and the sensitivity parameters applied

Direct relative risks	Base case value	Upper 95% confidence interval value applied to apixaban only	Lower 95% confidence interval applied to dabigatran
THR Symptomatic VTE			
Apixaban	0.199	1.705	
Dabigatran	6.026		0.727
THR asymptomatic VTE			
Apixaban	0.327	0.534	
Dabigatran	0.731		0.492
THR PE			
Apixaban	0.598	2.5	
Dabigatran	1.674		0.401
THR major bleed			
Apixaban	1.22	2.27	
Dabigatran	1.37		0.84
THR CRNM			
Apixaban	0.91	1.17	
Dabigatran	1.21		0.8
THR minor			
Apixaban	0.92	1.11	
Dabigatran	0.95		0.69
TKR Symptomatic VTE			
Apixaban	0.429	1.655	
Dabigatran	0.126		0.126
TKR asymptomatic VTE			
Apixaban	0.602	0.728	

Dabigatran	0.999		0.848
TKR PE			
Apixaban	9.006	167.128	
Dabigatran	0.34		0.01
TKR major bleed			
Apixaban	0.64	1.48	
Dabigatran	1.12		0.46
TKR CRNM			
Apixaban	0.76	1.12	
Dabigatran	1.09		0.71
TKR minor			
Apixaban	0.95	1.38	
Dabigatran	0.88		0.63

Note: Enoxaparin 40mg od pooled absolute risks were held constant; there was insufficient data to model rivaroxaban

Table 15: Efficacy and bleeding variables one-way sensitivity analysis results – upper confidence intervals applied to apixaban

TKR							
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**
Apixaban	£419.15	11.446	8.885				
Enoxaparin	£630.35	11.67	9.04	£211.20	0.22	0.15	£1,362.58
Dabigatran	£512.87	11.677	9.046	£93.72	0.23	0.16	£582.11
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus dabigatran (QALYs)**
Dabigatran	£512.87	11.677	9.046				
Enoxaparin	£630.35	11.67	9.04	£117.48	-0.01	-0.01	Dominated

THR							
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**
Apixaban	£224.82	12.266	9.533	-£238.44	0.012	0.013	Dominant
Enoxaparin	£463.26	12.255	9.520				
Dabigatran	£297.64	12.256	9.522	-£165.62	0.001	0.002	Dominant
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**
Apixaban	£224.82	12.27	9.53				
Dabigatran	£297.64	12.26	9.52	£72.82	-0.01	-0.01	Dominated

Table 16: Efficacy and bleeding variables one-way sensitivity analysis results – lower confidence intervals applied to dabigatran

TKR							
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**
Apixaban	£363.43	11.676	9.057	-£266.92	0.006	0.018	Dominant
Enoxaparin	£630.35	11.67	9.04				
Dabigatran	£509.16	11.678	9.047	-£121.20	0.008	0.007	Dominant
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**
Apixaban	£363.43	11.68	9.06				
Dabigatran	£509.16	11.68	9.05	£145.72	0.00	-0.01	Dominated
THR							
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus enoxaparin (QALYs)**
Apixaban	£222.89	12.268	9.535	-£240.37	0.013	0.014	Dominant
Enoxaparin	£463.26	12.255	9.520				
Dabigatran	£294.68	12.258	9.523	-£168.58	0.003	0.003	Dominant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus apixaban (QALYs)
Apixaban	£222.89	12.27	9.53				
Dabigatran	£294.68	12.26	9.52	£71.79	-0.01	-0.01	Dominated

Table 17: One-way sensitivity analysis results – discounting, costs, utilities and duration THR

Apixaban vs. Enoxaparin				Apixaban vs. Dabigatran		
Results	Cost difference	QALY difference	Cost/QALY	Cost difference	QALY difference	Cost/QALY
Base Case	-240.37	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
Discount rate 0%	-248.18	0.0202	Apixaban dominant	-80.14	0.0176	Apixaban dominant
Discount rate 6%	-236.37	0.0114	Apixaban dominant	-72.00	0.0101	Apixaban dominant
Health care unit costs -10%	-245.19	0.0141	Apixaban dominant	-78.16	0.0124	Apixaban dominant
Health care unit costs +10%	-235.55	0.0141	Apixaban dominant	-71.33	0.0124	Apixaban dominant
Health care unit costs PBR	-240.37	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
Duration of short term utility decrement -10%	-240.37	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
Duration of short term utility decrement +10%	-240.37	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
Utility treated VTE = -0.095	-240.37	0.0149	Apixaban dominant	-74.75	0.0133	Apixaban dominant
Weighted mean of LMWH costs = £3.76	-230.85	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
Dabigatran cost = £2.20	-240.37	0.0141	Apixaban dominant	-10.75	0.0124	Apixaban dominant
Treatment Duration reduced	-215.65	0.0141	Apixaban	-95.33	0.0124	Apixaban

			dominant			dominant
Time Horizon 1 year	-212.79	0.0012	Apixaban dominant	-55.80	0.0012	Apixaban dominant
Time Horizon 5 year	-230.98	0.0050	Apixaban dominant	-68.32	0.0045	Apixaban dominant
Time Horizon 10 year	-235.37	0.0087	Apixaban dominant	-71.28	0.0078	Apixaban dominant
Time Horizon 20 year	-239.48	0.0130	Apixaban dominant	-74.11	0.0114	Apixaban dominant
Age at surgery 40 years	-246.99	0.0226	Apixaban dominant	-79.39	0.0197	Apixaban dominant
Age at surgery 50 years	-245.71	0.0208	Apixaban dominant	-78.48	0.0181	Apixaban dominant
Age at surgery 80 years	-231.64	0.0075	Apixaban dominant	-68.80	0.0066	Apixaban dominant
LOS index hospitalisation +10%	-238.61	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
LOS index hospitalisation -10%	-242.12	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
LOS index hospitalisation +20%	-236.86	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
LOS index hospitalisation -20%	-243.88	0.0141	Apixaban dominant	-74.75	0.0124	Apixaban dominant
PE rate -10%	-240.18	0.0141	Apixaban dominant	-74.60	0.0124	Apixaban dominant
PE rate +10%	-240.56	0.0141	Apixaban dominant	-74.89	0.0124	Apixaban dominant
DVT rate -10%	-238.65	0.0142	Apixaban dominant	-73.52	0.0124	Apixaban dominant
DVT rate +10%	-242.01	0.0141	Apixaban dominant	-75.93	0.0124	Apixaban dominant
PTS rate -10%	-239.52	0.0138	Apixaban dominant	-74.12	0.0122	Apixaban dominant
PTS rate +10%	-241.15	0.0144	Apixaban	-75.33	0.0126	Apixaban

			dominant			dominant

Table 18: One-way sensitivity analysis results – discounting, costs, utilities and duration TKR

TKR						
Apixaban vs. Enoxaparin				**Apixaban vs. Dabigatran**		
Results	Cost difference	QALY difference	Cost/QALY	Cost difference	QALY difference	Cost/QALY
Base Case	-266.92	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
Discount rate 0%	-294.46	0.0260	Apixaban dominant	-175.58	0.0175	Apixaban dominant
Discount rate 6%	-252.61	0.0144	Apixaban dominant	-135.85	0.0094	Apixaban dominant
Health care unit costs -10%	-284.79	0.0180	Apixaban dominant	-166.32	0.0119	Apixaban dominant
Health care unit costs +10%	-249.05	0.0180	Apixaban dominant	-132.56	0.0119	Apixaban dominant
Health care unit costs PBR	-266.92	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
Duration of short term utility decrement -10%	-266.92	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
Duration of short term utility decrement +10%	-266.92	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
Utility treated VTE = -0.095	-266.92	0.0202	Apixaban dominant	-149.44	0.0135	Apixaban dominant
Weighted mean of LMWH costs = £3.76	-263.56	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
Dabigatran cost = £2.20	-266.92	0.0180	Apixaban dominant	-133.44	0.0119	Apixaban dominant
Treatment Duration reduced	-258.68	0.0180	Apixaban	-156.30	0.0119	Apixaban

			dominant			dominant
Time Horizon 1 year	-166.16	0.0011	Apixaban dominant	-53.74	0.0004	Apixaban dominant
Time Horizon 5 year	-233.71	0.0057	Apixaban dominant	-117.88	0.0034	Apixaban dominant
Time Horizon 10 year	-249.85	0.0108	Apixaban dominant	-133.25	0.0067	Apixaban dominant
Time Horizon 20 year	-264.14	0.0165	Apixaban dominant	-146.82	0.0108	Apixaban dominant
Age at surgery 40 years	-293.38	0.0318	Apixaban dominant	-174.48	0.0218	Apixaban dominant
Age at surgery 50 years	-288.67	0.0290	Apixaban dominant	-170.03	0.0198	Apixaban dominant
Age at surgery 80 years	-236.34	0.0096	Apixaban dominant	-120.35	0.0062	Apixaban dominant
LOS index hospitalisation +10%	-265.17	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
LOS index hospitalisation -10%	-268.68	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
LOS index hospitalisation +20%	-263.41	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
LOS index hospitalisation -20%	-270.43	0.0180	Apixaban dominant	-149.44	0.0119	Apixaban dominant
PE rate -10%	-266.24	0.0180	Apixaban dominant	-148.81	0.0119	Apixaban dominant
PE rate +10%	-267.60	0.0180	Apixaban dominant	-150.07	0.0119	Apixaban dominant
DVT rate -10%	-260.61	0.0182	Apixaban dominant	-143.49	0.0120	Apixaban dominant
DVT rate +10%	-272.96	0.0179	Apixaban dominant	-155.13	0.0117	Apixaban dominant
PTS rate -10%	-263.81	0.0170	Apixaban dominant	-146.52	0.0109	Apixaban dominant
PTS rate +10%	-269.79	0.0190	Apixaban	-152.12	0.0128	Apixaban

			dominant			dominant

Table 19: Cost-effectiveness acceptability at £20,000 and £30,000

	THR		TKR	
	£ 20,000	**£ 30,000**	**£ 20,000**	**£ 30,000**
Apixaban	100.00%	100.00%	64.10%	62.50%
Enoxaparin 40 mg	0.00%	0.00%	1.75%	2.55%
Dabigatran	0.00%	0.00%	34.15%	34.95%

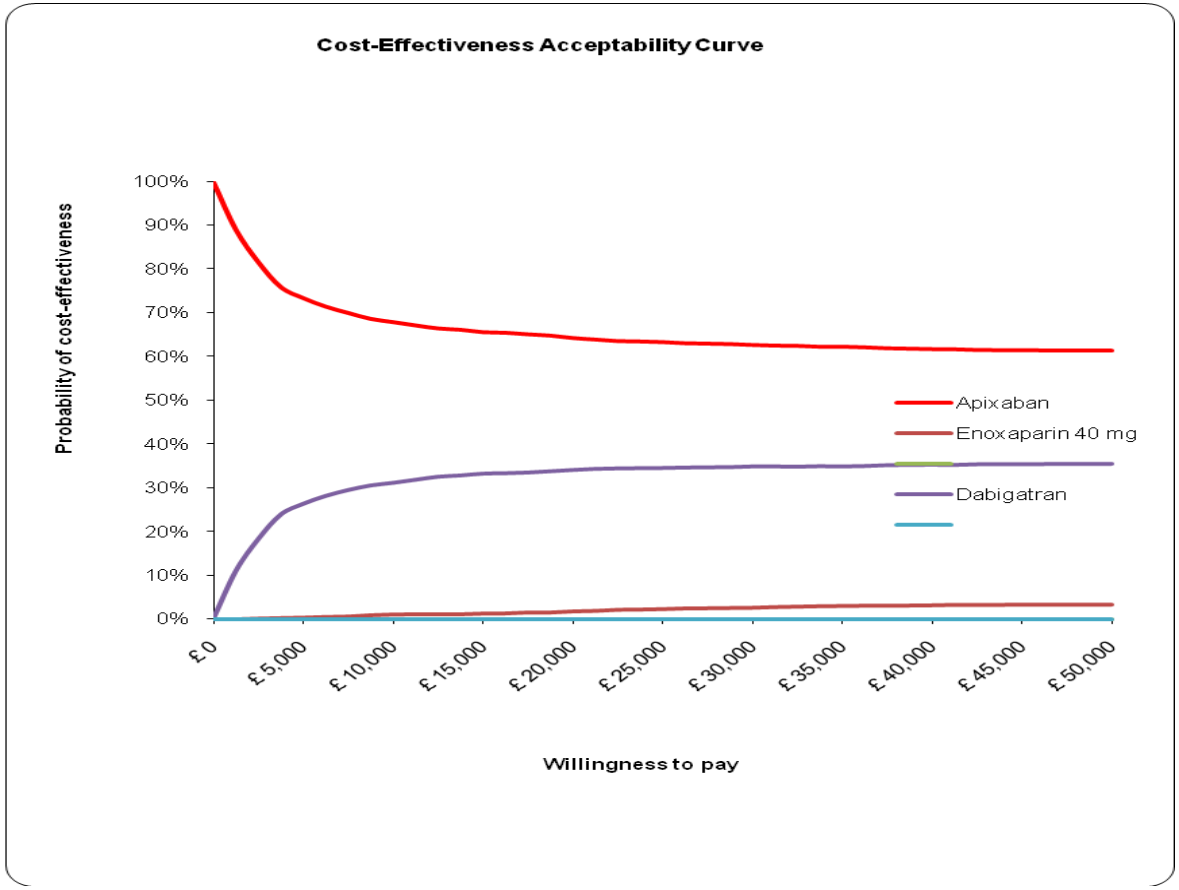

Figure 1: Cost-effectiveness acceptability curves for TKR

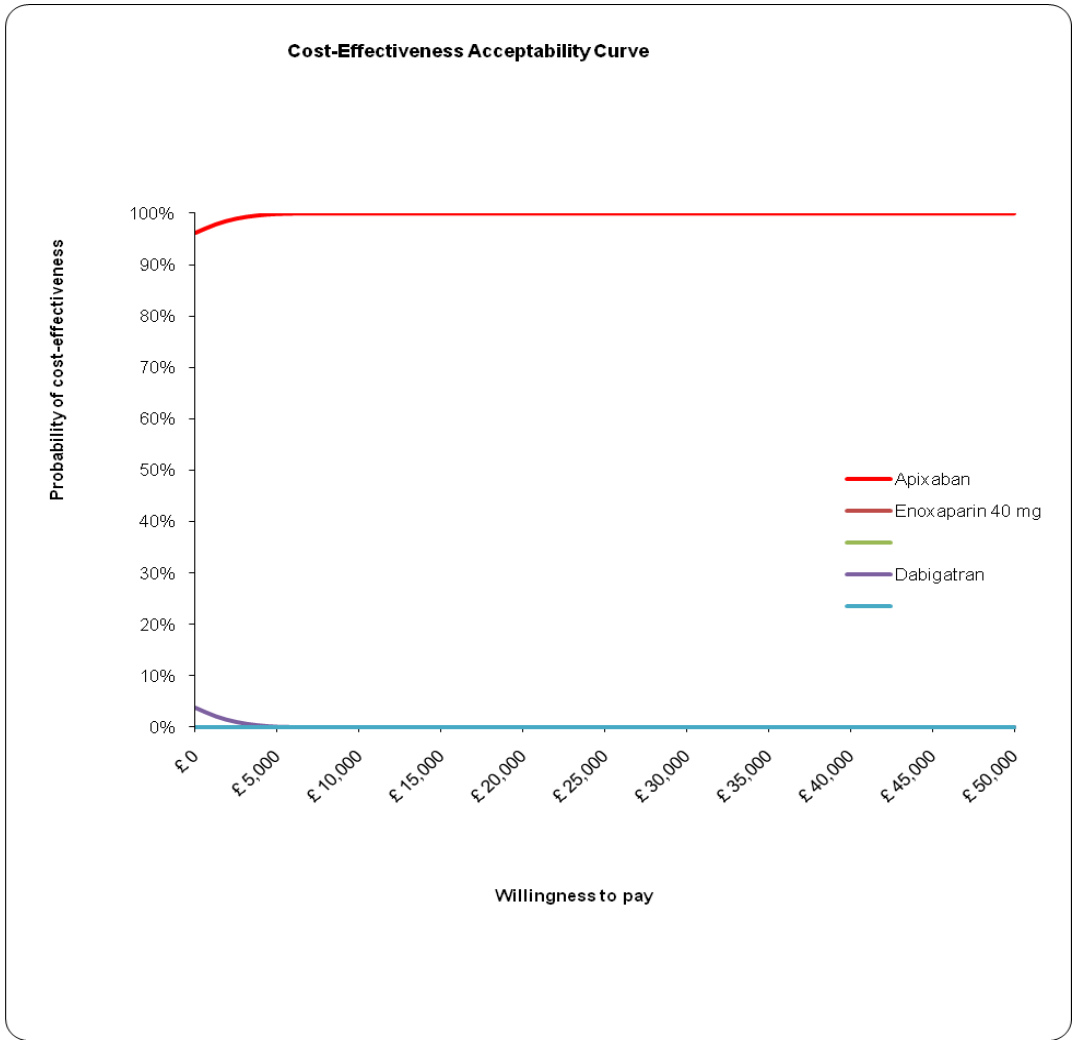

Figure2: Cost-effectiveness acceptability curves for THR

B3 **Priority request:** The cost-effectiveness model does not allow a full incremental analysis (only 2 comparators at the time). Because of this, it is not possible to run a PSA for all comparators simultaneously, as should be done. Please adapt the model in order to perform an incremental analysis and PSA for all comparators simultaneously.

Response:
The model has been adapted to allow incremental analysis and PSA for all comparators simultaneously. The PSA results are presented below in table 20 and figures 3 and 4. In THR at £20,000 and £30,000 only apixaban and rivaroxaban had a probability greater than zero of being the most cost-effective. At £20,000 apixaban had the highest probability of being the most cost-effective at 53.05%, whilst rivaroxaban had a probability of 46.95%. At £30,000 rivaroxaban had the highest probability of being the most cost-effective at 52.75% whilst apixaban had a probability of 47.25%. As in THR, only apixaban and rivaroxaban had a probability greater than zero of being the most cost-effective in TKR at £20,000 and £30,000. At £20,000 apixaban had a probability of 10.95 of being the most cost-effective intervention whilst rivaroxaban had a probability of 89.05. At £30,000 apixaban had a probability of 10.45 and rivaroxaban had a probability of 89.55. It is important to note that the differences between apixaban and rivaroxaban are small. Apixaban was less expensive with negligible efficacy difference (QALYs) to rivaroxaban in the THR base case. In TKR apixaban was minimally more expensive and had a negligible efficacy difference (QALYs) to rivaroxaban in the base case.

Table 20 PSA probabilities

	THR		TKR	
WTP	**£20,000**	**£30,000**	**£20,000**	**£30,000**
Enoxaparin 40 mg	0.00%	0.00%	0.00%	0.00%
Apixaban	53.05%	47.25%	10.95%	10.45%
Rivaroxaban	46.95%	52.75%	89.05%	89.55%
Dabigatran	0.00%	0.00%	0.00%	0.00%

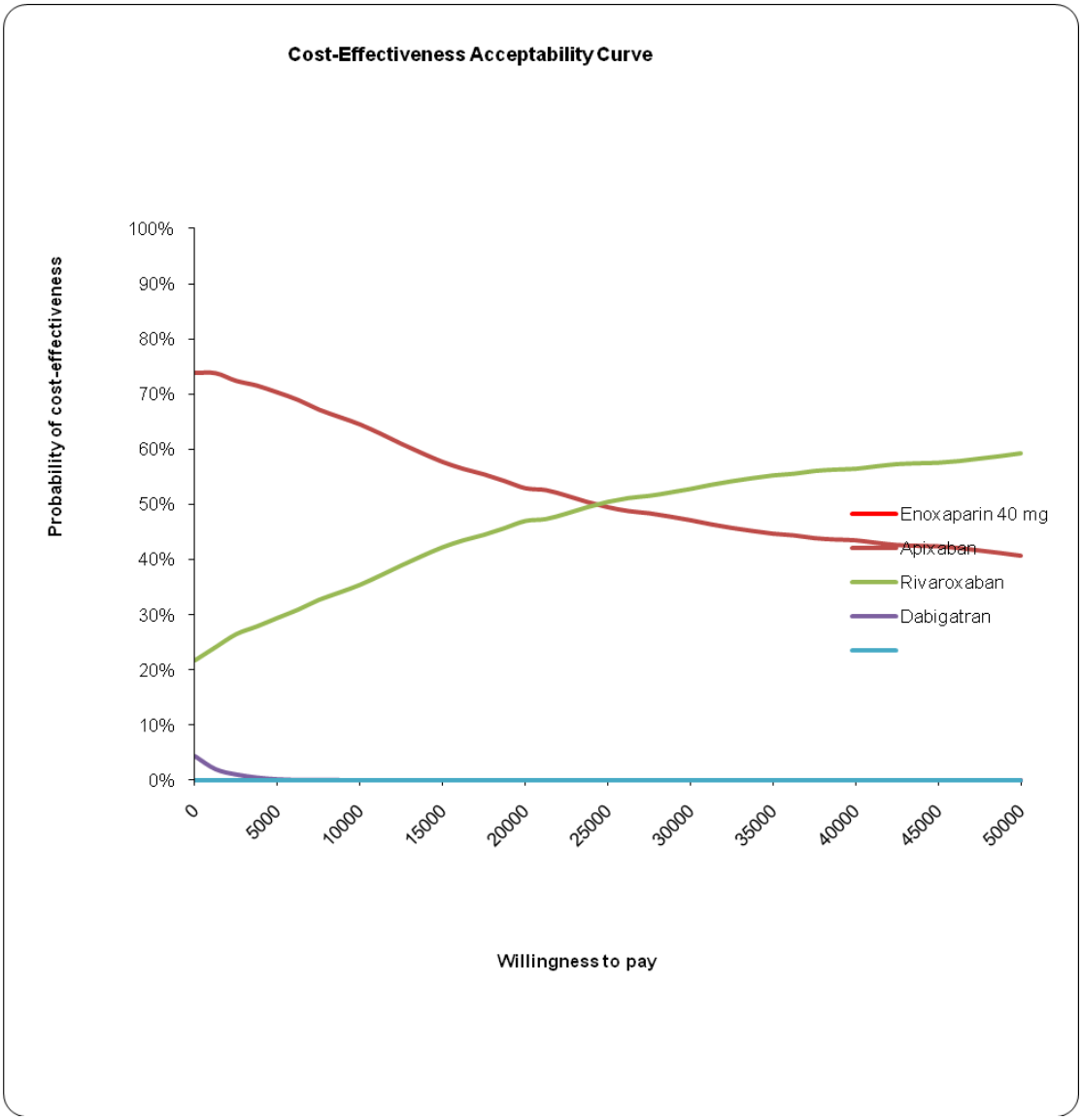

Figure3: THR probabalistic sensitivity analysis

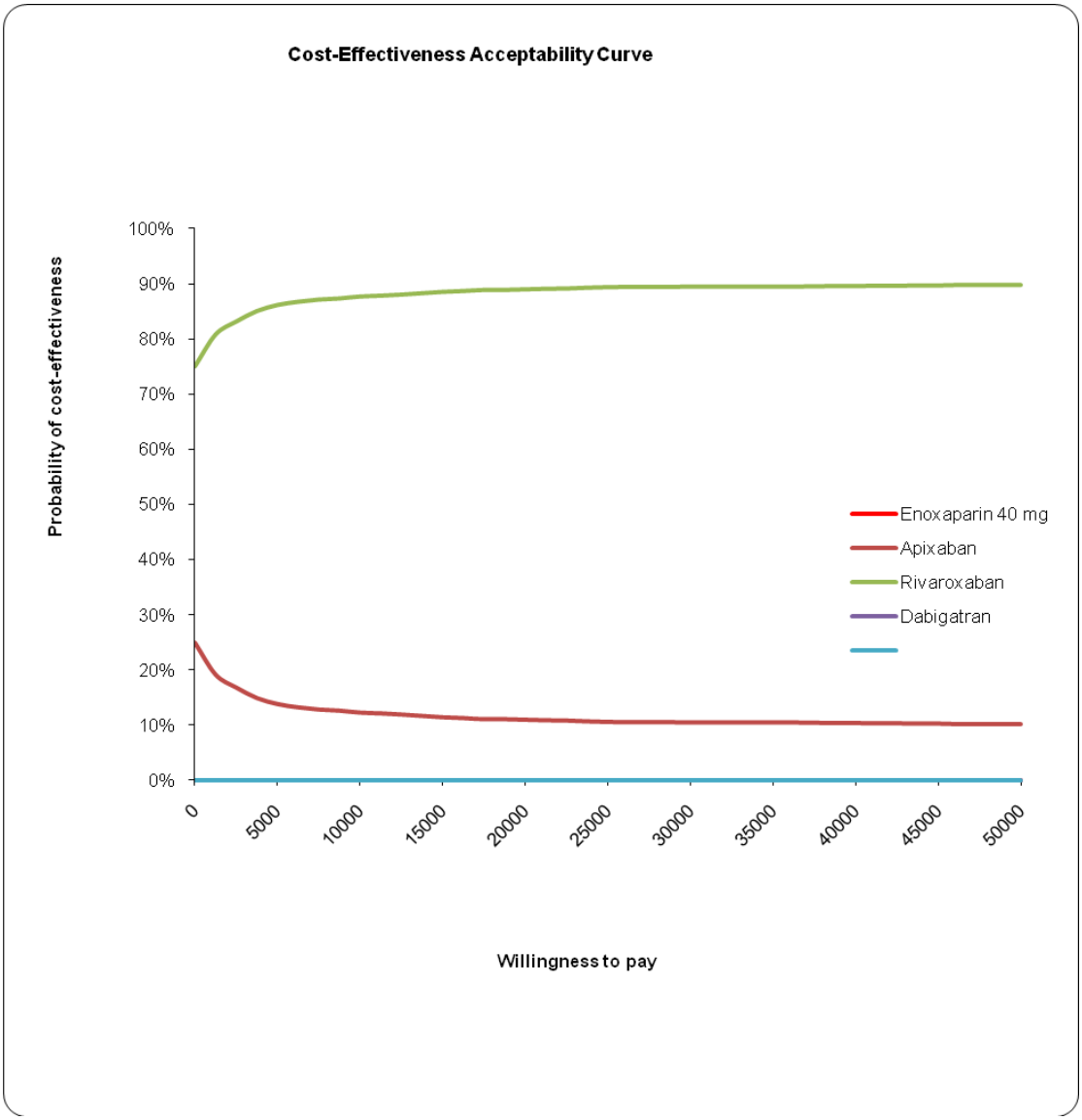

Figure 4: TKR probabalistic sensitivity analysis

B4 **Priority request:** Please explain why, for THR, fondaparinux 2.5 mg od was not included in the indirect comparison, as used in the CEA model? Please re-run the indirect comparison and include fondaparinux 2.5 mg od. The ERG notes that for THR the only trial (Lassen et al 2002) fondaparinux 2.5mg od is compared with enoxaparin 40 mg od, however the composite outcome (any VTE+death) is not reported. However, the study does report any VTE (PE or DVT) and death separately. Although there could be overlap between these two outcomes, the number of deaths is small (fondaparinux (n=2) and enoxaparin (n=4)). Therefore, if it is assumed that there is perfect overlap (that is, composite = any VTE) then the OR=0.416; or if it is assumed that there is no overlap (i.e. composite=any VTE+death) then the OR=0.418. Asthere is little difference between these two results please include fondaparinux 2.5 mg od data from the indirect comparison analysis in the CEA model for THR and conduct sensitivity analyses where appropriate.

Response:
As requested, data from Lassen et al. [14] has been included in the analysis. The results of the direct and indirect comparison versus Enoxaparin 40mg od are reported below. Details of the forest plots are provided in Appendix B Section 2.

ITT population analysis

- Direct Odds ratio: Fondaparinux 2.5 mg od (UK indication) - **ITT** = 0.41 (0.27-0.60)
- Indirect odds ratio: Fondaparinux 2.5 mg od (UK indication) – **ITT** = 1.139 (0.617, 2.101)
- Direct relative risks: Fondaparinux 2.5 mg od (UK indication) – **ITT** = 0.42 (0.29-0.62)

Evaluable patient population (EP) analysis

- Direct Odds ratio: Fondaparinux 2.5 mg od (UK indication) - **EP** = 0.41 (0.27-0.60)
- Indirect odds ratio: Fondaparinux 2.5 mg od (UK indication) – **EP** = 1.171 (0.636, 2.159)
- Direct relative risks: Fondaparinux 2.5 mg od (UK indication) – **EP** = 0.43 (0.30- 0.62)

Table 21: Data used from the Lassen 2002 study for Fondaparinux in VTE-Composite outcome for treatment study period

Treatment Arm (ITT)	N	n
Fondaparinux 2.5 mg od (UK indication)	1155	37[†]
Enoxaparin 40 mg	1154	87[‡]
Treatment Arm (Evaluable population)		
Fondaparinux 2.5 mg od (UK indication)	908	37[†]
Enoxaparin 40 mg	918	87[‡]

[†] Data calculated as VTE events = 37, any cause death = 0, for treatment period up to day 11
[‡] Data calculated as VTE events = 85, any cause death = 2, for treatment period up to day 11

The THR results with fondaparinux included are presented below. As the Lessen et al. [14] study does not record bleeding in the same fashion as the other studies contributing data to the indirect comparison it has been necessary to assume that major bleeds were the only bleeds patients experienced. However, we know that this was not the case from table 4 of the Lassen et al. [14] paper. We would suggest that the follow analysis be considered as a sensitivity analysis and not a base case analysis as it underestimates the health effects and cost associated with non major clinically relevant bleed and minor bleeds.

Table22: Base-case results in THR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus enoxaparin (QALYs)
Apixaban	£196.81	12.269	9.535	–£238.98	0.014	0.015	Dominant
Enoxaparin	£435.79	12.254	9.520				

Rivaroxaban	£226.28	12.270	9.536	–£209.51	0.015	0.016	Dominant
Dabigatran	£263.89	12.257	9.523	–£171.90	0.002	0.003	Dominant
Fondaparinux	£159.91	12.267	9.533	-£275.88	0.012	0.013	Dominant
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus fondaparinux (QALYs)**
Fondaparinux	£159.91	12.267	9.533				
Apixaban	£196.81	12.269	9.535	£36.90	0.002	0.002	£22,506.41
Rivaroxaban	£226.28	12.270	9.536	£66.37	0.003	0.003	£22,123.03
Dabigatran	£263.89	12.257	9.523	£103.98	-0.010	-0.011	Dominated
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**
Apixaban	£196.81	12.269	9.535				
Rivaroxaban	£226.28	12.270	9.536	£29.47	0.001	0.001	£21,661.08
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

In this analysis fondaparinux dominated both enoxaparin and dabigatran. Apixaban provided an ICER of £22,506.41 compared to fondaparinux. Rivaroxaban provided an ICER of £21,661.08 for additional QALYs compared to apixaban.

Table 23: One-way sensitivity analysis THR

		Apixaban vs. Fondaparinux		
Results	**Base Case Parameter(s)**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**
Base Case		£36.90	0.001639425	£22,506.41
Discount rate 0%	3.5%	£36.04	0.002335674	£15,430.48
Discount rate 6%	3.5%	£37.34	0.001325555	£28,166.66
Health care unit costs –10%	See 80.	£36.37	0.001639425	£22,184.67
Health care unit costs +10%		£37.43	0.001639425	£22,828.16
Health care unit costs PBR		£36.90	0.001639425	£22,506.41
Duration of short term utility decrement –10%	See 80.	£36.90	0.001639248	£22,508.84
Duration of short term utility decrement +10%		£36.90	0.001639602	£22,503.98
Utility treated VTE = –0.095	–0.01	£36.90	0.001726403	£21,372.51
Weighted mean of LMWH costs = £3.76	£4.04	£36.90	0.001639425	£22,506.41
Lowest LMWH (dalteparin) cost =£2.82	£4.04	-	-	-
Dabigatran cost = £2.20	£4.20	-	-	-
Apixaban wastage cost (35 days of pills)	34 days	£40.30	0.002	£24,580.31
Treatment Duration reduced to 28 days for apixaban	Apixaban 34 days, enoxaparin 34 days,	£16.32	0.002	£9,953.23
Treatment Duration extended to maximum recommended of 38		£50.62	0.002	£30,875.20

		Apixaban vs. Fondaparinux		
Results	**Base Case Parameter(s)**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**
days for apixaban	dabigatran 32 days, rivaroxaban 33 days, fondaparinux 7 days			
Time Horizon 1 year	35 years	£39.92	0.000144812	£275,674.69
Time Horizon 5 year		£37.93	0.000578568	£65,553.35
Time Horizon 10 year		£37.45	0.00101583	£36,862.76
Time Horizon 20 year		£37.00	0.001508703	£24,521.24
Age at surgery 40 years	THR males 65.89, females 68.51; TKR males 68.26, females 68.14	£36.17	0.002620912	£13,800.95
Age at surgery 50 years		£36.31	0.002410012	£15,066.87
Age at surgery 80 years		£37.85	0.000869529	£43,534.02
LOS index hospitalisation +10%	5 days	£36.90	0.001639357	£22,507.34
LOS index hospitalisation –10%		£36.90	0.001639493	£22,505.48
LOS index hospitalisation +20%		£36.90	0.00163929	£22,508.27
LOS index hospitalisation –20%		£36.90	0.00163956	£22,504.56
Apixaban worse composite 'Total VTE and all-cause death' +10%	See 80.	£39.72	0.000811371	£48,951.09
Comparator worse composite 'Total VTE and all-cause death' +10%		£33.52	0.002631245	£12,739.20
Apixaban worse composite 'Total VTE and all-cause death' - upper 95% CI		£52.29	-0.002881427	Apixaban dominated
Comparator worse composite 'Total VTE and all-cause death' - upper 95% CI		£21.97	0.006021884	£3,648.89
Apixaban worse 'bleeding events' +10%		£42.10	0.00163912	£25,682.18
Comparator worse 'bleeding events' +10%		£28.68	0.001639907	£17,489.06
Apixaban worse 'bleeding events' - upper 95% CI		£45.28	0.001638933	£27,629.20
Comparator worse 'bleeding events' - upper 95% CI		-£8.38	0.001642079	Dominant

With the exception of applying the upper 95% confidence interval for total VTE and all-cause death to apixaban, extending apixaban treatment duration to 38 days, applying a time horizon of one to ten years giving patients a mean age of 80 years at surgery and increasing the apixaban 'VTE composite' and 'any bleeding' variables by 10% apixaban produced ICERS of less than £30,000 per QALY or dominated fondaparinux.

Probabilistic sensitivity analysis

Table 24: PSA probabilities

	THR	
	£20,000	**£30,000**
Enoxaparin 40 mg	0.00%	0.00%
Apixaban	32.65%	33.40%
Rivaroxaban	30.85%	40.90%
Dabigatran	0.00%	0.00%
Fondaparinux	36.50%	25.70%

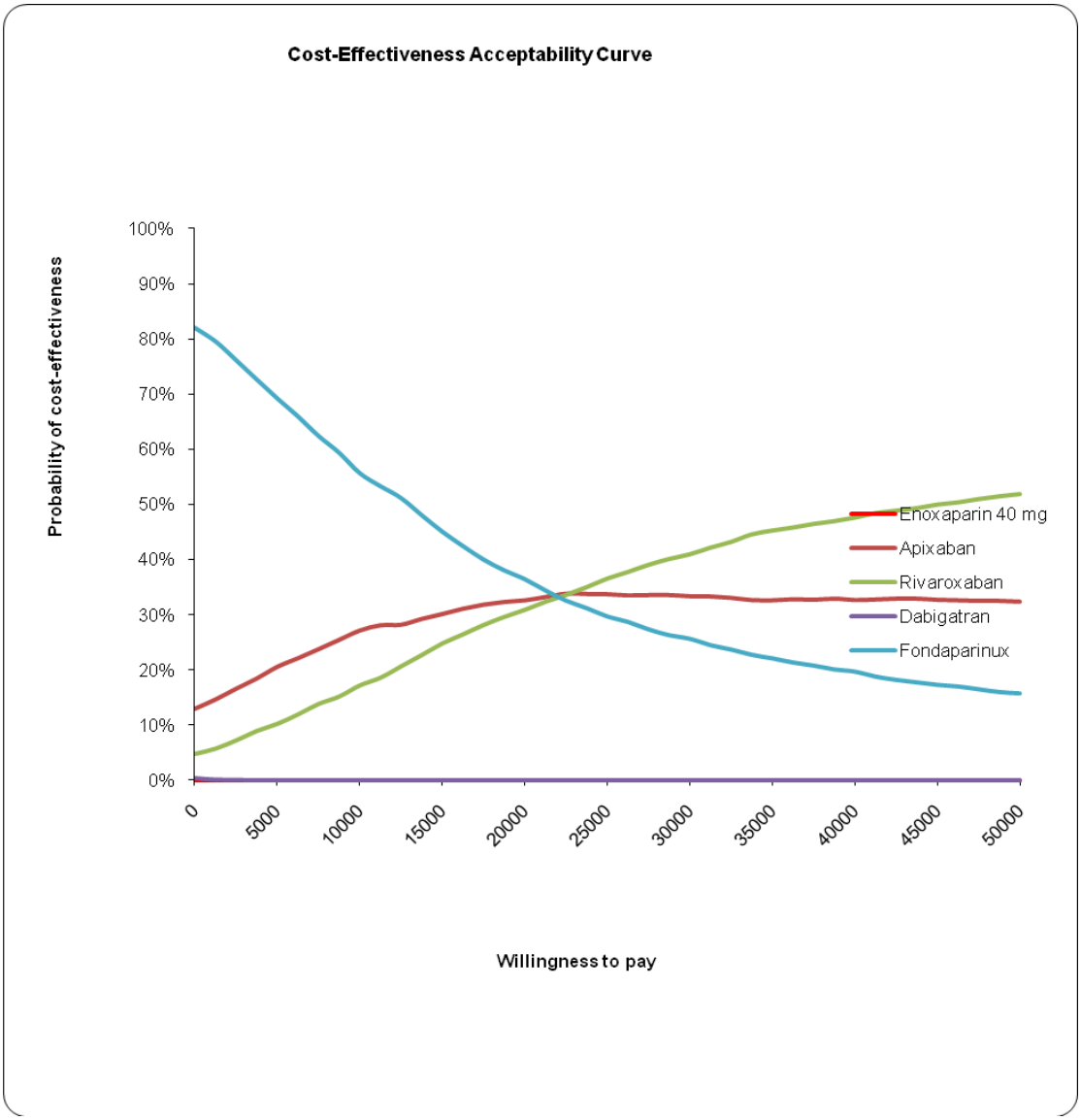

Figure 5: THR propbabalistic sensitivity analysis

Only apixaban, rivaroxaban and fondaparinux had probabilities greater than zero of being the most cost-effective intervention. At a threshold of £20,000 per QALY fondaparinux had the highest probability of being the most cost-effective drug,

followed by apixaban at 32.65% and rivaroxaban at 30.85%. At £30,000 per QALY rivaroxaban had the highest probability of being the most cost-effective at 40.9%. Apixaban had the second highest probability at 33.4% and fondaparinux had a probability of 25.7%

Table 25: Scenario analysis THR

		Apixaban vs. Fondaparinux		
Results	**Base Case Parameter(s)**	**Incremental costs**	**Incremental QALYs**	**ICER**
Indirect comparison group 2	See 80.	-	-	-
MTC Group 1		£128.98	-0.00138998	Fondaparinux dominant
MTC Group 2		£118.99	-0.001221221	Fondaparinux dominant
PE rate –10%	See 80.	£36.92	0.001639687	£22,515.58
PE rate +10%		£36.88	0.001639164	£22,497.25
DVT rate –10%		£37.09	0.001643877	£22,560.01
DVT rate +10%		£36.72	0.001635151	£22,454.74
PTS rate –10%		£36.99	0.001606797	£23,021.48
PTS rate +10%		£36.81	0.001670582	£22,035.19
All VTE & any bleeding components from Advance 2 & 3	See 80.	-	-	-

In the Scenario analysis (table 25) fondaparinux dominated apixaban when the MTC group 1 and group 2 data was used. When long term PE, DVT and PTS rates were varied apixaban produced ICERs of £22,035.19 to £23,021.48 per QALY compared to fondaparinux.

B5 **Priority request:** The manufacturer's submission suggests that apixaban may be associated with improved treatment compliance (pg 14) because it is an oral medication as opposed to an injection. However, it is possible that the reverse could be true given that compliance with oral medication depends largely on the individual, whereas compliance with injection might depend at least partly on others, including carers, who might be more motivated than the individual. In light of this, please provide estimates of compliance for each of the comparators and incorporate these in the cost effectiveness model.

Response:
Compliance is notoriously difficult to incorporate into economic model and given the time available it was not possible to do in a robust and credible way. However, the model currently assumes high levels of compliance with all therapies, as durations of therapy were based on protocol driven randomised controlled trials. Even though there is evidence to show that duration of therapy with low molecular weight heparins is considerably shorter than that assumed in the model, as no comparable data is available for apixaban this could not be used [15].

It is clear that patients prefer oral rather than injectable medications [16], but there is little evidence to link this preference with compliance rates. Furthermore, the benefits of having an oral anti-coagulant available in the VTE prophylaxis of patients undergoing orthopaedic surgery where injectable medicines predominate, have already been accepted by NICE in the appraisals of dabigatran and rivaroxaban [17, 18]. Indeed, in these appraisals compliance was not explicitly modelled by either manufacturer. As such the potential benefits of apixaban in terms of improving compliance could not be incorporated into the cost effectiveness model.

B6 **Priority request:** On page 86 (Table 36), results are reported as Odds Ratios (ORs). However on page 132 the manufacturer's submission states: "Relative risks (RR) are used in the economic model rather than odds ratios (OR) because they can be applied directly to an absolute probability of an event to generate the absolute event rate for the comparator treatment." It is unclear whether the ORs and RRs match, without full data extraction of included studies. Please provide tables with numbers of events and total number analysed for each outcome included in the economic model, together with the corresponding ORs and RRs.

Response:
Both the relative risks used in the model and the odds ratios reported in section five of the submission were based on the same patient number. In the tables below the ORs, RRs, event numbers and denominator sample size for the outcomes assessed in the model are presented.

Table 36 (from submission): VTE composite (primary efficacy population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2	Apixaban 2.5 mg bd	[redacted]
RECORD 1	Rivaroxaban 10 mg od Excluding RECORD 2		RECORD 3	Rivaroxaban 10 mg od	
RE-NOVATE Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od		RE-MODEL	Dabigatran etexilate 220 mg od	
N/A	Fondaparinux 2.5 mg od		N/A	Fondaparinux 2.5 mg od	
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2	Apixaban 2.5 mg bd	[redacted]
RECORD 1	Rivaroxaban 10 mg od Excluding RECORD 2		RECORD 3	Rivaroxaban 10 mg od	
RE-NOVATE Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od		RE-MODEL	Dabigatran etexilate 220 mg od	
Lassen 2002	Fondaparinux 2.5 mg od				
Data inputs					
		Ns			**Ns**
ADVANCE-3	Apixaban 2.5 mg bd	27/1949	ADVANCE-2	Apixaban 2.5 mg bd	147/976
	Enoxaparin 40 mg od	74/1917		Enoxaparin 40 mg od	243/997
RECORD 1	Enoxaparin 40 mg od	58/1558	RECORD 3	Enoxaparin 40 mg od	166/878
	Rivaroxaban 10 mg od	18/1595		Rivaroxaban 10 mg od	79/824
RE-NOVATE	Dabigatran etexilate 220 mg od	53/880	RE-MODEL	Dabigatran etexilate 220 mg od	183/503
	Enoxaparin 40 mg od	60/897		Enoxaparin 40 mg od	193/512
Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	61/792			

	Enoxaparin 40 mg od	69/785			
Lassen 2002	Enoxaparin 40 mg od		N/A	Fondaparinux 2.5 mg od	
	Fondaparinux 2.5 mg od				

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; N/A, non applicable

Table 42 (from submission): Any bleeding (ITT population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2	Apixaban 2.5 mg bd	[redacted]
RECORD 1	Rivaroxaban 10 mg od Excluding RECORD 2		RECORD 3	Rivaroxaban 10 mg od	
RE-NOVATE	Dabigatran etexilate 220 mg od		RE-MODEL	Dabigatran etexilate 220 mg od	
N/A	Fondaparinux 2.5 mg od		N/A	Fondaparinux 2.5 mg od	
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2	Apixaban 2.5 mg bd	[redacted]
RECORD 1	Rivaroxaban 10 mg od Excluding RECORD 2		RECORD 3	Rivaroxaban 10 mg od	
RE-NOVATE	Dabigatran etexilate 220 mg od		RE-MODEL	Dabigatran etexilate 220 mg od	
N/A	Fondaparinux 2.5 mg od		N/A	Fondaparinux 2.5 mg od	
Data inputs					
		Ns			**Ns**
ADVANCE-3	Apixaban 2.5 mg bd	313/2708	ADVANCE-2	Apixaban 2.5 mg bd	104/1528
	Enoxaparin 40 mg od	334/2699		Enoxaparin 40 mg od	126/1529
RECORD 1	Enoxaparin 40 mg od	131/2275	RECORD 3	Enoxaparin 40 mg od	142/1277
	Rivaroxaban 10 mg od	133/2266		Rivaroxaban 10 mg od	160/1254
RE-NOVATE	Dabigatran etexilate	141/1157	RE-MODEL	Dabigatran etexilate	110/694

	220 mg od			220 mg od	
	Enoxaparin 40 mg od	132/1162		Enoxaparin 40 mg od	115/699
Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	NR /792	N/A		
	Enoxaparin 40 mg od	NR /785			
Lassen 2002	Enoxaparin 40 mg od	NR /1154			
	Fondaparinux 2.5 mg od	NR /1155			

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

B7 **Priority request:** A possible typographical error was identified for the word analy* in line #74 of the Medline search for cost-effectiveness, where it appears as anlay*. The error appears to have been repeated in all subsequent strategies using this filter. Please clarify whether this could have influenced the results.

The typographical error was identified to have affected the Medline and Embase searches only (the Cochrane/NHS EED and EconLit searches did not contain any economic search terms). These databases were reinterrogated (accessed August 17th 2011) with the corrected free text term ('analy$'). However, on review of the title and abstract, none of these studies met the criteria for inclusion in the meta-analysis. The Search history is presented in the Appendix B Section 3.

B8 **Priority request**: Please explain why Medline Mesh terms were used to search Embase in lines #76-97 of the Embase cost-effectiveness strategy, and why the appropriate Emtree translations were not used.

The EMBASE search was updated with the appropriate Embase Mesh terms (accessed August 18th 2011). Eight additional citations were identified. However, on review of the title and abstract, none of the references met the inclusion criteria for the review. The Search history is presented in Appendix B Section 4.

B9 On page 154 (section 6.4.7) of the manufacturer's submission, please clarify which instruments were used for the different utility inputs, and justify if different instruments in addition to EQ-5D were used and for which estimates?

Table 26 below contains the utility inputs used in the economic model accompanied by their sources and the methods used in each study to elicit the utility values. The utilities for well/general population, PE, DVT (symptomatic proximal and distal DVT), aging, and the value of 0.095 for the sensitivity analysis of treated VTE were elicited using the EQ-5D (health state valuations established via time trade-off [19]). Both Kind et al [20] and Brunenberg [21] used the UK tariff [22] for the EQ-5D whilst Sullivan et al. [23] used the US tariff and Ingelgard et al. [24] did not specify which tariff they applied to the responses to the EQ-5D questionnaire.

The utility values used for the treated VTE state were taken from the study by Gage, [25] which were elicited using computerized time trade-off (with interviewer supervision). The utility for warfarin treatment was elicited by respondents to compare one year of life taking therapy with one year of life without therapy but a fraction of the year spent in a deep sleep (not dreaming or awakening refreshed) e.g. 51/52 weeks.

The utility value used for used for MM PTS from Lenert and Soetikno [26] and major bleed from Robertson et al. [27] were elicited using the standard gamble technique. Thirty healthy females (general public) and 30 physicians from Stanford USA were administered a computerized standard gamble questionnaire asking respondent to choose between a) living the remainder of their life with a specific health condition e.g. MM PTS and b) a probability of normal life with a probability of death e.g. 80% chance of full healthy and 20% chance of death.

Robinson et al. [27] elicited standard gamble utility values for major bleed from 57 patients with atrial fibrillation from three GP practices in the North East of England.

In the absence of utilities elicited from the appropriate UK clinical population using the EQ-5D (with UK valuation tariff) it has been necessary to select utility values elicited using alternative methods. We believe that the utility values selected are the most appropriate and robust from those available. The rationale for the selection of the utility values was outlined in section 6.4.9 of the submission and included in appendix B9 of this response.

Table 26: Utility Sources

Health state	Utility value	Source	Utility instrument
Treated VTE	–0.01	[25]	Time trade-off
	-0.095	[21]	EQ-5D
Well/General male population	0.78	[20]	EQ-5D
Well/General female population	0.78	[20]	EQ-5D
PE	–0.08	[24]	EQ-5D
Symptomatic Distal DVT	–0.08	[24]	EQ-5D
Symptomatic Proximal DVT	–0.08	[24]	EQ-5D
Mild/Moderate PTS (yr 1)	–0.02	[26]	Standard gamble
Mild/Moderate PTS (yr 2+)	–0.02	[26]	Standard gamble
Severe PTS (yr 1)	–0.07	[26]	Standard gamble
Severe PTS (yr 2+)	–0.07	[26]	Standard gamble
Major Bleed – other	–0.03	[27]	Standard gamble
Intracranial haemorrhage with disabled state	–0.49	[17]	Average of 109 published decrements for Stroke [17] (Awaiting appendix 9 Stroke utility weights from NICE)#
Aging (annual impact)	–0.00029	[23]	EQ-5D

Email correspondence in Appendix B Section 5.

B10 On page 154 (section 6.4.7) of the manufacturer's submission the ERG has noted that the standard errors for utilities and the utility decrements are all set to 10%, and considers that it would have been more appropriate to use estimates based on empirical evidence. Please amend the standard errors and utility decrements in line with the available evidence.

Response:
As suggested we returned to the original utility sources and re-examined them for standard errors or information that could be used to estimate or calculate a standard error. The well/general population standard error for both males and females was

unchanged as they were taken from the results of Kind et al. [20]. The utility values of zero for death, PE decrement following discharge, asymptomatic DVT, non major clinically relevant (NMCR) bleed and minor bleed were assumed and have been assumed to be constant (no standard error).

As Inglegard et al. [24] did not report any information on variation in utility scores for DVT it has been necessary to estimate the standard error. We conservatively estimated that the standard errors for the PE (prophylaxis and post-prophylaxis phase) and symptomatic distal and proximal DVT would be 10% of the disutility. As there was no measure of variation reported for the disutility of intracranial haemorrhage with disability [17] and aging [23] it has been necessary to assume the standard errors. We assumed that the standard errors would be 10% of the disutility value.

For major bleed [27] decrement we took the standard deviation for major bleed utility (0.172)an divided it by the square root of the sample size (N = 57) to obtain a standard error of 0.02278. The same method as was used for major bleed was used for MM PTS (Standard deviation = 0.04, N=30) and Severe PTS (Standard deviation = 0.04, N=30) [26], providing respective standard errors of 0.0073 and 0.01278.

For treated VTE Gage et al. [27] reported the 10th and 90th percentiles (0.953 - 1.0). By assuming the upper 95% confidence interval would be equal to 1.0 and assuming the lower confidence interval would be 10% less than the 10th percentile value at 0.8577 an estimated confidence interval was obtained. The confidence interval was transformed into a standard error by subtracting the upper confidence interval from the lower confidence interval and dividing the result by 2 * 1.96 (confidence interval for the standard normal distribution). Unfortunately this standard error occasionally produced values that would not allow a random value to be generated (using a Gamma or a beta distribution) and as a result it was necessary to revert to assuming that the standard error was 10% of the mean decrement.

All standard errors are presented in table 27 below, with new standard errors are in italic.

Table 27: Utility standard errors

Health state	Utility value	Original submission standard error	New standard error	New standard error value	Source
General male population	0.78	0.018543	No		[20]
General female population	0.78	0.015504	No		[20]
Death	0	-			Estimate
Events in prophylaxis & post-prophylaxis phases					
Hospitalization Period					
PE	–0.08	0.004082*	No		[24]
Symptomatic Distal DVT	–0.08	0.004082*	No		[24]
Symptomatic Proximal DVT	–0.08	0.004082*	No		[24]
Asymptomatic DVT	0	-	No		Estimate
ICH	–0.49	0.03*	No		[17]
Major Bleed – other	*–0.03*	*0.0015*	*Yes*	*0.022781957*	[27]

NMCR Bleed	0	-	No		Estimate
Minor Bleed	0	-	No		Estimate
PE	0				Estimate
Symptomatic Distal DVT	–0.08	0.004082*	No		[24]
Symptomatic Proximal DVT	–0.08	0.004082*	No		[24]
ICH Disabled	–0.49	0.03*	No		[17] Awaiting appendix 9 Stroke utility weights from NICE)
Long-term Markov phase					
Aging (annual impact)	–0.00029	0.000015*			[23]
Treated VTE	*–0.01*	*0.03630102*	*No*	*#0.03630102*	[25]
ICH Disabled State	–0.49	0.025000*			[17]
PE	–0.08	0.004082*			[24]
DVT	–0.08	0.004082*			[24]
Mild/Moderate PTS (yr 1)	*–0.02*	*0.007302967*	*Yes*	*0.007302967*	*[26]*
Mild/Moderate PTS (yr 2+)	*–0.02*	*0.007302967*	*Yes*	*0.007302967*	*[26]*
Severe PTS (yr 1)	*–0.07*	*0.012780193*	*Yes*	*0.012780193*	*[26]*
Severe PTS (yr 2+)	*–0.07*	*0.012780193*	*Yes*	*0.012780193*	*[26]*

* estimated; # could not be used (please see paragraph above this table)

B11 Please use standard deviation instead of standard error for the distribution of treatment duration in the model.

Response:
As requested standard deviations rather than standard deviations have been used for have been used for the distribution of treatment duration in the model. The standard deviations are presented in table 28 and 29 below. As the RE-MODEL study (Total knee replacement) did not report a standard error for the duration of dabigatran a standard deviation of 2 days was estimated based on 92% of patients having been treated for 6 to 10 days with a median duration of 8 days.

Table 28: VTE Prophylaxis duration in total knee replacement

	Rounded mean	Standard deviation	Comment	Reference
Apixaban	12	3.2		ADVANCE 2 [28]
Enoxaparin	12	2.8		ADVANCE 2 [28]
Rivaroxaban	12	2.5		RECORD4 [29]
Dabigatran	8*	2	Estimate - 92% were within 6 to 10 days	RE-MODEL [30]

* Median

As no standard deviation of treatment duration for dabigatran or rivaroxaban was reported in the RECORD 1 or RE-NOVATE trials we conservatively assumed they would be equal to the lowest standard deviation reported in the Advance 3 trial of 7.7 days. Duration of treatment for fondaparinux in the EPHESUS trial [14] was recorded as last day of active treatment with <1% before day 5, 97% days 5 to 9, 2% after day 9. We therefore assumed that the mean would be 7 days and that the standard deviation would be 2 days. Given the short duration of prophylaxis in the EPHESUS trial these assumptions would not disadvantage fondaparinux in cost terms.

Table 29: VTE Prophylaxis duration in total hip replacement

	Rounded mean	Standard deviation	Comment	Reference
Apixaban	34	7.7		Advance 3 [31]
Enoxaparin	34	7.8		Advance 3
Rivaroxaban	33	7.7	Set equal to lowest SE (apixaban)	REDCORD 1 [32]
Dabigatran	32*	7.7	Set equal to lowest SE (apixaban)	RE-NOVATE [33]
Fondaparinux	7	2	Estimated meads and standard deviation from last day of active treatment: <1% before day 5, 97% days 5 to 9, 2% after day 9 (N=908)	EPHESUS [14]

* Median

B12 On page 127, patients in the THR trial are described as being slightly younger than those in clinical practice. In the TKR trial, patients are described as being slightly less often male. Are sex and age predictors of bleeding and VTE? If so, please use adjusted baseline risks and relative risks in the model.

Response:

We agree with the ERG and NICE technology team that that ideally the outcomes (and subsequent risks and relative risk) would be assessed for statistically significant predictors such as age and gender and where appropriate the risks be adjusted. We did consider using meta-regression techniques (meta-regression model or mixed model) [34] to explore for significant predictors/covariates. However, such techniques are not advocated when a small number of studies is available [34], as the risk of obtaining a spurious 'explanation' for variable treatment effects is high in this

scenario (The Cochrane Collaboration 2011, Investigating sources of heterogeneity, http://www.cochrane-net.org/openlearning/html/mod13-5.htm). Unfortunately we have a small number of studies in hip [31, 33, 35, 36] and knee [28, 30, 37] populations in the base-case (vs. enoxaparin 40 mg od) indirect comparison of apixaban, dabigatran, and rivaroxaban that informs the economic model, and the age and gender profile of the participating patients is very similar. In TKR the mean ages vary by 2.9 years and in THR by 2.0 years. The gender split was also consistent in the trials with the number of males in the TKR trials varying by up to 10% and 8% in the THR trials. Given the low number of trials by surgery and the similarity in trial patient characteristics for age and gender we do not feel that conducting meta-regression to adjust baseline risks is appropriate.

B13 In table 81 of the manufacturer's submission, the results of the trial and the model do not exactly match. Please justify why recalibration has not been undertaken.

Response:
As the model submitted to NICE was based on the composite efficacy and safety endpoints and the probabilities for the events thereafter in the decision tree (e.g. types of VTEs and bleeds) are assumed to not differ between comparators, it is not surprising that the model results do not match the trial results. As there was a clear reason why there were differences between the model and trial results, recalibration was not thought to be necessary.

B14 In table 81 of the manufacturer's submission, results are provided for enoxaparin and apixaban. Please provide results for the other comparators as well.

Response:
Table 81 in the submission compared the predicted incidence of each event from the model with the actual incidence from the Advance 2 and 3 trials. However, as the model applies relative risks for Apixaban, dabigatran, rivaroxaban and fondaparinux to pooled absolute risks for enoxaparin from a number of trials, the table has been re-created below. The table is also based on the adapted version of the model, which allows type of VTE and bleed to vary by drug.

The table below shows that the predictions from the model are similar to the actual incidence rates from the relevant trials. Particularly for the enoxaparin arm, the pooled absolute risk was implemented directly into the model and so will match the absolute risks as pooled from the indirect comparison. The predicted rates for the types of VTE and bleed will not match exactly the rates from the individual trials or the pooled absolute risks for enoxaparin, as the split of the composite efficacy endpoint into All VTE and non-VTE death is not based on drug-specific information (see response to B2 for explanation as to why this was not possible).

Table 30: Comparison of model results compared with trial data (THR)

THR											
	Apixaban 2.5 mg bd		Enoxaparin 40 mg od (pooled)		Rivaroxaban 10 mg od		Dabigatran etexilate 220 mg od	Dabigatran etexilate 220 mg od		Fondaparinux 2.5 mg od	
	ADVANCE-3	Model	Indirect Comparison absolute risks	Model	RECORD 1	Model	RE-NOVATE	Huo 2010 (RE-NOVATE II)	Model	Lassen 2002	
VTE composite (primary efficacy population analysis)	1.39%	1.64%	4.58%	4.58%	1.13%	1.37%	6.02%	7.70%	4.06%	4.07%	1.97%
Asymptomatic DVT	1.08%	1.48%	5.73%	4.18%	NA	NA	4.58%	NA	3.05%	3.63%	1.50%
Symptomatic DVT	0.04%	0.02%	0.15%	0.11%	NA	NA	0.52%	NA	0.66%	0.26%	0.29%
PE (ITT population analysis)	0.11%	0.09%	0.18%	0.13%	0.18%	NA	0.43%	NR /792	0.22%	0.17%	0.12%
Any bleeding (ITT population analysis)	11.56%	8.73%	9.39%	9.39%	5.87%	9.58%	12.19%	NR /792	10.05%	NR /1155	13.80%
Major bleeding (ITT population analysis)	0.81%	1.15%	0.94%	0.22%	0.26%	0.55%	1.99%	1.77%	0.27%	4.07%	13.80%
CRNM bleeding (ITT population analysis)	4.03%	1.39%	3.34%	7.68%	2.87%	7.78%	4.15%	NR /792	8.48%	NR /1155	0.00%

Table 31: Comparison of model results compared with trial data (TKR)

TKR	Apixaban 2.5 mg bd		Enoxaparin 40 mg od (pooled)		Rivaroxaban 10 mg od		Dabigatran etexilate 220 mg od	
	ADVANCE-2	Model	Indirect comparison absolute risks	Model	RECORD 3	Model	RE-MODEL	Model
VTE composite (primary efficacy population analysis)	15.06%	16.25%	26.29%	26.29%	9.59%	13.33%	36.38%	25.37%
Asymptomatic DVT	14.36%	14.08%	29.50%	24.62%	NA	NA	35.98%	24.36%
Symptomatic DVT	0.20%	0.25%	0.73%	0.61%	NA	NA	0.14%	0.08%
PE (ITT population analysis)	0.26%	1.36%	0.19%	0.16%	0.00%	NA	0.00%	0.05%
Any bleeding (ITT population analysis)	6.81%	7.26%	8.75%	8.75%	12.76%	8.93%	15.85%	8.40%
Major bleeding (ITT population analysis)	0.59%	0.48%	0.86%	0.77%	0.56%	0.86%	1.44%	0.85%
CRNM bleeding (ITT population analysis)	2.88%	2.37%	3.57%	3.20%	2.63%	4.28%	5.76%	3.43%

B15 Please amend the cost per course of dabigatran (for THR) from £1324.40 to £134.40 in table 77.

Response:

The typographical error has been corrected in table 77 (from submission) below.

Table 77 (From submission): Drug acquisition, monitoring and administration costs

Drug	Dose	Pack price	Pills/ injections per pack	Pills per day of treatment	Cost per day	Days of TKR treatment	Days of THR treatment	Cost per TKR course	Cost per THR course
Enoxaparin	40mg[#]	£40.36 [38]	10	1	£4.04	12 [13, 39]	34 [12]	£48.48	£137.36
Rivaroxaban	10mg[#]	£441.45 [38]	100	1	£4.41	12 [40, 41]	33 [42]	£52.97	£145.68
Dabigatran*	220mg[#]	£126.00 [38]	60	2	£4.20	8 [43]	32 [44]	£33.60	£134.40
Apixaban	2.5[¥]	£102.90 (Pfizer/BMS)	60	2	£3.43	12 [13, 39]	34 [12]	£41.16	£116.62
	Inpatient				**Outpatient**				
	Number of blood counts	**Cost of blood count[@]**	**30 minutes training to self inject from a nurse**	**Cost of nurse* training for 30 minutes**	**Home visits from a community nurse to inject prophylaxis**	**Number of days where a home visit is required[¥]**		**Community nurse[#]**	**Total**
						TKR	**THR**		**THR** / **TKR**
Enoxaparin	4	£10.11	Yes 87% of patients	£25.00	Yes 13% of patients	7	29	£27.00	£163.98 / £86.76

[#]OD/ once a day; [¥]BID/ twice a day *First day of treatment only 110mg; a assumption; b TKR assumed to be the same as THR duration

*(24-hour ward [costs including qualifications]) [45]

[#](includes district nursing sister, district nurse) - home visit (including wages/salary, salary oncosts, qualifications, overheads, capital overheads and travel) [45]

[@]unit cost taken from the rivaroxaban STA submission to NICE [46] and updated to 2008/9 costs using the Hospital and Community Health Service Pay and Price Index [45] (See Appendix 19)

¥Treatment duration minus inpatient stay.

B16 It is unclear to the ERG how the costs in tables 91 and 92 relate to those in 93 and 94 in the manufacturer's submission. For example, in table 91 apixaban is £58 less costly than enoxaparin. In table 93 the difference in mean total treatment costs is £54. Please clarify the difference between these numbers.

Response:
The ERG are correct that there was a discrepancy in these tables. The revised tables 91 and 92 below now have discounted treatment costs and include the cost of bleeding. The total incremental costs in tables 91 and 92 now correspond to the increment for mean total treatment costs in tables 93 and 94. We have also amended tables 85 to 90 to include discounted life years and QALYs, and have included outcomes from the decision tree phase of the model (first 90 days).

Table 91 (From submission) Summary of costs by health state in THR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£1.65	£4.60	-£2.95	£2.95	5.44%
PE	£1.33	£3.70	-£2.37	£2.37	4.37%
DVT	£14.74	£41.05	-£26.31	£26.31	48.49%
M/M PTS Y1	£0.15	£0.43	-£0.28	£0.28	0.51%
Severe PTS Y1	£7.12	£19.84	-£12.72	£12.72	23.44%
M/M PTS Y2+	£0.13	£0.36	-£0.23	£0.23	0.42%
Severe PTS Y2+	£3.08	£8.57	-£5.49	£5.49	10.12%
ICH	£0.00	£0.00	£0.00	£0.00	0.00%
Major	£8.24	£8.86	-£0.62	£0.62	1.14%
NMCR	£29.79	£32.03	-£2.24	£2.24	4.13%
Minor	£13.96	£15.01	-£1.05	£1.05	1.94%
Total	£80.19	£134.45	-£54.26	£54.26	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£1.65	£1.38	£0.27	£0.27	2.81%
PE	£1.33	£1.11	£0.22	£0.22	2.26%
DVT	£14.74	£12.31	£2.42	£2.42	25.06%
M/M PTS Y1	£0.15	£0.13	£0.03	£0.03	0.26%
Severe PTS Y1	£7.12	£5.95	£1.17	£1.17	12.11%
M/M PTS Y2+	£0.13	£0.11	£0.02	£0.02	0.22%
Severe PTS Y2+	£3.08	£2.57	£0.51	£0.51	5.23%
ICH	£0.00	£0.00	£0.00	£0.00	0.00%
Major	£8.24	£9.04	-£0.80	£0.80	8.25%
NMCR	£29.79	£32.67	-£2.88	£2.88	29.82%
Minor	£13.96	£15.31	-£1.35	£1.35	13.98%
Total	£80.19	£80.58	-£0.40	£9.67	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£1.65	£4.08	-£2.43	£2.43	4.93%
PE	£1.33	£3.28	-£1.95	£1.95	3.96%
DVT	£14.74	£36.41	-£21.67	£21.67	43.96%
M/M PTS Y1	£0.15	£0.38	-£0.23	£0.23	0.46%
Severe PTS Y1	£7.12	£17.60	-£10.48	£10.48	21.25%
M/M PTS Y2+	£0.13	£0.32	-£0.19	£0.19	0.38%
Severe PTS Y2+	£3.08	£7.60	-£4.52	£4.52	9.18%
ICH	£0.00	£0.00	£0.00	£0.00	0.00%
Major	£8.24	£9.48	-£1.24	£1.24	2.52%
NMCR	£29.79	£34.27	-£4.48	£4.48	9.10%
Minor	£13.96	£16.06	-£2.10	£2.10	4.26%
Total	£80.19	£129.49	-£49.30	£49.30	100.00%

Table 92 (From submission) Summary of costs by health state in TKR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£21.17	£34.26	-£13.09	£13.09	7.29%
PE	£12.82	£20.74	-£7.92	£7.92	4.41%
DVT	£141.67	£229.23	-£87.57	£87.57	48.77%
M/M PTS Y1	£1.50	£2.42	-£0.93	£0.93	0.52%
Severe PTS Y1	£68.32	£110.55	-£42.23	£42.23	23.52%
M/M PTS Y2+	£1.25	£2.02	-£0.77	£0.77	0.43%
Severe PTS Y2+	£29.43	£47.61	-£18.19	£18.19	10.13%
ICH	£0.00	£0.00	£0.00	£0.00	0.00%
Major	£6.85	£8.25	-£1.40	£1.40	0.78%
NMCR	£24.77	£29.85	-£5.07	£5.07	2.83%
Minor	£11.61	£13.99	-£2.38	£2.38	1.32%
Total	£319.38	£498.93	-£179.55	£179.55	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£21.17	£17.37	£3.80	£3.80	6.39%
PE	£12.82	£10.51	£2.30	£2.30	3.87%
DVT	£141.67	£116.22	£25.44	£25.44	42.77%
M/M PTS Y1	£1.50	£1.23	£0.27	£0.27	0.45%
Severe PTS Y1	£68.32	£56.05	£12.27	£12.27	20.62%
M/M PTS Y2+	£1.25	£1.02	£0.22	£0.22	0.38%
Severe PTS Y2+	£29.43	£24.14	£5.29	£5.29	8.88%
ICH	£0.00	£0.00	£0.00	£0.00	0.00%
Major	£6.85	£8.42	-£1.57	£1.57	2.64%
NMCR	£24.77	£30.44	-£5.67	£5.67	9.53%
Minor	£11.61	£14.27	-£2.66	£2.66	4.47%
Total	£319.38	£279.68	£39.70	£59.50	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£21.17	£33.06	-£11.89	£11.89	7.35%
PE	£12.82	£20.01	-£7.20	£7.20	4.45%
DVT	£141.67	£221.21	-£79.54	£79.54	49.15%
M/M PTS Y1	£1.50	£2.34	-£0.84	£0.84	0.52%
Severe PTS Y1	£68.32	£106.68	-£38.36	£38.36	23.70%
M/M PTS Y2+	£1.25	£1.95	-£0.70	£0.70	0.43%
Severe PTS Y2+	£29.43	£45.95	-£16.52	£16.52	10.21%
ICH	£0.00	£0.00	£0.00	£0.00	0.00%
Major	£6.85	£7.92	-£1.07	£1.07	0.66%
NMCR	£24.77	£28.65	-£3.88	£3.88	2.40%
Minor	£11.61	£13.43	-£1.82	£1.82	1.12%
Total	£319.38	£481.20	-£161.82	£161.82	100.00%

Table 93 (From submission) Summary of predicted resource use by category of cost for THR

Item	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Technology cost	£116.62	£137.36	–£20.74	£20.74	8.68%
Mean total treatment cost (event cost)	£80.19	£134.45	–£54.26	£54.26	22.71%
Administration cost	£0.00	£123.54	–£123.54	£123.54	51.69%
Monitoring cost	£0.00	£40.44	–£40.44	£40.44	16.92%
Total	£196.81	£ 435.79	–£238.98	£238.98	100.00%
Item	**Apixaban**	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£116.62	£145.70	–£29.08	£29.08	98.65%
Mean total treatment cost (event cost)	£80.19	£80.58	–£0.40	£0.40	1.35%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£196.81	£226.28	–£29.47	£29.47	100.00%
Item	**Apixaban**	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£116.62	£134.40	–£17.78	£17.78	26.51%
Mean total treatment cost (event cost)	£80.19	£129.49	–£49.30	£49.30	73.49%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£196.81	£263.89	–£67.08	£67.08	100.00%

Table 94 (From submission) Summary of predicted resource use by category of cost for TKR

Item	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Technology cost	£41.16	£48.48	–£7.32	£7.32	2.68%
Mean total treatment cost	£319.38	£498.93	–£179.55	£179.55	65.62%
Administration cost	£0.00	£46.32	–£46.32	£46.32	16.93%
Monitoring cost	£0.00	£40.44	–£40.44	£40.44	14.78%
Total	£360.54	£634.17	–£273.63	£273.63	100.00%
Item	**Apixaban**	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£41.16	£52.98	–£11.82	£11.82	22.94%
Mean total treatment cost	£319.38	£279.68	£39.70	£39.70	77.06%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£360.54	£332.66	£27.88	£51.52	100.00%
Item	**Apixaban**	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£41.16	£33.60	£7.56	£7.56	4.46%
Mean total treatment cost	£319.38	£481.20	–£161.82	£161.82	95.54%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£360.54	£514.80	–£154.26	£169.38	100.00%

Table 85 (From submission) Mean per person model outputs by clinical outcomes for Apixaban

	Apixaban - TKR			Apixaban - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	9.868	7.672		12.07	9.39	
Untreated VTE	0.637	0.496		0.07	0.05	
Treated VTE	0.604	0.469	£21.17	0.06	0.05	£1.65
PE	0.003	0.002	£12.82	0.00	0.00	£1.33
DVT	0.051	0.039	£141.67	0.01	0.00	£14.74
M/M PTS Y1	0.032	0.024	£1.50	0.00	0.00	£0.15
Severe PTS Y1	0.015	0.011	£68.32	0.00	0.00	£7.12
M/M PTS Y2+	0.337	0.255	£1.25	0.04	0.03	£0.13
Severe PTS Y2+	0.152	0.108	£29.43	0.02	0.01	£3.08
ICH		0.000	£0.00		0.00	£0.00
Major		0.000	£6.85		0.00	£8.24
NMCR		0.000	£24.77		0.00	£29.79
Minor		0.000	£11.61		0.00	£13.96
	11.699	9.075	£319.38	12.269	9.535	£80.19

Table 86 (From submission) Mean per person model outputs by clinical outcomes for enoxaparin

	Enoxaparin - TKR			Enoxaparin - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	8.684	6.752		11.71	9.11	
Untreated VTE	1.031	0.803		0.19	0.15	
Treated VTE	0.977	0.758	£34.26	0.17	0.13	£4.60
PE	0.005	0.004	£20.74	0.00	0.00	£3.70
DVT	0.082	0.063	£229.23	0.01	0.01	£41.05
M/M PTS Y1	0.052	0.039	£2.42	0.01	0.01	£0.43
Severe PTS Y1	0.025	0.018	£110.55	0.00	0.00	£19.84
M/M PTS Y2+	0.545	0.412	£2.02	0.10	0.08	£0.36
Severe PTS Y2+	0.246	0.174	£47.61	0.05	0.03	£8.57
ICH		0.000	£0.00		0.00	£0.00
Major		0.000	£8.25		0.00	£8.86
NMCR		0.000	£29.85		0.00	£32.03
Minor		0.000	£13.99		0.00	£15.01
	11.647	9.023	£498.93	12.254	9.520	£134.45

Table 87 (From submission) Mean per person model outputs by clinical outcomes for rivaroxaban

	Rivaroxaban - TKR			Rivaroxaban - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	10.21	7.94		12.11	9.41	
Untreated VTE	0.52	0.41		0.06	0.04	
Treated VTE	0.50	0.38	£17.37	0.05	0.04	£1.38
PE	0.00	0.00	£10.51	0.00	0.00	£1.11
DVT	0.04	0.03	£116.22	0.00	0.00	£12.31
M/M PTS Y1	0.03	0.02	£1.23	0.00	0.00	£0.13
Severe PTS Y1	0.01	0.01	£56.05	0.00	0.00	£5.95
M/M PTS Y2+	0.28	0.21	£1.02	0.03	0.02	£0.11
Severe PTS Y2+	0.12	0.09	£24.14	0.01	0.01	£2.57
ICH		0.00	£0.00		0.00	£0.00
Major		0.00	£8.42		0.00	£9.04
NMCR		0.00	£30.44		0.00	£32.67
Minor		0.00	£14.27		0.00	£15.31
	11.714	9.089	£279.68	12.270	9.536	£80.58

Table 88 (From submission) Mean per person model outputs by clinical outcomes for dabigatran

	Dabigatran - TKR			Dabigatran - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	8.79	6.84		11.78	9.16	
Untreated VTE	1.00	0.77		0.17	0.13	
Treated VTE	0.94	0.73	£33.06	0.15	0.12	£4.08
PE	0.00	0.00	£20.01	0.00	0.00	£3.28
DVT	0.08	0.06	£221.21	0.01	0.01	£36.41
M/M PTS Y1	0.05	0.04	£2.34	0.01	0.01	£0.38
Severe PTS Y1	0.02	0.02	£106.68	0.00	0.00	£17.60
M/M PTS Y2+	0.53	0.40	£1.95	0.09	0.07	£0.32
Severe PTS Y2+	0.24	0.17	£45.95	0.04	0.03	£7.60
ICH		0.00	£0.00		0.00	£0.00
Major		0.00	£7.92		0.00	£9.48
NMCR		0.00	£28.65		0.00	£34.27
Minor		0.00	£13.43		0.00	£16.06
	11.652	9.025	£481.20	12.257	9.523	£129.49

Table 89 (From submission) Summary of QALY accrued per person by health state in THR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	9.39	9.11	0.28	0.28	51.36%
Untreated VTE	0.05	0.15	-0.09	0.09	17.36%
Treated VTE	0.05	0.13	-0.09	0.09	15.82%
PE	0.00	0.00	0.00	0.00	0.08%
DVT	0.00	0.01	-0.01	0.01	1.34%
M/M PTS Y1	0.00	0.01	0.00	0.00	0.82%
Severe PTS Y1	0.00	0.00	0.00	0.00	0.37%
M/M PTS Y2+	0.03	0.08	-0.05	0.05	9.02%
Severe PTS Y2+	0.01	0.03	-0.02	0.02	3.84%
ICH	0.00	0.00	0.00	0.00	0.00%
Major	0.00	0.00	0.00	0.00	0.00%
NMCR	0.00	0.00	0.00	0.00	0.00%
Minor	0.00	0.00	0.00	0.00	0.00%
Total	9.53	9.52	0.01	0.55	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	9.39	9.41	-0.03	0.03	51.35%
Untreated VTE	0.05	0.04	0.01	0.01	17.36%
Treated VTE	0.05	0.04	0.01	0.01	15.82%
PE	0.00	0.00	0.00	0.00	0.08%
DVT	0.00	0.00	0.00	0.00	1.34%
M/M PTS Y1	0.00	0.00	0.00	0.00	0.82%
Severe PTS Y1	0.00	0.00	0.00	0.00	0.37%
M/M PTS Y2+	0.03	0.02	0.00	0.00	9.02%
Severe PTS Y2+	0.01	0.01	0.00	0.00	3.84%
ICH	0.00	0.00	0.00	0.00	0.00%
Major	0.00	0.00	0.00	0.00	0.00%
NMCR	0.00	0.00	0.00	0.00	0.00%
Minor	0.00	0.00	0.00	0.00	0.00%
Total	9.53	9.54	0.00	0.05	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	9.39	9.16	0.23	0.23	51.36%
Untreated VTE	0.05	0.13	-0.08	0.08	17.36%
Treated VTE	0.05	0.12	-0.07	0.07	15.82%
PE	0.00	0.00	0.00	0.00	0.08%
DVT	0.00	0.01	-0.01	0.01	1.34%
M/M PTS Y1	0.00	0.01	0.00	0.00	0.82%
Severe PTS Y1	0.00	0.00	0.00	0.00	0.37%
M/M PTS Y2+	0.03	0.07	-0.04	0.04	9.02%
Severe PTS Y2+	0.01	0.03	-0.02	0.02	3.84%
ICH	0.00	0.00	0.00	0.00	0.00%
Major	0.00	0.00	0.00	0.00	0.00%
NMCR	0.00	0.00	0.00	0.00	0.00%

Minor	0.00	0.00	0.00	0.00	0.00%
Total	9.53	9.52	0.01	0.45	100.00%

Table 90 (From submission) Summary of QALY gain by health state in TKR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	7.67	6.75	0.92	0.92	51.54%
Untreated VTE	0.50	0.80	-0.31	0.31	17.18%
Treated VTE	0.47	0.76	-0.29	0.29	16.07%
PE	0.00	0.00	0.00	0.00	0.08%
DVT	0.04	0.06	-0.02	0.02	1.36%
M/M PTS Y1	0.02	0.04	-0.01	0.01	0.84%
Severe PTS Y1	0.01	0.02	-0.01	0.01	0.38%
M/M PTS Y2+	0.25	0.41	-0.16	0.16	8.82%
Severe PTS Y2+	0.11	0.17	-0.07	0.07	3.73%
ICH	0.00	0.00	0.00	0.00	0.00%
Major	0.00	0.00	0.00	0.00	0.00%
NMCR	0.00	0.00	0.00	0.00	0.00%
Minor	0.00	0.00	0.00	0.00	0.00%
Total	9.08	9.02	0.06	1.78	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	7.67	7.94	-0.27	0.27	51.32%
Untreated VTE	0.50	0.41	0.09	0.09	17.10%
Treated VTE	0.47	0.38	0.09	0.09	16.44%
PE	0.00	0.00	0.00	0.00	0.08%
DVT	0.04	0.03	0.01	0.01	1.35%
M/M PTS Y1	0.02	0.02	0.00	0.00	0.83%
Severe PTS Y1	0.01	0.01	0.00	0.00	0.38%
M/M PTS Y2+	0.25	0.21	0.05	0.05	8.78%
Severe PTS Y2+	0.11	0.09	0.02	0.02	3.71%
ICH	0.00	0.00	0.00	0.00	0.00%
Major	0.00	0.00	0.00	0.00	0.00%
NMCR	0.00	0.00	0.00	0.00	0.00%
Minor	0.00	0.00	0.00	0.00	0.00%
Total	9.08	9.09	-0.01	0.52	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	7.67	6.84	0.84	0.84	51.55%
Untreated VTE	0.50	0.77	-0.28	0.28	17.18%
Treated VTE	0.47	0.73	-0.26	0.26	16.06%
PE	0.00	0.00	0.00	0.00	0.08%
DVT	0.04	0.06	-0.02	0.02	1.36%
M/M PTS Y1	0.02	0.04	-0.01	0.01	0.84%
Severe PTS Y1	0.01	0.02	-0.01	0.01	0.38%

M/M PTS Y2+	0.25	0.40	-0.14	0.14	8.82%
Severe PTS Y2+	0.11	0.17	-0.06	0.06	3.73%
ICH	0.00	0.00	0.00	0.00	0.00%
Major	0.00	0.00	0.00	0.00	0.00%
NMCR	0.00	0.00	0.00	0.00	0.00%
Minor	0.00	0.00	0.00	0.00	0.00%
Total	9.08	9.02	0.05	1.62	100.00%

B17 The distributions (lognormal) for the relative risk model parameters for the comparators underestimate the uncertainty as observed in the trials. For instance, for rivaroxaban THR the 95% confidence interval (CI) in the trial was 0.18-0.51, while the distribution in the model results in a 95% CI of 0.26-0.35. Please adjust the distributions used in the model for the relative risks, in order to properly reflect uncertainty.

Response:
The distributions used in the model for relative risks have been amended to fully reflect the uncertainty. The revised lognormal distribution was applied using the methods proposed by Briggs et al. [47].

α was calculated by:

1. Taking the natural log ($\log_e$) of the mean RR.

β was calculated by:

1. Taking the natural logs ($\log_e$) of the 95% confidence interval.
2. Subtracting the log'd lower 95% confidence interval from the log'd upper 95% confidence interval and dividing the result by 2 * 1.96.

The randomly generated relative risk value was obtained by utilizing α and β in the following code in Microsoft Excel "=EXP(NORMINV(RAND(),α, β))".

B18 The RE-MODEL and RE-NOVATE trials do not present relative risks. Please clarify how the data inputs for the relative risks and uncertainty for dabigatran in the model were determined.

Response:
The two tables below summarise the data used to calculate the risks for dabigatran. The numerical data (numerators and denominators) below extracted for the VTE composite and any bleeding outcomes from the RE-NOVATE and RE-MODEL trial publications were used to calculate relative risks and 95% confidence intervals. Direct relative risks were calculated in STATA IC version 10.1 using the *metan* package SJ9_2: sbe24_3 [48, 49] for both pair-wise comparisons and single head-to-head studies.

Table 36 (from submission): VTE composite (primary efficacy population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
RE-NOVATE Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL	Dabigatran etexilate 220 mg od	[redacted]
Data inputs					
		Ns			**Ns**
RE-NOVATE	Dabigatran etexilate 220 mg od	53/880	RE-MODEL	Dabigatran etexilate 220 mg od	183/503
	Enoxaparin 40 mg od	60/897		Enoxaparin 40 mg od	193/512
Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	61/792			
	Enoxaparin 40 mg od	69/785			

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; N/A, non applicable

Table 42 (from submission): Any bleeding (ITT population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
RE-NOVATE	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL	Dabigatran etexilate 220 mg od	[redacted]
Data inputs					
		Ns			**Ns**
RE-NOVATE	Dabigatran etexilate 220 mg od	141/1157	RE-MODEL	Dabigatran etexilate 220 mg od	110/694
	Enoxaparin 40 mg od	132/1162		Enoxaparin 40 mg od	115/699
Huo 2010 (RE-NOVATE II)	Dabigatran etexilate 220 mg od	NR /792			
	Enoxaparin 40 mg od	NR /785			

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

B19 A disparity between the dates listed for the Embase "Measurement and Valuation of Health Effects" was noted. Section 9.12.1 in the manufacturer's submission records that Ovid Embase 1980 to present day was searched, but in section 9.12.4 the strategy records 1996 to week 27 2010. Please confirm the start date of the search strategy and explain whether the discrepancy in start dates could have influenced the results?

Response:
The QoL search was re-run in OVID Embase from 1980 onwards. The relevant search strategy is reported in Appendix B Section 6. One additional 'hit' was reported (published 1995). However, on review of the title and abstract, this study did not meet the criteria for inclusion in the review.

B20 On page 182 (table 92) should be amended to Tables 91 and 92

Response:
We agree

B21 On page 15 in the last sentence, THR should read TKR and vice versa.

Response:
We agree

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