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Single Technology Appraisal (STA)

Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID662]

Dear Adrian,

The Evidence Review Group, BMJ Technology Assessment Group, and the technical team at NICE have now had an opportunity to take a look at the submission by Daiichi Sankyo received on the 13 February 2015. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Wednesday 25 March 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]. Any procedural questions should be addressed to [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A – clarifications of the clinical data

A1. **Priority question:** Please provide the details in section 1.3, page 14 of the company submission (CS) for the UK marketing authorisation of edoxaban for its use in the treatment and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The current information refers to a different indication.

This has been amended to state: "Edoxaban tosylate does not currently have a UK marketing authorisation for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults."

A2. **Priority question:** Please clarify how many patients had their edoxaban dose adjusted in the Hokusai-VTE trial in the following analysis sets and a breakdown of when during the trial the dose adjustments took place:

a) modified intention-to-treat (mITT) analysis set, overall study period;

b) mITT analysis set, on treatment period ;

c) safety analysis set overall study period;

d) safety analysis set on-treatment period.

Please note, the safety analysis for Hokusai-VTE was conducted for the on-treatment period only, and is thus identical to the population represented in the mITT, on treatment analysis. For this reason we cannot provide the safety analysis set overall study period as requested in (c) above.

Furthermore, we can only provide data for dose adjustment for patients who were on treatment. Therefore we cannot provide the data requested in a) above.

Finally, the mITT analysis set, on treatment period and the safety analysis set on-treatment period (b and d) are identical.

In the table below, the data are broken down into dose adjustment during the following periods: Day 1-14 inclusive; Day 15-98 inclusive; Day 99-186 inclusive; Day 187-365 inclusive. The mean and median timepoints of dose adjustment during the study are also provided.

Table: Overview of the number of patients with edoxaban dose adjustment - mITT analysis set, on treatment period

	Edoxaban (N=4118)	Warfarin (N=4122)	Total (N=8240)
	n (%)	n (%)	n (%)
No. of Patients with No Dose Adjustment at Randomisation	3385 (82.2)	3403 (82.6)	6788 (82.4)
No. of Patients with Dose Adjustment at Randomisation	733 (17.8)	719 (17.4)	1452 (17.6)
No. of patients with Dose Adjustment(s) after Randomisation [a]	68 (2.0)	55 (1.6)	123 (1.8)
Timepoint of 1st Dose Adjustment after Randomisation [a, b]			
- Mean	108.1	119.3	113.1
- Median	74.5	99.0	87.0
- Minimum	7	10	7
- Maximum	344	337	344
- [Day 1, Day 14]	5 (0.1)	1 (< 0.1)	6 (< 0.1))
- [Day 15, Day 98]	34 (1.0)	25 (0.7)	59 (0.9)
- [Day 99,Day 186]	14 (0.4)	15 (0.4)	29 (0.4)
- [Day 187, Day 365]	15 (0.4)	14 (0.4)	29 (0.4)

[a] Percentages for Patients with Dose Adjustment after Randomisation are based on Number of Patients with No Dose Adjustment at Randomisation.
[b] Summary statistics are based on Patients with Dose Adjustment after Randomisation.

A3. **Priority question:** Please clarify the source of the data and the analysis sets used for each of the studies in the network meta-analysis (NMA) for all outcomes (CS, Tables B 31 to B 40, pages 87–90).

Missing references were found in the PE subpopulation tables. Updated tables are provided below.

1. **All VTE patients**

Efficacy endpoint: VTE recurrence

Table B 31. Data used in the NMA for recurrence (6 month)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	73/4122 (1.77%)	61/4118 (1.48%)
AMPLIFY (68)	VKA regimen apixaban 5mg bd	71/2635 (2.69%)	59/2609 (2.26%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	27/1265 (2.13%)	30/1274 (2.35%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	28/1289 (2.17%)	30/1279 (2.35%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	53/1718 (3.08%)	34/1731 (1.96%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	44/2413 (1.82%)	46/2419 (1.90%)

Safety endpoint: Composite of Major and CRNM Bleeding

Table B 32. Data used in the NMA for Composite Bleeding (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	461/4122 (11.18%)	405/4118 (9.83%)
AMPLIFY (68)	VKA regimen apixaban 5mg bd	261/2689 (9.71%)	115/2676 (4.30%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	111/1266 (8.77%)	71/1273 (5.58%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	102/1288 (7.92%)	64/1280 (5.00%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	132/1711 (7.71%)	137/1718 (7.97%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	268/2405 (11.14%)	243/2412 (10.07%)

Safety endpoint: Major Bleeding

Table B 33. Data used in the NMA for Major bleeding (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	53/4122 (1.29%)	49/4118 (1.19%)
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	49/2689 (1.82%)	15/2676 (0.56%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	24/1266 (1.90%)	20/1273 (1.57%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	22/1288 (1.71%)	15/1280 (1.17%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	13/1711 (0.76%)	11/1718 (0.64%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	49/2405 (2.04%)	24/2412 (1.00%)

Safety endpoint: Clinically Relevant Non-Major Bleeding

Table B 34. Data used in the NMA for Clinically Relevant Non-Major Bleeding (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	313/4122 (7.59%)	250/4118 (6.07%)
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	215/2689 (8.00%)	103/2676 (3.85%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	87/1266 (6.87%)	51/1273 (4.01%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	80/1288 (6.21%)	49/1280 (3.83%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	77/1711 (4.50%)	97/1718 (5.65%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	178/2405 (7.40%)	174/2412 (7.21%)

Safety endpoint: VTE related death

Table B 35. Data used in the NMA for VTE Related Death (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	8/4122 (0.19%)	12/4118 (0.29%)
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	16/2689 (0.60%)	12/2676 (0.45%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	3/1265 (0.24%)	1/1274 (0.08%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	0/1289 (0.00%)	3/1279 (0.23%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	6/1711 (0.35%)	3/1718 (0.17%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	7/2413 (0.29%)	8/2419 (0.33%)

Other endpoint: Net Clinical Benefit

Table B 36. Data used in the NMA for Net Clinical Benefit (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	79/4122 (1.92%)	72/4118 (1.75%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	73/1711 (4.27%)	48/1718 (2.79%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	96/2405 (3.99%)	77/2412 (3.19%)

Net Clinical Benefit is defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, Major bleeding, and all-cause mortality

1. Subpopulation: PE population

Efficacy endpoint: VTE recurrence

Table B 37. Data used in the NMA for VTE Recurrence in PE population (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	25/1669 (1.50%)	16/1650 (0.97%)
AMPLIFY (68)	VKA regimen apixaban 5mg bd	23/886 (2.60%)	21/900 (2.33%)
RE-COVER/Re-COVER II (136)	VKA regimen vs dabigatran 150 mg bd	21/807 (2.60%)	18/795 (2.26%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	44/2413 (1.082%)	46/2419 (1.90%)

Safety endpoint: Composite of Major and CRNM Bleeding

Table B 38. Data used in the NMA for Composite Bleeding in PE population (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	208/1669 (12.46%)	193/1650 (11.70%)
RE-COVER/Re-COVER II (136)	VKA regimen vs dabigatran 150 mg bd	55/768 (7.16%)	71/1273 (5.58%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	268/2405 (11.14%)	243/2412 (10.07%)

Safety endpoint: Major Bleeding

Table B 39. Data used in the NMA of Major bleeding in PE population (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	20/1669 (1.20%)	22/1650 (1.33%)
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	25/902 (2.77%)	4/928 (0.43%)
RE-COVER/Re-COVER II (136)	VKA regimen vs dabigatran 150 mg bd	8/768 (1.04%)	4/759 (0.53%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	49/2405 (2.04%)	24/2412 (1.00%)

Safety endpoint: Clinically Relevant Non-Major Bleeding

Table B 40. Data used in the NMA of Clinically Relevant Non-Major Bleeding in PE population (6 months)

Trial Name	Comparison	n/N – VKA regimen	n/N – NOAC
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	144/1669 (8.63%)	121/1650 (7.33%)
RE-COVER/RE-COVER II (136)	VKA regimen vs dabigatran 150 mg bd	47/768 (6.12%)	32/759 (4.22%)
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	179/2405 (7.44%)	174/2412 (7.21%)

A4. **Priority question:** Please provide working WinBUGS code files including the priors, initial values, and the formatted data used for all NMAs (including sensitivity/subgroup analyses) presented in the submission.

All WinBUGS codes including the priors, initial values, and the formatted data used for all NMAs (including sensitivity/subgroup analyses) presented in the submission are provided in the zip file attached.[a]

A5. Please provide further details of the criteria used to determine the treatment duration (minimum 3 months, maximum 12 months) for patients in the Hokusai-VTE.

The treatment durations varied from 3 to 12 months at the discretion of the treating physician; at randomisation, the physician recorded an intended treatment duration. In addition, after 3 months of treatment, the intended treatment duration could be adapted at any time depending on the patient's clinical features, including risk of recurrent VTE, risk of bleeding, and the patient's own preference. This important feature of the study was included so as to closely reflect the clinical practice situation.

A6. Please clarify the type and frequency of monitoring performed in the Hokusai-VTE trial? (e.g. were patients weighed at each visit?)

Details of procedures conducted at each visit are given in Table 9.2 of the CSR, as follows:

Table 9.2: Schedule of Visits and Procedures

	SQ/Rand		Treatment Period [a]														
	Day -3	Day 1	Day 2-12		Day 30	Day 60	Month										
			n/a	1st Edoxaban Visit			3	4	5	6	7	8	9	10	11	12	F/UP
Visit Window (days) [b]	nA	n/a	±1	n/a	±3	±5	±5	±7	±7	±5	±7	±7	±7	±7	±7	±7	±7
Study Informed Consent	X																
Diagnosis of VTE	X																
Inclusion/Exclusion Criteria	X																
Demographic Information	X																
Medical/Surgical History	X																
Alcohol and Tobacco Use	X																
Physical Examination	X[c]																X
Vital Signs/Weight	X	X					X			X			X			X	X
12-lead ECG		X[j]			X												X
IXRS Randomization Visit Worksheet		X															
Liver function assessment includes ALT, AST, TBL, and ALP	X[d]	X[d]			X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry panel excluding liver function assessment	X[d]	X[d]			X		X			X			X			X	X
Hematology	X[d]	X[d]					X			X			X			X	
Urinalysis		X					X			X			X			X	
Archive Serum Sample		X															
Urine pregnancy Test		X															
AE Reporting[e]	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
Endpoint and other event reporting [e] – VTE, CV and bleeding events	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
Prior and Concomitant Medication	X	X					X			X			X			X	X
In-clinic study drug administration							X										
Study drug dispensing				X	X	X	X	X	X	X	X	X	X	X	X		
Study drug compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	
Contact IXRS for study drug assignment or to enter subject status changes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INR [f] measurement with IXRS contact			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PD sampling		X[g]					X[g]	X[g]								X[g]	X[g]
PK sampling							X[h]									X[h]	
Record date and time of subject's last dose (before PK sampling)							X									X	
Pharmacogenomics informed consent (optional)	X																
Pharmacogenomic sampling (optional)	X[i]																

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CV = cardiovascular; ECG = electrocardiogram; F/U = follow-up; INR = international normalized ratio; IXRS = interactive voice response system; PD = pharmacodynamics; PK = pharmacokinetics; Rand = randomization; SAE = serious adverse event; SQ = study qualification; TBL = total bilirubin; VTE = venous thromboembolism.

a: Subjects no longer taking study drug were to be followed for primary and secondary efficacy and safety endpoints and SAEs by visit or telephone contact every 3 months until Month 12. The subjects with temporary study drug interruptions/permanent discontinuations were to have the appropriate eCRFs completed. All randomized subjects were expected to have both a Month 12 visit and a F/U visit 1 month after permanently (premature or otherwise) discontinuing treatment.

b: Scheduling of visits within visit windows was to be done with caution to the drug supply available in a dispensing unit.

c: Targeted physical exam performed by an Investigator or other healthcare professional designated by the Investigator.

d: Samples taken as part of routine care outside study auspices could have been analyzed by local laboratories and the results used to qualify the subject provided the tests were performed within 48 hours of randomization. Alternatively, the central laboratory could have been utilized for these study qualification laboratory tests.

e: Endpoint events should have been reported as soon as site personnel learned of the event. Endpoint event and AE reporting occurred throughout the study and was not restricted to specific visits.

f: INR assessment for adjustment of warfarin dosages was to be done at least every 2 or 3 days per Investigator discretion during Days 2 through 12. Once the INR was stable, it was to be assessed at least every month. Additional interim evaluations may have been done at the discretion of the Investigator.

g: On Day 1, prior to dosing, three PD samples were to be collected; at Month 3, three PD samples were to be collected before dosing and one additional PD sample was to be collected 1 to 3 hours post-dose, concurrently with PK sample collection; at Month 12 or last study drug dosing visit, one PD sample was to be collected; in conjunction with an event, two PD samples were to be collected; at the study Follow-up visit, one PD sample was to be collected. PD sampling did not apply if the subject was in study drug interruption or had permanently discontinued study drug. It was critical to record the date/time of last study drug dose as well as the date/time of the last meal prior to each PD sample collection.

h: At Month 3, one PK sample was to be collected before dosing and one PK sample was to be collected 1 to 3 hours post-dose; at Month 12, one random PK sample was to be collected; and in conjunction with an event, one PK sample was to be collected. It was critical to record the date/time of the last dose as well as the date/time of the last meal prior to each PK sample collection.

i: Pharmacogenomics sample may have been collected at any treatment visit if it was not obtained at Day 1 and a Pharmacogenomics Informed Consent had been obtained.

j: An ECG obtained within 1 week of randomization was acceptable.

Further details are provided in Appendix 16.1.1, as follows:

Starting with the Day 30 visit, subjects will return to the clinic monthly (every 30 days ± visit window shown in Appendix 17.4) until the Month 12 visit or study drug interruption/discontinuation. During study drug interruptions and after study drug discontinuation, subjects will be followed for primary and secondary efficacy and safety endpoints and SAEs by visit or telephone contact every 3 months until the Month 12 visit or until study drug treatment (and regularly scheduled protocol-specified visits) is resumed.

At these monthly on-site visits, INR assessments will be done using the POC device provided by the Sponsor (or back-up method as described in Section 5.4) for adjustment of warfarin (or placebo-to-match warfarin) doses. Additional interim visits may be scheduled, at the Investigators discretion, for INR monitoring.

At specified visits per the visit schedule in Appendix 17.4, the following will be performed:
• Record concomitant medications.
• Count unused study drug tablets.
• Record vital signs (sitting BP and heart rate) and weight.
• Record 12-lead ECG.
• Take PK samples and record date/time of the last dose of study drug taken prior to sampling, as well as the date/time of the last meal prior to each PK sample collection (See Appendix 17.8 and Study Laboratory Manual for further instructions).
• Take samples for PD analyses (D-dimer, anti-FXa activity, and exploratory biomarkers) and record date/time of the last dose of study drug taken prior to sampling and the PD sample collection (Appendix 17.8 and Study Laboratory Manual for instructions).
• Take blood samples for the following laboratory tests:
− Liver function tests [ALT, AST, TBL, and ALP] at all monthly visits,
− Other serum chemistry analytes at identified visits,
− Hematology at identified visits,
− Samples should be sent to the central laboratory.
• Urinalysis at identified visits.
− Samples should be sent to the central laboratory.

In preparation for the Month 3 visit, subjects will be instructed to do the following:
• Record date/time of the last study drug dose taken before the Month 3 visit,
Record date/time of the last meal taken before the Month 3 visit,
• Not to take the study drug dose on the day of the Month 3 visit until administered the dose at the clinic.

During the Month 3 visit, blood samples for PK and PD will be taken. This involves the following procedures:
• Record date/time of the last study drug dose and last meal taken before the visit,
• Collect a PK sample and three PD samples (2 plasma and 1 serum) prior to in clinic study drug administration,
• Administer and record date/time of study drug given in the clinic,
• Collect an additional PK and an additional PD sample 1 to 3 hours after study drug administration,
• Refer to Appendix 17.8 for sample collection, processing, and storage instructions.

During the Month 12 visit, blood samples for PK and PD will be taken. This involves the following procedures:
• Record date/time of the last study drug dose and last meal taken before the visit,
• Collect a PK sample and PD samples at anytime during the visit,
• Refer to Appendix 17.8 for sample collection, processing, and storage instructions.

At PK and PD sampling visits other than Month 3 (Appendix 17.8), the PK and PD samples can be taken without in-clinic study drug administration. Date/time of last dose before the PK and PD sampling will be recorded along with date/time of both the PK and the PD sample collection. In case of an event (VTE or major or clinically relevant nonmajor bleeding), every attempt will be made to collect one PK and two PD samples (including date/time of sample) along with the date/time of last study drug dose before the PK and PD sampling.

At study drug dispensing visits specified in the visit schedule in Appendix 17.4:
• Collect unused study drug tablets,
• Call the IXRS to get new study drug kit numbers,
• Dispense study drug and record amount (number of tablets) dispensed.

All used/unused study drug supplies should be retrieved from subject at the monthly visits and new supplies dispensed. Study drug may be retrieved/dispensed at unscheduled visits if needed, e.g., due to warfarin dose changes.

A7. Please provide an explanation for the early excess of recurrent venous thromboembolism (VTE) in the edoxaban treatment arm of Hokusai-VTE (CS, page 64).

The excess early index events in the edoxaban treated DVT subjects was driven by an early excess of recurrent VTE in the edoxaban subjects with index DVT (CSR, Section 11.4.1.1.1, Table 14.2.1.31, and Figure 11.2). It should be noted that by protocol design, subjects in the edoxaban cohort received only active low molecular weight or unfractionated heparin ((LMW) heparin) until the sham INR reached 2.0, (median of 7 days). In contrast, the warfarin cohort received both active (LMW) heparin and active warfarin (subtherapeutic) during this same time period. The warfarin DVT group did experience less early recurrent VTE but with more bleeding during the first 10 days than the edoxaban DVT group (VTE: 21 [0.9%] vs. 15 [0.6%], Major/CRNM bleed: 20 [0.8%] vs.31[1.3%], edoxaban vs. warfarin, respectively. By 30 days, the difference between treatment groups was even less pronounced for recurrence (VTE DVT subjects: 30 (1.2%) vs. 26 (1.1%), edoxaban vs. warfarin, respectively) with even less bleeding in the edoxaban 60-mg group compared to the warfarin group (Major/CRNM bleed DVT subjects: 56 (2.3 %) vs. 101 (4.1%), edoxaban vs. warfarin, respectively) (CSR, Table 14.2.1.31 and Table 14.3.1.149). Given the efficacy and half–life of (LMW) heparin and the rapid onset of action of edoxaban (edoxaban: Tmax 1-3 hours), it is unlikely that additional overlap of (LMW) heparin with edoxaban (standard or reduced dose) would contribute to significantly increased efficacy and would most likely increase the bleeding risk. Overall, given the small early imbalance in VTE recurrence, this finding may likely be a reflection of real-world variability in a large population.

A8. Please provide a further breakdown of when in the time “from index event to 14 days” the recurrent VTE events occurred in each of the edoxaban and warfarin groups for the safety analysis set, on-treatment period reported in Table B 57 (page 131) of the company submission and Table 1.4.9.4.2 of the Hokusai-VTE post-hoc analysis.

We present a LIFETEST procedure detailing these events in the attached document.[b]

A9. Please provide the equivalent data already provided in Table B 57 (CS, page 131) on recurrent VTE as a function of the time period based on Hokusai-VTE using the mITT analysis set, on-treatment period for both the edoxaban arm and warfarin arm.

Please see the table below.

Table: Recurrent VTE separately by treatment arm as a function of the time period based on Hokusai VTE - mITT population (N=8240), On-Treatment Period

	Warfarin			
Time period	**N**	**n**	**p**	**95% CI**
From Index event to 14 days	4122	23	0.558%	0.331% - 0.785%
From 15 days to 98 days	3972	43	1.083%	0.761% - 1.404%
From 99 days to 448 days	3578	16	0.447%	0.229% - 0.666%
	Edoxaban			
Time period	**N**	**n**	**P**	**95% CI**
From Index event to 14 days	4118	30	0.729%	0.469% - 0.988%
From 15 days to 98 days	3967	21	0.529%	0.304% - 0.755%
From 99 days to 448 days	3614	17	0.470%	0.247% - 0.693%
Source: Hokusai-VTE post-hoc analysis table 1.4.9.4.2				

A10. Please provide the definition of “Temporary baseline risk factors” used in the subgroup analysis presented in Figure B 7 (CS, page 66).

Temporary risk factors are transient and include trauma, recent surgery, immobilisation, oestrogen therapy, etc. According to the label a short duration of therapy (at least 3 months) should be based on transient risk factors.

A11. Please provide details of any subsequent treatment received by the subjects in each treatment arm after permanent study drug discontinuation (CS, Table B 17, page 71).

The summary of all post-treatment medications in the Hokusai VTE study is supplied as an attachment.[c]

A12. Please clarify the rationale for the per protocol analysis of recurrent VTE during the treatment + 30 days study period presented in Appendix 14, page 38.

The Per Protocol analysis was conducted to fulfil the requirements of the European Medicines Agency. The treatment +30 days analysis is a sensitivity analysis that accompanies those data.

A13. Please provide the Deviance Information Criterion (DIC) and a comparison of the residual deviance with the number of unconstrained data points for each outcome when using a fixed and random effects model for the NMA (CS, Tables B 41 to B 50).

Due to the nature of the network (few studies comparing the same treatments), a random-effect model was not recommended because the between-study heterogeneity could not be estimated with enough precision.

This phenomenon can be quantified through the number of unconstrained data points estimated through the DIC. The number of unconstrained data points provides an estimate for the impact of the priors when compared to the number of parameters to estimate in our model: the lower this number is, the greater the influence of the priors on the posterior estimation.

When priors are non-informative, this influence needs to be near to zero (non-informative priors are used to avoid making incorrect inference).

For most of the outcomes in our model, the choice of a random-effects model results in fewer unconstrained data points than estimated parameters in the model. Because of this, the random-effect model is under-determined and by consequence, the model is not robust to the specification of its priors.

However, both models have been run and the comparison for the total residual of variance, the number of unconstrained parameters and the deviance information criterion are given in the table below.

Table: Deviance information Criterion in fixed-effects and random-effects model

Outcomes	Deviance	Fixed-effects model	Random-effects model
Composite bleeding – GP	DIC	103.000	104.591
	Deviance	93.020	93.446
	p_d	9.998	11.145
Composite bleeding – PEP	DIC	51.600	51.624
	Deviance	45.620	45.635
	p_d	5.978	5.989
Clinically relevant non major bleeding – GP	DIC	100.600	101.701
	Deviance	90.640	90.285
	p_d	9.988	11.416
Clinically relevant non major bleeding – PEP	DIC	50.020	50.410
	Deviance	44.040	44.049
	p_d	5.983	5.991
Major bleeding – GP	DIC	81.890	83.182
	Deviance	71.960	72.050
	p_d	9.9310	11.132
Major bleeding – PEP	DIC	52.000	51.951
	Deviance	44.080	44.048
	p_d	7.925	7.903
Net clinical benefits – GP	DIC	47.300	48.201
	Deviance	42.300	42.424
	p_d	4.996	5.777
VTE recurrence – GP	DIC	89.830	90.445
	Deviance	79.860	78.984
	p_d	9.970	11.461
VTE recurrence – PEP	DIC	56.330	56.329
	Deviance	48.360	48.361
	p_d	7.9690	7.968
VTE-related death – GP	DIC	65.520	64.226
	Deviance	55.780	53.23
	p_d	7.9250	10.996

DIC: Deviance Information Criterion; GP: Global VTE Population; p_d: number of unconstrained parameters; PEP: Pulmonary Embolism population

We also have added before each model, the model selection based on the DIC but also on the unconstrained data parameter in order to select the model with the best fit but also the model the more robust to the prior specification (non-informative prior).

We have furnished hereafter the results for the random-effect model for each outcome for comparison to fixed-effect model.

A burn-in period of 240, 000 has been used for achieving the convergence and an additional 60, 000 iterations has been used for the estimation of posterior distribution.

Table: Results for random-effect model for composite bleeding in general population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

Table: Results for random-effect model for composite bleeding in pulmonary embolism population

Comparator	VKA regimen	Edoxaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)				
Edoxaban OR (95% CrI)				
Dabigatran OR (95% CrI)				
Rivaroxaban OR (95% CrI)				

Table: Results for random-effect model for clinically relevant non-major bleeding in general population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

Table: Results for random-effect model for clinically relevant non-major bleeding in pulmonary embolism population

Comparator	VKA regimen	Edoxaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)				
Edoxaban OR (95% CrI)				
Dabigatran OR (95% CrI)				
Rivaroxaban OR (95% CrI)				

Table: Results for random-effect model for major bleeding in general population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

Table: Results for random-effect model for major bleeding in pulmonary embolism population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

Table: Results for random-effect model for net clinical benefit

Comparator	VKA regimen	Edoxaban	Rivaroxaban
VKA regimen OR (95% CrI)			
Edoxaban OR (95% CrI)			
Rivaroxaban OR (95% CrI)			

Table: Results for random-effect model for VTE recurrence in general population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

Table: Results for random-effect model for VTE recurrence in pulmonary embolism population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

Table: Results for random-effect model for VTE-related death in general population

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)					
Edoxaban OR (95% CrI)					
Apixaban OR (95% CrI)					
Dabigatran OR (95% CrI)					
Rivaroxaban OR (95% CrI)					

A14. Please populate the table below with the results only from patients who were still on treatment at 6 months.

To populate the table, we removed all patients who permanently discontinued before 6 months in Hokusai VTE, and counted events that occurred in the remaining patients during the first 6 months of the study.

Table: Number of patients with specific events, On-Treatment Period (only first 6 months [up to Day 182]) mITT population restricted to patients with treatment duration >= 182 days (N=5674)

Hokusai-VTE trial		**Edoxaban (N=2865) n (%)**	**Warfarin (N=2809) n (%)**
Efficacy endpoint			
Recurrence at 6 months	VKA regimen vs edoxaban 60mg od	[redacted]	[redacted]
Safety endpoints			
Composite bleeding	VKA regimen vs edoxaban 60mg od	[redacted]	[redacted]
Major bleeding	VKA regimen vs edoxaban 60mg od	[redacted]	[redacted]
Non-major bleeding	VKA regimen vs edoxaban 60mg od	[redacted]	[redacted]
VTE related death	VKA regimen vs edoxaban 60mg od	[redacted]	[redacted]

A15. Please re-run the NMA using the results provided in A14.

Time and resources did not allow for the network meta-analysis to be repeated with these data. Although odds ratios are not provided, we note that the relative effects of edoxaban versus warfarin appear to be more favourable than in the prespecified analyses of the study data.

Section B – clarifications of the economic data

Manufacturer's note to NICE: In response to these clarification questions, we have updated several model input values. As a result, both of the models that were originally submitted have changed and the updated versions are supplied alongside this document. Since the results of both models have also changed (although not fundamentally so), we have also provided an updated version of section 7 of the STA.

B1. **Priority question:** Please provide the rationale for the following assumptions within the economic model:

a) The duration of the model cycles is 2 weeks. Previous VTE models have used 1-month cycles.

Previous VTE models used 1-month cycles. In the rivaroxaban and dabigatran STA submissions, the manufacturers argued that this was deemed sufficiently short to reproduce the underlying disease process of DVT and PE.

Many of the effects associated with VTE episodes occur over an acute timeframe, and the rate of recurrences and bleeding events associated with anticoagulants is heavily time-dependent, particularly in the weeks after an index VTE event. Therefore we aimed to use shorter cycles; 2 weeks was deemed appropriate.

The 2 week cycle length was chosen for a number of reasons. Firstly, the effect of the heparin lead-in and the initial treatment phases of the various comparators could be more accurately modelled with a shorter cycle. Moreover, this choice allowed the risk of HIT and the risk of VTE recurrence after the index event to be more accurately captured. The risk of HIT exists only after the administration of heparin/LMWH, which should not be longer than 2 weeks. Furthermore all of the studies of NOACs in this indication have shown that the risk of VTE recurrence decreases markedly with time after the VTE index event, so it was considered more accurate to consider a short cycle.

We note that there is no loss of accuracy by using a shorter cycle length. If anything, the model provides more granularity by using a 2-week cycle.

Finally, this was validated by UK experts in the advisory board, held in February 2014.[1] This cycle length was said to be "relevant to capture most of the relevant events associated with anticoagulant therapies".

b) The risk of further complications like chronic thromboembolic pulmonary hypertension (CTEPH), post-thrombotic syndrome (PTS), recurrent VTE and mortality do not change with the number of VTE events experienced by individuals.

The model assumes that risk of CTEPH, PTS, VTE recurrence and mortality do not change with the number of VTE recurrences experienced by individuals. Although there are reports

[1] Clinical experts that contributed to this advisory board: Prof. Martin Buxton (Chair); Dr Ameet Bakhai; Dr Ander Cohen; Mrs Pippa Anderson; Dr Jonathan Belsey

in the literature that the risk of complications such as CTEPH is increased in patients with a history of PE,[2] there is little evidence that the number of recurrence events should increase the risk further. In addition, such complications are relatively rare events, and retrospective epidemiological studies would be unlikely to capture such an effect if it was clinically meaningful.

Regarding the question of incorporating the increasing risk of recurrence with multiple events, we did not attempt this for a number of reasons:

1. The incidence of these events is already low, and the rate of VTE recurrence is not a critical driver of cost-effectiveness in our model. Therefore it is not expected that adding complexity to these estimates would have a significantly impact on cost-effectiveness results.

2. In practice, patients who experience recurrent events and are therefore at increased risk of further recurrence, tend to receive long-term anticoagulation. This has the effect of negating that increased risk.

3. Moreover, as edoxaban was associated with reduced rates of recurrence compared with warfarin in the pivotal Hokusai VTE study, and indirect comparisons suggest that this efficacy benefit is maintained in comparisons versus other NOACs, we believe that this assumption leads to an underestimation of the value of edoxaban, and was therefore considered as conservative.

If we did not make the assumption that the risk of VTE recurrence was fixed, the model would have to be fundamentally altered; one solution would be to adapt an individual patient level simulation or other highly sophisticated structure to account for this variability. However, we note that this approach was not used in the dabigatran and in the rivaroxaban models submitted to NICE.

In the dabigatran STA, multiple events in individual patients are accounted for by allowing patients to be exposed to a new risk of recurrent VTE or MCRB after initiation of a 6 months standard treatment course of LMWH followed by warfarin and allowing patients to be exposed to a new risk of recurrent VTE after discontinuation to no treatment, thus rates of recurrent VTE and MCRBE applied in the model are reflective of first recurrent event or first MCRBE.

In the model submitted with the rivaroxaban STA, no allowance was made for the number of previous recurrences experienced by a patient in the model.

c) Please provide the rationale for aggregating the PE and the DVT states together in the overall VTE state.

The primary efficacy outcome in the pivotal Hokusai VTE study is VTE recurrence. We used these data to determine the probability of VTE recurrence in the model. The other NOACs used a similar approach to data collection, analysis and economic model design.

[2] Pepke-Zaba et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011; 124:1973-1981

d) For recurrent VTE, all patients are assumed to be hospitalized but are not on any anticoagulation treatment (HRG codes used to estimate the cost of recurrent VTE are based on the costs of hospitalisation which do not include diagnosis and treatment). Please justify why all patients are hospitalised and why no patients receive anticoagulation treatment while in hospital.

We assumed that all patients are hospitalised when VTE recurrence is experienced. Although efforts are underway to increase the proportion of VTE that is treated in the ambulatory setting, the great majority of cases are hospitalised. The associated HRG codes (QZ20A, QZ20B, QZ20C, QZ20D, QZ20E, DZ09A, DZ09B, DZ09C) don't include diagnosis and treatment as mentioned in the label of the cells.

The cost of anticoagulation treatment corresponding to the first cycle after the index event (treatment for the acute event) has been added in this health state in the updated model we supply with these responses.

e) After recurrence of VTE, patients go back to their original anticoagulation therapy. Please provide your justification for assuming that patient revert to their original treatment after a VTE event.

We consulted clinical experts via an online anonymised UK clinical expert forum, specifically to ask if the assumption used in the dabigatran STA on this question was appropriate. The manufacturer of dabigatran assumed that after a recurrence, all patients were re-initiated on treatment with warfarin. Clinical experts that we consulted suggested that it would be more appropriate to re-initiate patients on the same therapy as they had previously been receiving.

f) Please explain why patients are not at risk of PTS in all health states?

Patients are considered at risk of PTS only in the "On treatment" and "Off treatment" states. The risk of PTS was considered as minor for the other health states such as CRNMB, MB, CTEPH and Stroke. Patients in "post-stroke" or "LT-CTEPH" are considered as out of scope from the population considered for the treatment of VTE.

The data below demonstrate that this assumption means that a very large proportion of all patients in the model are still at risk of PTS.

Proportion of patients in "On treatment" and "Off treatment" after one year:

- Warfarin
  - "on" and "off treatment": 97.22%
  - dead: 1.48%
- Edoxaban:
  - "on" and "off treatment": 97.35%
  - dead: 1.44%
- Dabigatran
  - "on" and "off treatment": 97.39%
  - dead: 1.47%

- Rivaroxaban
  - “on” and “off treatment”: 97.34%
  - dead: 1.37%

Proportion of patients in “on” and “off treatment” after 20 years:

- Warfarin
  - “on” and “off treatment”: 70.17%
  - dead: 29.07%
- Edoxaban
  - “on” and “off treatment”: 70.20%
  - dead: 29.04%
- Dabigatran
  - “on” and “off treatment”: 70.17%
  - dead: 29.06%%
- Rivaroxaban
  - “on” and “off treatment”: 70.25%
  - dead: 28.99%

g) Please justify why patients off treatment receive no further anticoagulation treatment?

Patients in “Off treatment” can be moved to this state for two different reasons:

- After an adverse event, there is a given probability that patients will discontinue their treatment
- The duration of the treatment is over and they are not treated any more.

h) Please explain why patients are not at risk of CTEPH or stroke when off treatment?

CTEPH and stroke are considered as complications of treatment in the model; therefore we assumed that it was relevant to consider their occurrence only when the patients are being treated.

i) Please justify why patients with CTEPH receive no further anticoagulation treatment?

While mild CTEPH has been found to be treatable with anticoagulation alone,[3] the definitive treatment remains pulmonary endarterectomy.[4] Patients with CTEPH could receive life-long anticoagulation but given the substantial other costs, we do not believe that this would not make a significant impact on the model.

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[3] Romaszkiewicz et al. Clinical course of unoperated mild chronic thromboembolic pulmonary hypertension. Kardiol Pol. 2011; 69(5):438-43.
[4] McNeil et al. Chronic thromboembolic pulmonary hypertension (CTEPH). Heart. 2007 Sep; 93(9): 1152–1158.

j) Inclusion of the stroke health state in the model. The ERG is concerned with the inclusion of the stroke health state in the model as it seems to include haemorrhagic strokes. These are also included in the major bleed (MB) health state as they are effectively a bleeding event. Please explain the rationale for having a discrete stroke health state and clarify if any adjustments were made to account for the apparent double counting of haemorrhagic strokes in the model.

Stroke was included as a health state because anticoagulant treatment affects stroke outcomes in patients who receive these agents. The double counting issue as it applies to bleeding and haemorrhagic strokes is a commonly raised issue in this field, and studies of all anticoagulants have the same issue. Disambiguation or adjustments for the different stroke types is difficult. We did not adjust for this, and made the assumption that all anticoagulants included in the analysis are affected to a similar degree. Therefore there may be some systematic over-representation of haemorrhagic stroke but this should not affect the comparative analyses presented here. Furthermore this is likely a conservative assumption in the case of edoxaban, which demonstrated significant reductions in haemorrhagic stroke compared with warfarin in the ENGAGE study.

k) No rationale was provided as to why stroke was included but myocardial infarction (MI) and systemic embolic events were not?

Stroke was included in order to capture the effect of anticoagulants on intracranial haemorrhage. Other cardiovascular events have not been shown to occur at different rates using warfarin or other NOACs and therefore would not have a significant impact on the model.

l) Please provide justification that 40% of patients discontinue due to heparin-induced thrombocytopenia (HIT)?

The true figure for discontinuation due to diagnosed HIT is likely to be 100%, but we chose a lower number in order to be conservative; patients with VTE only receive a short duration of treatment with heparin in the initial stages of treatment and most patients with HIT do not experience symptoms.

B2. **Priority question:** The percentage of patients experiencing PTS, taken from Prandoni et al. 1997, is based on the number of severe cases of PTS. The same paper reports the average probability of experiencing PTS (across mild, moderate and severe categories) of 18%. Please explain why the probability for severe cases was used in the economic model?

No cases of PTS were recorded in the Hokusai-VTE clinical trial. Published evidence suggests that mild PTS had little detrimental effect on quality of life;[5] therefore, the model includes only severe PTS. A similar assumption was mentioned in the dabigatran submission.

[5] Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc 1997; 4(1):49-56.

B3. **Priority question:** Regarding the mortality estimates used in the model (Table 1) could you please:

a) Provide the rationale for using the mITT analysis set (overall study period) for the estimation of VTE related death when the safety analysis set (on treatment period) was used for all the other estimates.

This is a conservative assumption specific to VTE-related mortality. The data clearly show that VTE recurrence increases when patients are off treatment (as evidenced by the divergence of the Kaplan Meier curves for the overall study period and on-treatment populations in the mITT analysis), and therefore VTE related death should follow the same pattern. However, VTE related deaths were adjudicated on an overall study period basis in Hokusai VTE, and these estimates provide more authoritative information on VTE as the cause of death. If VTE related deaths were adjudicated on an on-treatment basis, we would certainly have used this as a source. Our primary concern was to avoid misallocation of VTE as the causative factor in these deaths, and we believe that this is an acceptable and conservative trade-off in the case of this question.

b) Please provide the rationale for using the Prandoni *et al*. 2015 paper to estimate the mortality associated with HIT. The odds ratio used in your analysis (and reported in Prandoni *et al*. 2015) represents the probability of HIT patients developing thromboembolic complications (VTE, ischemic stroke, MI and arterial embolism) compared with patients who did not experience HIT and not the probability of dying from HIT. Please also note that the estimate used reflects a 1 year analysis.

This estimate should not have been used. An alternative estimate from another study that put the risk of HIT related death at 1.7% has been incorporated into the model.[6]

c) Explain why the probabilities used for MB-related death, stroke related-death and recurrent VTE-related death were not adjusted to reflect the 2-week cycle length?

These probabilities were calculated as the risks of death associated with an event and no adjustment are required to adapt to the two-week cycle length. Moreover, they are considered only over one cycle in the model.

d) Provide the rationale for using the 11.3% estimate for the probability of dying associated with VTE recurrence (Table 4 in Carrier *et al.* 2010) throughout the different periods of the analysis when you could have used more accurate data from the same study to reflect the 6 month-probability of dying from recurrent VTE?

[6] Joseph et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. J Thromb Haemost. 2014; 12(7): 1044-53.

We agree, the 6-month case-fatality rate of 13.7% is more appropriate to our analysis and the model has been updated to reflect this.

e) Can you also please provide the rationale for using the VTE estimate instead of the PE and DVT estimates to create a weighted average as you have done with several other estimates in the model?

As noted in the answer to a) above, in the Hokusai VTE study, the endpoint "VTE-related death" was adjudicated by the Clinical Events Committee and therefore there is a high degree of confidence around these estimates. We also note that, with regards to death due to VTE, there would be little obvious benefit from distinguishing between the two clinical manifestations, since VTE related mortality is associated with the same utility and costs regardless of whether it was caused by DVT or PE. In any case, DVT that occurs without any co-existing PE is rarely fatal, so any source that captures VTE related mortality reflects primarily death due to PE.

Table 1. Probabilities of disease-related death used in the economic model

Event	N	n	Increase in mortality risk	P used in the model (2- weeks)	Source	Analysis set
VTE-related death	8,240	48	0.58%	0.022%	Hokusai-VTE CSR, table 11.10	mITT Analysis Set - Overall Study Period (1 year = 26 cycles)
CRNMB related death	666	0	0%	0%	Hokusai-VTE post-hoc analysis, table 1.4.3.6.2	Safety Analysis Set – On-Treatment Study Period
MB related death	124	12	9.7%	9.7%	Hokusai-VTE post-hoc analysis, table 1.4.6.5	Safety Analysis Set – On-Treatment Study Period
Stroke related death	52	2	3.85%	3.85%	Hokusai-VTE CSR, table 12.15	Safety Analysis Set – On-Treatment Study Period
HIT related death	-	-	1.7%	1.7%	Joseph et al 2014	LMWH population, over 1 year
VTE recurrence related death	-	-	13.7%	13.7%	Carrier et al, 2010	VTE population, over 3 months

B4. **Priority question:** Please provide the rationale for splitting the utility associated with the “recurrent VTE” state between DVT utility and PE utility, when the health state “on treatment/index VTE” considers the overall VTE utility and doesn’t desegregate between PE and VTE.

The decrement in utility associated with the “recurrent VTE” state is a weighted average of disutility. This estimate takes the decrements for DVT and PE and weights them according to the breakdown of index events in the Hokusai VTE study. This was done to accurately determine the disutility that accrued when a recurrent VTE event (the primary efficacy outcome in the Hokusai and other studies of NOACs in this indication) was experienced. We disagree that this is a splitting of the utility; rather, it is a weighted aggregate of utilities associated with two types of clinical manifestation of recurrence.

As for the utility value taken from European Hokusai VTE patients for the “on treatment/index VTE”, this is an average value taken from patients with DVT and PE±DVT. Therefore we see no inconsistency between the approaches used to produce these estimates.

B5. **Priority question:** Given that the PTS condition is associated with specific costs and QALYs, modelling PTS as a separate health state would have increased model transparency and avoided potential formulae mistakes. The ERG has identified several errors in the calculation of the PTS utility. For example, looking at the "warfarin engine" tab, column F7 and H7 – the probability of PTS is not changing from year 1 onwards as it is meant to be but more fundamentally, the formulae is overestimating the total utility experienced in the on treatment and off treatment states since it takes the weighted average of: (2-week probability of PTS)*PTS utility + [1- (2-week probability of PTS)]*utility norm. The same problem applies to all the other engines in the model (i.e. non-vitamin K antagonist oral anticoagulants [NOACs]). The ERG suggests that the correct formula should be (2-week probability of PTS)*PTS utility + [(1- raw annual probability of having PTS) adjusted to reflect the 2 week period)]*utility norm. Please make the appropriate adjustments to the calculation of PTS utility.

Two mistakes were found in our original calculations for PTS.

First we have two annual cumulative incidence estimates: one for the first year and another one for the second year. The annual probability is the increased incidence over one year.

Secondly, it was not appropriate to calculate the proportion of patients each year (difference between the proportion of new patients with PTS in each cycle and the proportion of patients with PTS in each cycle) in the calculation of transition probability.

The calculation has been modified as follows:

$$1 - (1 - annual\ proba)^{number\ of\ cycle/26}$$

Thus, after cycle 26 in the model, the cumulative incidence is equal to the 1-year estimate.

The second cumulative incidence estimate given by Prandoni is 8.1% at 5 years. Thus we have updated the model in the same way as noted above for the 1-year incidence, and assumed that the proportion of patients with PTS remains stable at 8.1% after 5 years.

B6. **Priority question:** It seems that costs have not been updated to reflect the same cost year. Please clarify if this is the case. If costs have not been adjusted to reflect the same year please adjust all costs in the economic analysis to 2014 costs and present the revised results for the base case analysis, subgroup analysis and sensitivity analysis.

Costs had not been updated to reflect the same cost year, although a large majority of inputs were reflecting costs of the fiscal year 2012/2013.

The model has been updated to use either NHS reference costs for 2013/2014, the latest version of the BNF, or were inflated using the PSSRU Hospital and Community Health Services index (HCHS). All updated inputs are listed in the table below.

Cost unit	Initial value	Initial reference	Updated value	Updated reference
Instructions of self-administration of LMWH	£38.00	NHS reference cost 2012-2013:N02AF "District Nurse, Adult, Face to face" 24,729,481 stays $38	£37.00	NHS reference cost 2013-2014:N02AF "District Nurse, Adult, Face to face"27,354,007 stays £37
Administration of LMWH by professionals	£38.00	NHS reference cost 2012-2013:N02AF "District Nurse, Adult, Face to face" 24,729,481 stays $38	£37.00	NHS reference cost 2013-2014:N02AF "District Nurse, Adult, Face to face"27,354,007 stays £37
Cost of tinzaparin per day	£11.90	BNF Price:£11.90,dose:20 000 units/mL:0.7-mL (14 000-unit) syringe	£8.34	BNF Price:£8.34,dose:20 000 units/mL:0.7-mL (14 000-unit) syringe
INR monitoring	£24.00	NHS reference cost 2012-2013: -"324 Non- consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,149,507 stays £18.00 -"324 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,588,225 stays £29	£27.02	NHS reference cost 2013-2014: -"324 Non- consultant led,Non-Admitted Face to Face Attendance, Follow-up"868,357 stays £19 -"324 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,400,160 stays £32
Number of INR monitoring visits per cycle	1.1	Rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year)*	0.9	Rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year)
Daily cost of warfarin	£0.06	BNF price:Dose: 5–10 mg ,28-tab pack = 88p; 5mg	£0.02	eMIT : average ex-VAT price of 28 tab pack is £0.23
Doppler Ultrasound	£51.00	NHS reference cost 2012-2013"RA23Z Ultrasound Scan less than 20 minutes": 3,253,774 £51	£49.00	NHS reference cost 2013-2014"RA23Z Ultrasound Scan less than 20 minutes": 3,812,801 £49
CT angiography	£90.00	NHS reference cost 2012-2013"RA08Z Computerised Tomography Scan, one area, no contrast": 651,669 £90	£91.00	NHS reference cost 2013-2014"RA08A Computerised Tomography Scan, one area, no contrast, 19 years and over": 627,759 £91
Electrocardiogram (ECG)	£31.00	NHS reference cost 2012-2013"DA01 CECG [12 Lead]": 241,662 £31	£118.00	NHS reference cost 2013-2014: EA47Z, Electrocardiogram Monitoring and stress testing, service code 324, Anticoagulant Service,23 , £118
D-dimer	£12.00	Assumption from Rivaroxaban submission	£13.06	NICE CG92 costing from 2008/2009: £12 inflated to 2013/2014 using HCHS index

Cost unit	Initial value	Initial reference	Updated value	Updated reference
Diagnosis and treatment of DVT (first or recurrence)	£732.00	NHS reference cost 2012-2013: "QZ20A Deep Vein Thrombosis with CC Score 12+": 3,108 stays £726 "QZ20B Deep Vein Thrombosis with CC Score 9-11" :3,093 stays £884 "QZ20C Deep Vein Thrombosis with CC Score 6-8": 4,773 stays £1,102 "QZ20D Deep Vein Thrombosis with CC Score 3-5": 9,441 stays £869 "QZ20E Deep Vein Thrombosis with CC Score 0-2": 16,764 stays £522	£711.53	NHS reference cost 2013-2014: "YQ51A Deep Vein Thrombosis with CC Score 12+": 3,264 stays £949 "YQ51B Deep Vein Thrombosis with CC Score 9-11" 3,803 stays £874 "YQ51C Deep Vein Thrombosis with CC Score 6-8": 5,685 stays £1,015 "YQ51D Deep Vein Thrombosis with CC Score 3-5": 10,481 stays £785 "YQ51E Deep Vein Thrombosis with CC Score 0-2": 16,650 stays £478
Diagnosis and treatment of PE (first or recurrence)	£1 500	NHS reference cost 2012-2013: -DZ09A "Pulmonary Embolus with Major CC":15,799 stays £1,876 -DZ09B "Pulmonary Embolus with CC":15,404 stays £1,354 -DZ09C "Pulmonary Embolus without CC":6,330 stays £920	£1 596	NHS reference cost 2013-2014: "DZ09D Pulmonary Embolus with CC Score 12+": 1,623 stays £4,343 "DZ09E Pulmonary Embolus with CC Score 9-11": 3,656 stays £2,840 "DZ09F Pulmonary Embolus with CC Score 6-8": 8,482 stays £1,989 "DZ09G Pulmonary Embolus with CC Score 3-5" 15,647 stays £1,419 "DZ09H Pulmonary Embolus with CC Score 0-2" 15,676 stays £986
Cost of vascular surgery outpatient appointment (first)	£162.00	Goodacre et al. 2006 (131) In the first year three vascular surgery outpatient appointments. NHS reference cost	£161.76	Goodacre et al. 2006 In the first year three vascular surgery outpatient appointments. NHS reference cost 2013-2014: "W701B service code 107 Non Consultant-led, Non-Admitted Face to Face Attendance, First"22,843 stays £111 "W701B service code 107 Consultant led,Non-Admitted Face to Face Attendance, First" 160,273 stays £169
Cost of vascular surgery outpatient appointment (following)	£111.00	Goodacre et al. 2006 (131) In the first year three vascular surgery outpatient appointments. NHS reference cost	£135.50	Goodacre et al. 2006 In the first year three vascular surgery outpatient appointments. NHS reference cost 2013-2014: "W701A service code 107 Non Consultant-led, Non-Admitted Face to Face Attendance, Follow-up"24,516 stays £82 "W701A service code 107 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 201,718 stays £142

Cost unit	Initial value	Initial reference	Updated value	Updated reference
Cost of one GP visit	£36.00	Goodacre et al. 2006 (131) Thereafter two GP visits per year. NHS reference cost	£46.00	PSSRU 2014: General practitioner unit cost: per patient contact lasting 11.7 minutes, including direct care staff costs, with qualification costs: £46
HIT (Cost of hospitalisation)	£693.00	NHS Reference costs year 2012-13, weighted average of: - SA12G "Thrombocytopenia with CC score 8+" : 619 stays, £2,452 - SA12H "Thrombocytopenia with CC score 5-7" : 1,146 stays, £1,279 - SA12J "Thrombocytopenia with CC score 2-4" : 3,346 stays, £816 - SA12K "Thrombocytopenia with CC score 0-1" : 9,764 stays, £470 All pertaining to ICD10 code D69.5 "Secondary thrombocytopenia"	£617.61	NHS Reference costs year 2013-14, weighted average of: - SA12G "Thrombocytopenia with CC score 8+" : 667 stays, £2,504 - SA12H "Thrombocytopenia with CC score 5-7" : 1,327 stays, £1,236 - SA12J "Thrombocytopenia with CC score 2-4" : 4,302 stays, £649 - SA12K "Thrombocytopenia with CC score 0-1" : 9,990 stays, £396 All pertaining to ICD10 code D69.5 "Secondary thrombocytopenia"
CRNMB (Cost of hospitalisation)	£138.00	NHS Reference Costs year 2012-2013: VB07Z "Emergency Medicine, Category 2 Investigation with Category 2 Treatment" Activity:1,966,223	£149.00	NHS Reference Costs year 2013-2014: VB07Z "Emergency Medicine, Category 2 Investigation with Category 2 Treatment" Activity:20,55,465
MB (Cost of hospitalisation)	£1 092.00	NHS Reference costs year 2012-13, weighted average of: - FZ38G Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+: 774 stays, £4993 - FZ38H Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4: 1217 stays, £3097 - FZ38J Gastrointestinal Bleed, with Single Intervention, with CC Score 8+: 661 stays, £3591 - FZ38K Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7: 1721 stays, £2693 - FZ38L Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4: 7265 stays, £1872 - FZ38M Gastrointestinal Bleed, without Interventions, with CC Score 9+: 1619 stays, £2121 - FZ38N Gastrointestinal Bleed, without Interventions, with CC Score 5-8: 10300 stays, £1373 - FZ38P Gastrointestinal Bleed, without Interventions, with CC Score 0-4: 66817 stays, £791 All HRGs related to bleeds	£1 136.00	NHS Reference costs year 2013-2014, weighted average of: - FZ38G Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+: 1,023 stays, £5,040 - FZ38H Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4: 1,331 stays, £3,167 - FZ38J Gastrointestinal Bleed, with Single Intervention, with CC Score 8+: 1,031 stays, £3,048 - FZ38K Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7: 1,957 stays, £2,763 - FZ38L Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4: 7,285 stays, £1,996 - FZ38M Gastrointestinal Bleed, without Interventions, with CC Score 9+: 2,273 stays, £2,084 - FZ38N Gastrointestinal Bleed, without Interventions, with CC Score 5-8: 11,367 stays, £1,344 - FZ38P Gastrointestinal Bleed, without Interventions, with CC Score 0-4: 65,047 stays, £788 All HRGs related to bleeds

Cost unit	Initial value	Initial reference	Updated value	Updated reference
CTPEH: Pulmonary endodartectomy	£7 006.00	NHS Reference costs year 2012-13, weighted average of: - DZ02E "Complex Thoracic Procedures with CC score 5-7" in "Cardiothoracic surgery": 463 stays, £8,061 - DZ02E "Complex Thoracic Procedures with CC score 5-7" in "Thoracic surgery": 1,015 stays, £8,246 - DZ02F "Complex Thoracic Procedures with CC score 2-4" in "Cardiothoracic surgery": 1,361 stays, £7,211 - DZ02F "Complex Thoracic Procedures with CC score 2-4" in "Thoracic surgery": 2,519 stays, £6,894 - DZ02G "Complex Thoracic Procedures with CC score 2-4" in "Cardiothoracic surgery": 825 stays, £6,465 - DZ02G "Complex Thoracic Procedures with CC score 2-4" in "Thoracic surgery": 1,469 stays, £6,125 All pertaining to OPCS code L041 "Pulmonary thromboendodartectomy"	£7 412.09	NHS Reference costs year 2013-2014, weighted average of: - DZ02H "Complex Thoracic Procedures, 19 years and over, with CC Score 6+" : 1,944 stays, £10,284 - DZ02J "Complex Thoracic Procedures, 19 years and over, with CC Score 3-5": 3,314 stays, £7,254 - DZ02K "Complex Thoracic Procedures, 19 years and over, with CC Score 0-2": 4,578 stays, £6,307 All pertaining to OPCS code L041 "Pulmonary thromboendodartectomy"
Stroke (Cost of hospitalisation)	£3 118.00	NHS Reference costs year 2012-13, weighted average of: -AA35A "Stroke with CC Score 16+" :1,970 stays,£9,105 -AA35B "Stroke with CC Score 13-15":6,187 stays,£6,844 -AA35C "Stroke with CC Score 10-12":13,534 stays,£5,104 -AA35D "Stroke with CC Stroke 7-9":26,807 stays,£3,442 -AA35E "Stroke with CC Score 4-6":46,942 stays, £2,590 -AA35F "Stroke with CC Score 0-3":44,927,£2,100	£3 182.41	NHS Reference costs year 2013-2014, weighted average of: -AA35A "Stroke with CC Score 16+" :2,829 stays,£8,858 -AA35B "Stroke with CC Score 13-15":7,511 stays,£7,145 -AA35C "Stroke with CC Score 10-12":15,671 stays,£5,169 -AA35D "Stroke with CC Stroke 7-9":28,755 stays,£3,566 -AA35E "Stroke with CC Score 4-6":46,153 stays, £2,489 -AA35F "Stroke with CC Score 0-3":41,484,£1,833
Annual cost for stroke survivors	£6 880.00	Luengo-Fernandez et al. 2012	£7 485.54	Luengo-Fernandez et al., 2012 (2008/2009 costs inflated to 2013/2014 using HCHS index)

B7. **Priority question:** Please clarify what was the assumed average weight of patients in the calculation of heparin costs. If this hasn't been considered, can the company please adjust the cost so it reflects this?

Heparin is dosed by weight, with additional consideration for patient factors such as renal function. The dose selected in our model (100mg/1ml) is appropriate for patients weighing 55-65kg, as per the dosage chart for 1.5mg/kg enoxaparin, which is shown below.

Dosage chart for 1.5mg/kg SC treatment of DVT, PE or both				
Patient weight	**Kg**	**Syringe label**	**Dose (mg)**	**Injection volume (ml)**
100mg/ml	40	60mg / 0.6ml	60 od	0.60
Solution for Injection CLEXANE syringes	45	80mg / 0.8ml	67.5 od	0.675
	50	80mg / 0.8ml	75 od	0.75
	55	100mg / 1ml	82.5 od	0.825
	60	100mg / 1ml	90 od	0.90
	65	100mg / 1ml	97.5 od	0.975
150mg/ml	70	120mg / 0.8ml	105 od	0.70
Solution for Injection CLEXANE Forte syringes	75	120mg / 0.8ml	112.5 od	0.76
	80	120mg / 0.8ml	120 od	0.80
	85	150mg / 1ml	127.5 od	0.86
	90	150mg / 1ml	135 od	0.90
	95	150mg / 1ml	142.5 od	0.96
	100	150mg / 1ml	150 od	1.00

B8. **Priority question:** Please revise the PTS cost calculations. There seems to be a significant underestimation of the costs since these are not capturing the bi-weekly proportion of patients who would develop PTS at every cycle (and their respective costs). The way in which the costs are calculated would only make sense if the annual probability of PTS was being used in the calculations.

The calculations for PTS cost were updated as mentioned in answer to question B5.

B9. **Priority question:** The diagnostic outpatient costs (applied to the first cycle only) include a doppler ultrasound, CT angiography, electrocardiogram and d-dimer. Please explain why:

a) Only 50% of patients receive these tests.

These tests are for the diagnosis of PE; 50% estimate was used in the submission for rivaroxaban.

b) The costs, which relate to diagnostic tests, are not also incurred during a recurrent VTE event when a second diagnosis of DVT or PE will need to be made.

We have updated the model so that these costs are incurred during all VTE episodes, not just the index event.

c) The costs are not applied according to the type of VTE event.

Procedures and associated diagnosis costs were not assumed to be different between PE and DVT.

We believe that this is a conservative assumption. The first effect of not distinguishing the higher costs of PE diagnosis from those of DVT is that there will be a systematic underestimate of the costs associated with index events accruing to patients treated with all of the comparators in the analysis; this will not affect the ICERs. Secondly, this will potentially underestimate the costs associated with recurrent events. Since edoxaban s associated with a very low comparative rate of recurrence, we believe that this assumption could underestimate the comparative cost savings with this agent.

d) A chest x-ray and echocardiogram have not been included.

We have updated the model so that these costs are incurred during all VTE episodes not just the index event using the following data:

- Chest x-ray: £106 from PSSRU 2014 13.5 Hospital radiographer - outpatient contact (p.239)
- Echocardiogram: £65 from NSRC 2013-2014 "RA60A Simple Echocardiogram, 19 years and over": 196,524 £65.

e) An outpatient appointment or emergency admission has not been included.

We have updated the model so that these costs are incurred during all VTE episodes not just the index event using the following data:

- Outpatient appointment: PSSRU 2014 13.5 General practitioner - per patient contact (p.195): £46 (Per patient contact lasting 11.7 minutes) and £67 (Per patient contact lasting 17.2 minutes)

- Emergency admission: NSRC 2013-2014 "VB01Z Emergency Medicine, Any Investigation with Category 5 Treatment": 234,259 £81

B10. **Priority question:** Please explain the rationale for assuming that the same proportion of patients (25%) receives unfractionated heparin, dalteparin, tinzaparin and enoxaparin.

Patients are likely to receive a LMWH for VTE treatment but there are quite marked regional differences in the brand of LMWH used. For simplicity, we applied an equal share to the available brands. Unfractionated heparin tends to be used in more severe hospitalised patients and while the number of patients treated with UFH is smaller, the duration of treatment with UFH is longer. Therefore we felt that a 25% share for all four products was justifiable.

B11. **Priority question:** On page 190 of the company submission it is stated that "evidence did not allow for subgroup analyses in the DVT population (with respect to the NMA), therefore no results for a DVT-only subgroup are presented". Can the company please clarify why this subgroup analysis would not be possible given that such data were available at least for warfarin and rivaroxaban?

The primary objective of the network meta-analysis was to derive estimates of the relative effect of edoxaban versus the other NOACs and warfarin on efficacy and safety outcomes in patients with VTE. As a secondary objective, we evaluated the subgroup of patients with PE, where a) the unmet clinical need remains high, and b) sufficient data to compare a number of agents are available. Thus, the DVT-only subgroup was outside the scope of the NMA and a full analysis across the class would not have been possible.

B12. **Priority question:** The ERG identified mistakes in the PE subgroup model. Some of the model estimates, for example the probability of experiencing CTEPH, are adjusting the total population to reflect the proportion of patients with DVT only and the proportion of patients with PE. This is incorrect as everyone is the PE subgroup model should be exposed to the probability of developing CTEPH. Please amend this and check that no other errors similar to this have occurred.

The proportion of DVT only (cell C18) impacts the following inputs:

- Utility for a VTE recurrence
- Probability of CTEPH 4 months-12 months on warfarin and on NOAC
- Total cost per recurrence
- The associated values in the DSA

This cell in the PE model is supposed to impact only the inputs related to VTE recurrence as no DVT only can occur in the index event. The probability of CTEPH 4 months-12 months on warfarin and on NOAC as well as the associated values in the DSA/PSA were recalculated based on the fact that all patients have a PE event as index event.

This mistake has been corrected. Other parameters were checked, and nothing similar was found.

B13. **Priority question:** Please run the following scenario analyses and present total costs, total quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for each relevant comparison:

a) Subgroup analysis for patients with index PE (with or without DVT) using the Hokusai-VTE trial data (mITT, overall treatment) for each subgroup, thus comparing edoxaban with warfarin.

b) Subgroup analysis for patients with DVT only using the Hokusai-VTE trial data (mITT overall treatment) for each subgroup, thus comparing edoxaban with warfarin.

c) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the mITT population, overall treatment period.

It is not possible to run these scenarios using overall study period data. Safety endpoints (major bleeding, clinically relevant non-major bleeding and the composite of these) were only collected for the safety (i.e. mITT on-treatment) analysis set; this included events that happened up to 3 days after the last dose of study drug. Therefore it is not possible to run the model and include these events using estimates from the overall study period.

B14. **Priority question:** The ERG was unable to identify several model parameters in the respective sources provided (Table 2) and also identified several discrepancies between values reported in the model and values reported in the

B16. P arameter	Value in the model	Location in the model	Location in the submission	Value in the submissi

submission (Table 3). Therefore, could the company please:

a) For the values presented in Table 2 , pinpoint where in the sourced documents the estimates are located (and in the case where additional analysis was done to obtain these, please present the analysis and the raw data).

b) Which values in Table 3 are the correct ones.

Please see updated table.

Please note, the model has been updated to use cost inputs from the NHS reference cost database for 2013-14 in many places (as noted in our response to B6 above). Thus the updated values for cost inputs are given in the right-most column in the table.

B15. The ERG was unable to identify several model parameters in the respective sources provided for the PE subgroup model (Edoxaban VTE_PE subgroup_FINAL_13 02 15_AIC CIC). Can the company please, for the values presented in

Total cost of edoxaban (first cycle)	£114.04	'Inputs Costs'E43	Page164, Table B81 and Table B83	Values in the submission refer to a cos (page164) and £114.04.
Rivaroxaban (first cycle)	£73.50	'Inputs Costs'E51	Page165, Table B82 and Table B83	£88.20
Rivaroxaban (following cycles)	£29.40	'Inputs Costs'E52	Page165, Table B82 and Table B83	£30.76 and £29.40
Number of INR monitoring visits	1.1	'Inputs Costs'E15	Table B81 and Table B83	Rivaroxaban submission: 9 visits in firs then 5 visits per quarter (=24 per year) 24/26 = 0.9 visits per cycle; 1.1 visits p imply 28.6 visits per year.
LT CTEPH total QALYs, warfarin	0.0207	'Warfarin engine'CR24	Table B87	11.7432
Post stroke total QALYs, warfarin	0.0710	'Warfarin engine'CR26		0.0024
LT CTEPH total QALYs, edoxaban	0.0208	'Edoxaban engine'CR24		11.7483
Post stroke total QALYs, edoxaban	0.0712	'Edoxaban engine'CR26		0.0019
LT CTEPH total QALYs, dabigatran	0.0208	'Dabigatran engine'CR24		11.7433
Post stroke total QALYs, dabigatran	0.0713	'Dabigatran engine'CR26		0.0014
LT CTEPH total QALYs, rivaroxaban	0.0208	'Rivaroxaban engine'CR24		11.7563
Post stroke total QALYs, rivaroxaban	0.0711	'Rivaroxaban engine'CR26		0.0026
Probability of CTEPH 4 months-12 months	0.0195 (calculated from Guérin et al, 2014, 4.8%)	'Inputs – Clinical'C19	Table B64	0.0155 (calculated from Pengo et al. 2

Abbreviations used in the table: CRNMB, clinically relevant on-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension term; PTS, post thrombotic syndrome

B17. Table 4, pinpoint where in the sourced documents the estimates are located and provide any missing sources?

Please see updated table.

Table 2: Discrepancies between the model and submission with the source provided

Parameter	Value in the model and submission	Location in submission	Value in source	Source	Location in source (to be completed by the company)
Utility inputs					
Recurrent VTE	-0.1047 = (-0.17 * (1 - Settings!$C$18) - 0.06*Settings!$C$18) where 'Settings'!$C$18 refers to the proportion of DVT patients	Table B79	Recurrent DVT, -0.17; recurrent PE, -0.06. The ERG believes the company has switched these values for a recurrent PE and DVT in the model.	Sullivan *et al.* 2011 (112)	Updated. The new value is: -0.1253
CRNMB	0.648*		Median valuation (IQR) 0.76 (0.59-0.95) for muscular bleeding health state.	Locadia *et al.* 2004 (119)	Values in the model are adjusted to the population norm (in Locadia 2004, the norm is reported to be 0.95) Adjustment was done using UK utility norm (0.81 being the midpoint between [45-54 years] and [55-64 years]) Example: $\frac{0.76 * 0.81}{0.95} = 0.648$ However, there were mistakes in the calculations for MB and PTS. The model was updated accordingly. The correct data are:
MB	0.494*		Median valuation (IQR) 0.65 (0.49-0.86) for gastro-intestinal bleeding health state.		0.65*0.81/0.95 = 0.554
PTS	0.673*		Median valuation (IQR) 0.82 (0.66-0.97) for PTS health state.		0.82*0.81/0.95 = 0.699

Parameter	Value in the model and submission	Location in submission	Value in source	Source	Location in source (to be completed by the company)
VTE index event	0.5519		Unable to verify 0.5519 in the source provided. The ERG has identified a baseline mean value of 0.5298 (Table 2.1.2 Summary statistics on EQ-5D-3L: INDEX VALUE (using UK TTO index values for all assessments) separately by (actual) treatment group and visit - Safety Analysis Set restricted to patients with EQ-5D-3L assessment).	Hokusai VTE EQ-5D analysis European data[d] Table 2.2.1	Updated source provided. See Table 2.2.1 on page 67. The baseline mean value identified by the ERG is the value for all patients in the study; the value provided by the manufacturer (0.5519) is that for all European patients. We believe this is a more accurate estimate for the UK population.
VTE index event (PE subgroup**)**	0.5196**	NR	Unable to verify 0.5196 in the source provided. The ERG is unclear as to why a European subgroup would be used to inform the utility for the PE subgroup when the type of VTE is not reported separately.	Hokusai VTE EQ-5D analysis European data Table 3.2.1	Updated source provided See Table 3.2.1 on page 88 The manufacturer believes the EQ5D data from the European patient group provides the most accurate estimate of baseline utilities for this model. This baseline utility after a PE index event is only used in the PE subgroup model.
Cost inputs					
Daily cost of warfarin	£0.06	Table B81 and Table B83	Unable to verify with the BNF. The ERG notes eMIT should be used as the source cost for warfarin based on the recommendations in NICE Guides to Methods of Technology Appraisal 2013.	BNF price: Dose: 5–10 mg ,28-tab pack = 88p; 5mg	We assume a dose of 10mg daily. 28 tab pack of 5 mg tabs costs 88p; (0.88/28)*2 = £0.063 eMIT suggests the average ex-VAT price of 28 tab pack is £0.23; this would change the daily cost to £0.0164
Electrocardiogram	£31	Table B83	Unable to verify/ find the HRG codes provided. HRG identified by the ERG:	NHSRC 2012-2013 "DA01 CECG [12 Lead]": 241,662	The correct source from the original value was NHSRC 2010-2011 "DA01 CECG [12 Lead]":

Parameter	Value in the model and submission	Location in submission	Value in source	Source	Location in source (to be completed by the company)
			EA47Z, Electrocardiogram Monitoring and stress testing, service code 324, Anticoagulant Service,17, £74 (£25 to £157)	£31	241,662 £31. Updated to 2013/14 with HCHS index: £32.55 HRG identified by the ERG: NHS reference cost 2013-2014: EA47Z, Electrocardiogram Monitoring and stress testing, service code 324, Anticoagulant Service,23 , £118
INR monitoring cost	£24	Table B81 and Table B83	Unable to verify/find the HRG codes provided. HRGs identified by the ERG: WF01A, Non-consultant led, Non-Admitted Face to Face Attendance, Follow-up, 324, Anticoagulant Service, 833,218 stays, £21 (£9 to £28) WF01A, Consultant led, Non-Admitted Face to Face Attendance, Follow-up, 324, Anticoagulant Service, 1,515,603 stays, £28 (£14 to £29)	NHSRC 2012-2013: "324 Non-consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,149,507 stays £18 "324 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,588,225 stays £29	The values we originally provided are in line with those in the NHS reference cost database 2012-13. Updated as follows: Weighted average: £27 NHS reference cost 2013-2014: -"WF10A service code 324 Non-consultant led,Non-Admitted Face to Face Attendance, Follow-up"868,357 stays £19 -"WF10A service code 324 Consultant led, Non-Admitted Face to Face Attendance, Follow-up" 1,400,160 stays £32
Diagnosis and treatment of PE, inpatient costs	£1,500	Table B83	Unable to verify/ find the HRG codes provided. The ERG found these codes which seem to be the appropriate ones to use for PE: DZ09D, Pulmonary Embolus with CC Score 12+, 1,174 stays £4,011 DZ09E, Pulmonary Embolus with CC Score 9-1,1 2,973 stays £2,862 DZ09F, Pulmonary Embolus with CC Score 6-8, 7,160 stays £2,025 DZ09G, Pulmonary Embolus with CC Score 3-5, 15,283 stays £1,429	NHSRC 2012-2013: DZ09A "Pulmonary Embolus with Major CC":15,799 stays £1,876 DZ09B "Pulmonary Embolus with CC":15,404 stays £1,354 DZ09C "Pulmonary Embolus without	Values updated as suggested by ERG Weighted average: £1,596 NHS reference cost 2013-2014: "DZ09D Pulmonary Embolus with CC Score 12+": 1,623 stays £4,343 "DZ09E Pulmonary Embolus with CC Score 9-11": 3,656 stays £2,840 "DZ09F Pulmonary Embolus with CC Score 6-8": 8,482 stays £1,989

Parameter	Value in the model and submission	Location in submission	Value in source	Source	Location in source (to be completed by the company)
			DZ09H, Pulmonary Embolus with CC Score 0-2, 17,007 stays £981	CC":6,330 stays £920	"DZ09G Pulmonary Embolus with CC Score 3-5" 15,647 stays £1,419 "DZ09H Pulmonary Embolus with CC Score 0-2" 15,676 stays £986
Cost of vascular surgery outpatient appointment (first)	£162	Table B83	Unable to verify £162 with NHSRC. HRG identified by the ERG: WF01B, Non-Admitted Face to Face Attendance, First, service code 10, Vascular Surgery, £163 (£107 to £211)	NHSRC 2012-2013, HRG codes not reported	Consultant-led outpatient attendance £147 Weighted average: £162 NHS reference cost 2013-2014: "WF01B service code 107 Non Consultant-led, Non-Admitted Face to Face Attendance, First"22,843 stays £111 "WF01B service code 107 Consultant led,Non-Admitted Face to Face Attendance, First" 160,273 stays £169
Cost of vascular surgery outpatient appointment (following)	£111	Table B83	Unable to verify £111 with NHSRC. HRG identified by the ERG: WF01A, Non-Admitted Face to Face Attendance, Follow-up, service code, 107, Vascular Surgery, 132, £133 (£90 to £158)		Non consultant-led outpatient attendance £102 Weighted average : £135 NHS reference cost 2013-2014: "WF01A service code 107 Non Consultant-led, Non-Admitted Face to Face Attendance, Follow-up"24,516 stays £82 "WF01A service code 107 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 201,718 stays £142
Cost of one GP visit	£36	Table B83	Unable to verify £36 with NHSRC. Cost identified by the ERG: Unit Costs of Health and Social Care 2013, 11.7 minute visit including direct staff care and qualification costs, £45 per visit		Value has been updated PSSRU 2014: General practitioner unit cost: per patient contact lasting 11.7 minutes, including direct care staff costs, with

Parameter	Value in the model and submission	Location in submission	Value in source	Source	Location in source (to be completed by the company)
					qualification costs: £46

*Used to calculated the relative decrement at 55 years of age
**Edoxaban VTE_PE subgroup_FINAL_13 02 15_AIC CIC
Abbreviations used in the table: CRNMB, clinically relevant on-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ERG, Evidence Review Group; GP, general practitioner; HRG, Health Resource Group; INR, international normalised ratio; MB, major bleed; NHSRC, NHS Reference Costs; PE, pulmonary embolism; PTS, post thrombotic syndrome

Table 3: Discrepancies between the value reported in the model and the value reported in the submission

Parameter	Value in the model	Location in the model	Location in the submission	Value in the submission	Correct value (to be completed by the company)
Total cost of edoxaban (first cycle)	£114.04	'Inputs Costs'E43	Page164, Table B81 and Table B83	Values in the submission refer to a cost of £138.00 (page164) and £114.04.	The correct value is £114.04.
Rivaroxaban (first cycle)	£73.50	'Inputs Costs'E51	Page165, Table B82 and Table B83	£88.20	The correct value is £73.50
Rivaroxaban (following cycles)	£29.40	'Inputs Costs'E52	Page165, Table B82 and Table B83	£30.76 and £29.40	The correct value is £29.40
Number of INR monitoring visits	1.1	'Inputs Costs'E15	Table B81 and Table B83	Rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year) 24/26 = 0.9 visits per cycle; 1.1 visits per month would imply 28.6 visits per year.	The correct value is 0.9
LT CTEPH total QALYs, warfarin	0.0207	'Warfarin engine'CR24	Table B87	11.7432	The correct values are those from the model. All Table B 87 is not.
Post stroke total QALYs, warfarin	0.0710	'Warfarin engine'CR26		0.0024	
LT CTEPH total QALYs, edoxaban	0.0208	'Edoxaban engine'CR24		11.7483	
Post stroke total QALYs, edoxaban	0.0712	'Edoxaban engine'CR26		0.0019	
LT CTEPH total QALYs, dabigatran	0.0208	'Dabigatran engine'CR24		11.7433	
Post stroke total QALYs, dabigatran	0.0713	'Dabigatran engine'CR26		0.0014	
LT CTEPH total	0.0208	'Rivaroxaban engine'CR24		11.7563	

QALYs, rivaroxaban					
Post stroke total QALYs, rivaroxaban	0.0711	‘Rivaroxaban engine’CR26		0.0026	
Probability of CTEPH 4 months-12 months	0.0195 (calculated from Guérin et al, 2014, 4.8%)	‘Inputs – Clinical’C19	Table B64	0.0155 (calculated from Pengo et al. 2004, 3.8%)	The correct value is 0.0195.
Abbreviations used in the table: CRNMB, clinically relevant on-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; INR, international normalised ratio; LT, long term; PTS, post thrombotic syndrome					

Table 4. Discrepancies between the model values and source provided in PE model

Parameter	Value in the model	Location in model	Value in source	Source	Correct value/location in source (to be completed by the company)
Probability of VTE Recurrence 1-14 days	0.0048 = 8/1669	'Inputs – Clinical'C6	Unable to verify. Table 1.4.9.4.2 reports the the composite of DVT, non-fatal PE, and fatal PE	DS internal statistical analysis - post hoc for model - PE Population[e] Table 1.4.9.4.2	0.0048 = 8/1669 The composite of DVT, non-fatal PE, and fatal PE is VTE recurrence, as defined in Hokusai VTE CSR section 9.5.3.1
Probability of VTE Recurrence 15 days-3 months	0.0095 = 15/1586	'Inputs – Clinical'C7			0.0095 = 15/1586 The composite of DVT, non-fatal PE, and fatal PE is VTE recurrence, as defined in Hokusai VTE CSR section 9.5.3.1
Probability of VTE Recurrence 4 months-12 months	0.0056 = 8/1441	'Inputs – Clinical'C8			0.0056 = 8/1441 The composite of DVT, non-fatal PE, and fatal PE is VTE recurrence, as defined in Hokusai VTE CSR section 9.5.3.1
Probability of CRNMB	0.1001 = 167/1669	'Inputs – Clinical'C13	Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2[f]	0.1001 = 167/1669 See attachment (page C-21)
Probability of MB	0.0138 = 23/1669	'Inputs – Clinical'C14			0.0138 = 23/1669 See attachment (page C-21)
Probability of stroke	0.0077 = 13/1679	'Inputs – Clinical'C20	Source not provided	Hokusai EUR0060 Subgroup Analysis Page 16[g]	0.0077 = 13/1679 See attachment
Probability of death due to VTE	0.0072 = 12/1669	'Inputs – Clinical'C25	Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-	UPDATED Value: 0.0039 = 13/3319

Parameter	Value in the model	Location in model	Value in source	Source	Correct value/location in source (to be completed by the company)
				7.1.2[f]	
Probability of death due to recurrence	0.113	'Inputs – Clinical'C26 'Inputs – Clinical'I26	The ERG is unclear why the total VTE event rate has been used in the PE subgroup model. Fatality event rate reported in the source for a PE at 3 months, 30.1%; 6 months, 20.6%.	Carrier *et al*. 2010	0.206
Probability of going off treatment after CRNMB	Number of permanent discontinuations=8	'Inputs – Clinical'C45	Unable to verify. Table 1.4.3.7 reports 19 patients discontinued permanently from warfarin treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.3.7[e]	Data confirmed **Source provided**
	N = 1669, Subjects with CRNMB=167		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2[f]	Data confirmed **Source provided**
Probability of going off treatment after MB	Number of permanent discontinuations=6	'Inputs – Clinical'C49	Unable to verify. Table 1.4.6.7 reports 26 patients discontinued permanently from warfarin treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.6.7[e]	Data confirmed **Source provided**
	N = 1669, Subjects with MB=23		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2[f]	Data confirmed **Source provided**
Probability of death after MB	Total number of fatal events= 3+1	'Inputs – Clinical'C50	Unable to identify, Table 1.4.6.6.2 is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE population Table 1.4.6.6.2[e]	Data confirmed **Source provided**
	Subjects with		Source not provided	Hokusai Post-Hoc	Data confirmed

Parameter	Value in the model	Location in model	Value in source	Source	Correct value/location in source (to be completed by the company)
	MB=23+25			analysis for NMA Table 1-3.2[f]	**Source provided**
Probability of HIT	0 = 0/1650	'Inputs – Clinical'I12	Unable to verify. Table 1.4.2.4.1 is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.2.4.1[e]	Data confirmed **Source provided**
Probability of stroke	0.00419 = 7/1671	'Inputs – Clinical'I20	Source not provided	Hokusai EUR0060 Subgroup Analysis[g] Page 16	Data confirmed **Source provided**
Probability of going off treatment after CRNMB	Number of permanent discontinuations=10	'Inputs – Clinical'I45	Unable to verify. Table 1.4.3.7 reports 25 patients discontinued permanently from edoxaban treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.3.7[e]	Data confirmed **Source provided**
	N = 1650, Subjects with CRNMB=144		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2[f]	Data confirmed **Source provided**
Probability of going off treatment after MB	Number of permanent discontinuations=6	'Inputs – Clinical'I49	Unable to verify. Table 1.4.6.7 reports 17 patients discontinued permanently from edoxaban treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.6.7[e]	Data confirmed **Source provided**
	N = 1650, Subjects with MB=25		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2[f]	Data confirmed **Source provided**

Parameter	Value in the model	Location in model	Value in source	Source	Correct value/location in source (to be completed by the company)
Probability of death after MB	Total number of fatal events=3+1	'Inputs – Clinical'I50	Unable to verify. Table 1.4.6.6.2 is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE population[e] Table 1.4.6.6.2	Data confirmed **Source provided**
	Subjects with MB= 23+25		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2[f]	Data confirmed **Source provided**
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ERG, Evidence Review Group; MB, major bleed; NMA, network meta-analysis; PE, pulmonary embolism; PTS, post thrombotic syndrome					

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B18. Please explain the rationale for using the safety analysis (on treatment) for the efficacy outcomes used in the economic model? Please explain why other analyses (for example, mITT, overall treatment, etc.) were not deemed appropriate.

The safety analysis set is identical to the mITT, on-treatment analysis. The mITT on-treatment analysis is not the primary efficacy endpoint in Hokusai VTE, but it is reported widely, and is clinically meaningful. The manufacturer believes that it is the most appropriate source of event rate estimates for economic modelling purposes. If the purpose of the economic model is to simulate the effects of a specific treatment on a patient who is receiving that treatment, then the mITT on-treatment analysis from Hokusai is the best available option.

The reason that this analysis is favoured in these models is primarily due to the design of the Hokusai VTE study. Note that the follow-up period was 12 months for all patients (hence, the overall study period analyses); however, there was a flexible treatment duration that was at the discretion of the treating physician, which meant that many patients were discontinued treatment many months before the 12 month timepoint was reached. The effect of this study design on outcomes is clear from an inspection of the Kaplan-Meier curve for recurrence below. There is a clear difference in the accumulation of events among the mITT on-treatment groups who continue to receive anticoagulant therapy and the mITT overall study period analysis, in which events are recorded up to 12 months irrespective of whether those patients are still receiving anticoagulant. Consideration of the overall study period analysis shows that more efficacy events occurred between discontinuation of treatment (i.e. when patients' agreed period of anticoagulant therapy had finished) and the end of the 12 month follow-up, than occurred during the on-treatment period.

Edoxaban has demonstrated non-inferiority to warfarin on both analyses. For the purposes of deriving accurate absolute event rates associated with treatment, the manufacturer believes that the mITT on treatment analysis provide the closest estimates.

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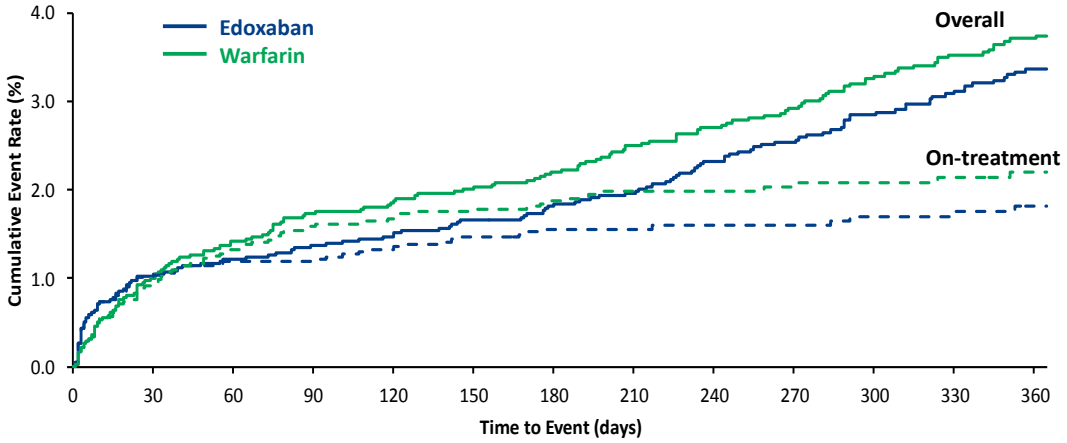
Figure: Kaplan-Meier cumulative event rate estimates for the primary endpoint (adjudicated symptomatic recurrent VTE), mITT analysis set (overall and on-treatment period)



Number at Risk:													
Edoxaban Overall	4118	4050	4024	4002	3985	3974	3959	3885	3692	3524	3358	3190	2918
Warfarin Overall	4122	4055	4023	4001	3992	3975	3962	3864	3683	3519	3367	3184	2936
Edoxaban On-tx	4118	3892	3793	3724	3539	3478	3200	2320	2169	2029	1890	1769	1308
Warfarin On-tx	4122	3893	3791	3703	3499	3423	3170	2305	2140	2015	1880	1740	1306

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B19. Please explain the difference in the Hokusai-VTE trial outcomes between the mITT on treatment set and the safety analysis on treatment set, given that there were no treatment misallocations (as reported in page 61 of the submission). More precisely, please explain why the total number of events differs from Table B 10 (CS, p65) to Table 1.4.9.4.2 (post-hoc analysis, p 620), respectively.

The results in Table B10 present the results for the primary efficacy parameter: adjudicated symptomatic recurrent VTE. According to the pre-specified Statistical Analysis Plan, the time to first event was analysed using a Cox proportional hazards model including model terms for treatment and the randomisation stratification factors (as binary variables) as covariates.

In contrast, the post-hoc analysis presented in Table 1.4.9.4.2 is a phase-specific analysis. In this analysis, it is possible that a patient may be counted multiple times (maximum: 3). In each of the phases, only the first event of a patient is taken into account in the counting process. However, a patient would be counted again as having an event if this event would have occurred in another phase.

The difference in the number of patients is fully explained by the different methodological approaches: the main analysis (Table B10) is a 1-cycle approach, whereas the post-hoc analysis (Table 1.4.9.4.2) is a 3-cycle approach.

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B20. Please populate **Error! Reference source not found.** below with the data for the primary efficacy endpoint for the mITT population (on treatment and overall treatment period).

See table below

Table: First adjudicated recurrent VTE separately by treatment arm as a function of the time period based on Hokusai VTE - mITT population (N=8240), On-Treatment Period

	Warfarin			
Time period (Treatment days)	**N**	**n**	**p**	**95% CI**
From Index event to 14 days	4122	23	0.558%	0.331% - 0.785%
From 15 days to 98 days	3972	41	1.032%	0.718% - 1.347%
From 99 days to 364 days	3578	16	0.447%	0.229% - 0.666%
	Edoxaban			
Time period (Treatment days)	**N**	**n**	**p**	**95% CI**
From Index event to 14 days	4118	30	0.729%	0.469% - 0.988%
From 15 days to 98 days	3967	20	0.504%	0.284% - 0.725%
From 99 days to 364 days	3614	16	0.443%	0.226% - 0.659%

Remarks: N is indicating the number of patients being on treatment at the beginning of the time period.
n is indicating the number of patients with event within the time period.
In this analysis, only the first adjudicated event of a patient has been taken into account.

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B21. Please explain the discrepancies between the safety population and mITT population given there were no study misallocations for:

a) VTE- related deaths in Table 12.21 (page 155) in the CSR and Table 11.10 (page 115) in the same document.

To clarify, the safety analysis population is identical to the mITT, on-treatment analysis.

The primary efficacy outcome was evaluated for the mITT overall study period.

Table 11.10 shows data for the mITT, overall study period. This analysis captures more events than the on-treatment analysis, because it includes all patients in the mITT analysis set, regardless of whether they were still receiving treatment, up to the end of the 12-month follow up period. Please note the footnote: “Events are included in the Overall Study Period if they occurred on or after the randomization date up to Day 365.” The analysis in this table is for a secondary efficacy variable (a composite of VTE recurrence and all-cause mortality); it is not the dataset used in the safety analyses of this study.

The majority of the safety data, including the primary safety analysis, are determined on an on-treatment basis. However, Table 12.21 deviates from this, so that all mortality can be captured and analysed. Please see the footnote in the table: “Deaths are included in the Overall Study Period if they occurred on or after the date of first dose of any study drug. All deaths that occurred prior to last study follow-up contact are considered for the Overall Study Period.” This is a subtly different approach to capturing fatal events than that used for the secondary efficacy variable described in the footnote to Table 11.10.

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B22. Please explain the discrepancies between:

a) The number of MB events in Table 12.10 (CSR, page 135) and Table 1.4.6.5 (post-hoc analysis, page 510).

b) The number of patients experiencing a clinically relevant non-major bleed (CRNMB) event is different for the warfarin treatment group in the post-hoc analysis (n=371) (Table 1.4.3.7, page 381) and in the Hokusai-VTE CSR (n=368) (Table 12.6, page 160).

c) The number of patients experiencing a CRNMB event is different for the edoxaban treatment group in the post-hoc analysis (n=304) (Table 1.4.3.7, page 381) and in the Hokusai-VTE CSR (n=298) (Table 12.6 , page 160)

a) The results in Table 12.10 (CSR, page 135) present the results for the primary safety parameter: adjudicated major bleeding during the 'On-Treatment Study Period'. According to the pre-specified Statistical Analysis Plan, the time to first event was analyzed using a Cox proportional hazards model including model terms for treatment and the randomization stratification factors (as binary variables) as covariates. The 'On-Treatment Study Period' was defined as follows: the time-period the patients was taking study drug up to 3 days after their last dose for that time period. A subject may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study.
In total, major bleeding events were observed in 56 edoxaban treated patients and 66 warfarin treated patients during the 'On-Treatment Study Period'.

In contrast, the post-hoc analysis presented in Table 1.4.6.4.2 (page 510) is a phase-specific analysis taking the 'Treatment Period plus 3 days' into account. In this analysis, it is possible that a patient may be counted multiple times (maximum: 3). In each of the phases, only the first event of a patient is taken into account in the counting process. However, a patient would be counted again as having an event if this event would have occurred in another phase. The 'Treatment Period plus 3 days' was defined as follows: time period from date of first dose of study medication to date of last dose of study medication plus 3 days [remark: interruptions of study medication are not taken into account].

Adding up the number of patients with a major bleeding over the three cycles gives 58 for the edoxaban group and 68 for the warfarin group during the 'treatment Period plus 3 days'. In the edoxaban arm, 57 patients had at least one major bleeding during the three phases compared with 67 patients in the warfarin arm. One patient in each treatment group had at least two major bleedings.

When comparing Table 12.10 (CSR, page 135) and Table 1.4.6.4.2 (post-hoc analysis, page 510), the difference in the number of patients is fully explained by the different

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methodological approaches: 'On-Treatment Study Period' as compared to the 'Treatment Period plus 3 days' i.e. a 1-phase approach as compared to a 3-phase approach.

b) and c) The results in Table 12.6 (CSR, page 130) present an overview about different types of adjudicated bleeding events during the 'On-Treatment Study Period'. According to the pre-specified Statistical Analysis Plan, for the various types of adjudicated bleeding event the time to first event was analyzed using a Cox proportional hazards model including model terms for treatment and the randomization stratification factors (as binary variables) as covariates. The 'On-Treatment Study Period' was defined as follows: the time-period the patients was taking study drug up to 3 days after their last dose for that time period. A subject may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study.
In total, CRMB bleeding events were observed in 298 edoxaban treated patients and 368 warfarin treated patients during the 'On-Treatment Study Period'.

In contrast, the post-hoc analysis presented in Table 1.4.3.4.2 (page 377) is a phase-specific analysis taking the 'Treatment Period plus 3 days' into account. In this analysis, it is possible that a patient may be counted multiple times (maximum: 3). In each of the phases, only the first event of a patient is taken into account in the counting process. However, a patient would be counted again as having an event if this event would have occurred in another phase. The 'Treatment Period plus 3 days' was defined as follows: time period from date of first dose of study medication to date of last dose of study medication plus 3 days [remark: interruptions of study medication are not taken into account].
Adding up the number of patients with an adjudicated CRNM bleeding over the three cycles gives 324 for the edoxaban group and 392 for the warfarin group.

The difference in the number of patients is fully explained by the different methodological approaches: the main analysis (CSR, Table 12.6) is a 1-cycle approach based on patient's first event during the On-Treatment Study Period, whereas the post-hoc analysis (Table 1.4.6.4.2) is a 3-cycle approach based on patient's first events within each cycle during the Treatment Period plus 3 days.

The results presented in Table 1.4.3.7 (page 381) are based on number of CRNMB events using the phase-specific analysis taking the 'Treatment Period plus 3 days'. Based on these CRNMB events, it was determined what type of consequences the event had on the use of edoxaban using the following categories for action taken on study medication:
4 – discontinued permanently
3 – interrupted
2 – reduced
1 – none
0 – missing information

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Per patient, the event with the 'strongest' action taken on study medication has been chosen for the presentation in Table 1.4.3.7 with priority on events with permanent discontinuation, interruption, reduction in this order.

The number of patients with at least one adjudicated CRNMB event during the 'Treatment Period plus 3 days' is 304 in the edoxaban arm and 371 in the warfarin arm.

When comparing Table 12.6 (CSR, page 130) and Table 1.4.3.7 (post-hoc analysis, page 381), the difference in the number of patients is fully explained by the different methodological approaches: 'On-Treatment Study Period' as compared to the 'Treatment Period plus 3 days'.

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B23. Please provide the rationale for assuming that the probability of discontinuation after CRNMB and MB are the same across all NOACs.

The manufacturer believes that the decision to discontinue anticoagulant therapy after a bleeding event is likely to be determined primarily by clinical events and assessment of patient factors, and that these would have more impact than the treatment itself on discontinuation. We sought expert clinical advice on this question and believe this is the most conservative and clinically plausible approach. We believe that this is especially the case if we are only considering the NOACs and not including warfarin in this discussion.

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B24. Please explain why the total number of adjudicated confirmed fatal major intracranial bleeding events (n=23) is greater than the number of adjudicated confirmed fatal MB events (n=12) in the post-hoc analysis report (Table 1.4.5.5 page 450 and Table 1.4.6.5 page 511).

The number of patients with an adjudicated confirmed fatal major intracranial bleeding event, presented in the post-hoc analysis report (Table 1.4.5.5, page 450) is incorrect due to a typo in the underlying SAS programme.

The correct numbers are presented below.

The number of confirmed fatal major intracranial bleeding events is in fact 6 (6 in the warfarin arm and 0 in the edoxaban arm).

Table 1.4.5.5: Frequency distribution on the number of patients with an adjudicated confirmed fatal major intracranial bleeding event starting within treatment period plus 3 days - Safety Analysis Set (restricted to patients with major intracranial bleeding event(s)

PATIENT WITH FATAL EVENT	ACTUAL TREATMENT GROUP				Total	
	Hep./Warfarin		Hep./Edoxaban			
	n	%	n	%	n	%
no	12	66.7	5	100.0	17	73.9
yes	6	33.3	0	0.0	6	26.1
Total	18	100.0	5	100.0	23	100.0

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B25. Please provide the rationale for using the probability of PTS reported in Prandoni et al. 1997 in the PE subgroup model, when the proportion of patients in this study with PE is only 14%.

As PTS is primarily associated with DVT, it is difficult to find estimates for the incidence of PTS in a PE population. However, many patients with PE also have co-existing DVT such that the clinical outcomes (including PTS) are often coincident. The PE subgroup in the Hokusai VTE study included a substantial number of patients with co-existing DVT, therefore believe that the assumption on the probability of PTS occurring in this cohort is conservative.

B26. Please justify the reason for including a decrement associated with a CRNMB event given that previous STAs (TA261 and TA287) did not include a decrement for CRNMB and this decrement was removed in the ERG analysis for TA327.

We believe that these events have an impact of the utility of patients that is worth capturing in an economic analysis. The definition of CRNM bleeding, as per the Hokusai VTE protocol (available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1306638/suppl_file/nejmoa1306638_protocol.pdf)
includes events not meeting the criteria for major bleeding, but associated with medical interventions, unscheduled contact with a physician, etc., and can also include events such as epistaxis leading to an intervention, haematuria, and intramuscular haematoma, all of which have direct cost implications and non-trivial impacts on health-related quality of life.

In TA327, the manufacturer of dabigatran derived a decrement of 0.04 based on EQ5D data collected in the pivotal studies and applied it to the model, which had a cycle length of one month. The ERG raised concerns that the disutility associated with several categories of these bleeds would not last for the full duration of a one-month cycle. There were also concerns about the implementation of the disutility in the model engine.

Furthermore, the submission to NICE from the manufacturers of apixaban includes a utility decrement of 0.0054 for clinically relevant non-major bleeds (see recent FAD for ID726), although the cycle length in this model is three months.

Our model has a cycle length of two weeks, which allows the effect on utility to be captured at a greater level of granularity than in other models.

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B27. Within the model, the utility associated with the CRNMB, MB, CTEPH (including long-term), stroke (including long-term) and PTS states is calculated as a relative decrement compared with the UK population norm at 55 years. The company has assumed that the baseline age is the 55-64 age range for all the studies, which is incorrect for some studies like for example Locadia et al. 2004 where the baseline age is 53 years. Can the company please adjust all estimates so they accurately reflect the baseline age of the respective studies, by using the appropriate population norm to estimate the relative utility loss for each health state?

We have assumed that the baseline age is the 55-64 age range for all the studies, as this was the case in most of them. As examples: for the state “Treatment with warfarin”, Marchetti et al. (2001) interviewed patients aged 57±15 years (range, 23 to 78); for the states “CTEPH” and “LT CTEPH”, Meads et al. (2008) included patients aged 56.6±15.4 years (range 17.0–90.0).

In addition, 55-64 years is likely to be very representative of the age of the population who experience a VTE, as shown in literature, and as reported in the baseline results of the Hokusai-VTE study, which was designed in order to show a high level of generalisability. Finally, we feel the impact of using a different population norm for utilities would be negligible in terms of total QALYs, as well as ICER.

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B28. Please explain how the following sources were identified and selected given that these are used in the economic model but are not reported in the studies included for data extraction (CS, Table B 79, page 157) resulting from the company's systematic review:

a) Marchetti *et al*. 2001 (107), warfarin treatment;

b) Gould *et al*. 1999 (123), HIT;

c) Meads *et al*. 2008 (124), CTEPH;

d) Lunde, 2013 (125), post stroke.

The literature review performed for the purpose of retrieving measurement and valuation of health effects was probably not targeted enough. Indeed, the search terms used included "VTE", "DVT", "PE" and extensions of these key words, but did not include any term relative to "warfarin treatment", "HIT", "CTEPH" and "post-stroke", considered as complications of treatment. It was not abnormal that none of the included study reported utility value associated with warfarin treatment, with HIT, with CTEPH or with post-stroke.

When necessary, additional targeted searches were conducted and other sources were checked, including the dabigatran STA.

- In the dabigatran STA, Marchetti et al. was used as the main source for utility decrement associated with warfarin treatment.
- Gould et al. 1999, Meads et al. 2008 and Lunde 2013 were found via an additional targeted search on Medline

These values were not found via the systematic literature search, nevertheless they were found to be relevant for this submission.

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B29. Please provide more details on the rationale for choosing the sources for all QoL values presented in Table B 79 (CS, page 157). For example, why was Locadia et al. 2004 chosen to inform the value for PTS related utility instead of Enden et al. 2013 and why was the utility for VTE taken from the Hokusai VTE EQ-5D analysis rather than Cohen et al. 2014 (which was identified in the systematic search).

The rationales for choosing the sources for all QoL values are listed below:

- For the state "Treatment with warfarin", no article retrieved from the systematic literature review was identified. Marchetti et al. (2001) was identified from the dabigatran STA, checked for relevance in terms of available information, and selected as it presents well documented limitations of warfarin (frequent INR monitoring, numerous food and drug interactions, etc.)

- For the state "Treatment with NOAC", no reference was used as the utility was set to 0.

- For the state "Recurrent VTE", Sullivan et al. (2011) was identified from the systematic literature search, as the only source providing utility values from the EQ-5D approach using UK tariffs.

- For the state "HIT", Gould et al. (1999) was selected as the only source available.

- For the state "VTE index event", it was felt more appropriate to use the value from the Hokusai-VTE study rather than the value from Cohen et al. (2014) which presented data from patients in the PREFER in VTE registry.

- For the states "CRNMB" and "MB", values from Locadia et al. (2004) were identified as the only source. In addition, this source was found to be one of the major references available. Although there were limitations in this study due, for example, to its elicitation of preferences from patients rather than the general public, this study provided time trade-off utilities for various states considered in the economic model submitted for dabigatran and rivaroxaban as sources for CRNMB and MB.

- For the states "CTEPH" and "LT CTEPH", no relevant publication was found from the systematic literature review. Meads et al. (2008) was identified, checked for relevance and selected.

- For the state "Stroke", Locadia et al. was found to be the only source providing utilities. It should be noted that the reference was not well displayed in the submission (119 instead of 118), this has been corrected.

- For the state "Post-stroke", no relevant publication was found from the systematic literature review. Lunde et al. (2008) was identified, checked for relevance and selected.

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- For the state “PTS”, Locadia et al. (2004) was preferred to Enden et al. (2013) as the population of interest in Enden et al. (2014) includes patients with DVT only. To better reflect the population of the model, the Locadia et al. values were selected, as based on a VTE population.

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B30. Please explain why, for the purpose of estimating the cost of DVT, day cases, regular day/night admissions and procedures in outpatients were included when all patients are assumed to be hospitalized (i.e. inpatients) in the model?

We do not believe that this is the case in our model.

B31. Please provide the rationale for assuming that the proportion of patients receiving drug therapy is equal for a CTEPH and LT-CTEPH.

Our understanding of clinical practice is that the treatment of CTEPH is not different after one cycle of our model (2 weeks), and that this is an acceptable assumption for that reason (see response to question B30).

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B32. Out of the proportion of CTEPH or CTEPH long-term patients receiving drug therapy (50%), the proportion of patients receiving sildenafil or bosentan does not add up to 100%. Please explain why or what other drug therapy those remaining patients should receive.

As mentioned in the Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 36), of over 2078 patients on monotherapy in 2013:

- 588 are treated with endothelin receptor antagonist (bosentan, 28.30%)
- 1,441 are treated with phosphodiesterase-5 inhibitor (sildenafil, 69.35%)
- 28 are treated with prostanoids (1.34%)
- 8 are treated with Calcium Channel Blockers for vasoreactive PAH (0.4%)
- 13 are treated with an unknown treatment (0.6%)

Only the main categories were considered.

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B33. Can the company please provide the missing estimates from Table 84 (CS, page 177) for the number of HIT and CTEPH events in the economic model?

Outcome	**Hokusai-VTE events***		**Model events**	
	Edoxaban N=4118	**Warfarin N=4122**	**Edoxaban N=4118**	**Warfarin N=4122**
Recurrent VTE	66	80	74	86
HIT	0	0	1	1
CRNMB	298	368	296	376
MB	56	66	61	65
Stroke	26	26	26	26
CTEPH	1	0	27	27
Death	35	33	39	40

B34. On page 177 of the company submission it is reported that Markov traces are presented in Appendix 19 and Appendix 20. However, the ERG could not find these. Could you please provide them?

These were provided as Excel files in the reference pack; we have included them again in this submission.[h]

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B35. On page 183 of the company submission, it is mentioned that because edoxaban is dominant compared with warfarin in the base-case analysis, it is not possible to generate a tornado diagram. The ERG does not agree with this statement. It is possible to produce tornado diagrams when base case ICERs are dominant or dominated. Since some of the ICERs resulting from the sensitivity analysis will be dominant whilst others can reach values such as £43,743 (as per page 183 in the submission), the ERG requests that the company presents tornado diagrams in terms of the net monetary benefit (NMB, evaluated at a £20,000 threshold value). Using the NMB overcomes the problem of some of the ICERs resulting from sensitivity analysis being negative. Tornado diagrams are crucial to understand what the key model drivers are in a systematic and unbiased manner. If this is not possible, please describe, for each analysis, the top ten variables that model results are most sensitive to. Please present total costs, total QALYs, and ICERs for the upper and lower value for each variable.

Tornado diagrams showing the effects of various parameters on net monetary benefit are supplied in the updated version of section 7 of our STA that accompanies these responses.[i]

B36. In the probabilistic sensitivity analysis, a normal distribution was used to model cost and utility data. Please provide the rationale for using the normal distribution instead of the gamma distribution for costs and the beta distribution for utilities.

As suggested, the model has been updated so that gamma distributions are now used in the probabilistic sensitivity analysis to model costs and beta distributions to model utility data.

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B37. Please confirm if the results presented for a lifelong treatment duration in Tables B 102 and B 103 are erroneously presenting the base case results (treatment duration = 12 months) and if the results presented in Table 5 and

B38. Table 6 are the correct ones.

We confirm that the original tables were erroneous. Table 6 and Table 7 below are correct.

Table 5: Incremental results (treatment duration = lifelong), ERG results

	Edoxaban	Warfarin	Dabigatran	Rivaroxaban
Cost per QALY gained	NA	£3,860	£111,610	Dominated
Incremental QALYs	NA	0.1838	-0.0071	-0.0743
Incremental costs	NA	£709	-£789	£25

Table 6: Cost-effectiveness analysis (treatment duration = lifelong), ERG results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Warfarin	£21,068.4	12.492	-	-	-
Rivaroxaban	£21,752.5	12.750	£684.1	0.258	2,651
Edoxaban	£21,777.9	12.676	£25.3	-0.074	Dominated
Dabigatran	£22,567.4	12.683	£789.5	0.007	Dominated

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B39. Please run the following scenario analyses and present total costs, total QALYs and ICERs for each relevant comparison:

a) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the safety population, overall treatment period.

b) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the safety population, on treatment period.

c) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the mITT population, on treatment period.

There is no safety population for the overall treatment period, as requested in a). Safety analyses were run on an on-treatment basis (events that occurred up to 3 days after the last dose of study drug were collected for the primary safety analysis.

As noted previously, the safety population, on-treatment period and the mITT population, on-treatment period, as in b) and c) above, are identical.

Please note that the model submitted to the ERG already allows this comparison (i.e. edoxaban vs warfarin using Hokusai data to be run, by using a radio button on the results sheet.

The results are given below:

	Edoxaban	Warfarin
Total costs	£4,076.0	£4,032.6
Delta cost	£43.40	
Total QALYs	12.4200	12.3979
Delta QALY	0.0222	
ICER	£1,958	

In addition, this requested scenario analysis is also presented in the updated results part of the STA.

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Section C: Search strategies, textual clarifications and additional points

C1. Regarding the cost-effectiveness search:

a. Please explain the rationale for not searching the HTA database within the Cochrane search to identify cost-effectiveness studies and resource use data.

The specifications for our literature search included only the NHS Economic Evaluations Database [NHS EED] within the Cochrane library. This was an oversight on our part. We checked the bibliography of our literature search and found that all of the studies identified from the search strategy specified in the dabigatran submission were also identified in our searches. Therefore, this does not seem to have resulted in a material difference to the search results.

b. According to Appendix 10, the search was conducted in December 2014 alone. Please clarify why it is suggested on page 111 of the submission that the initial search was conducted in May 2014, and why the results from this search are not presented in Appendix 10.

The statement presented in Appendix 10 is incorrect. All systematic reviews presented in this submission were done in two steps. All initial searches were performed in May 2014, and all updates were conducted in December 2014. Tables showing the details are given below.

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Medline

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	24,608	26,108
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	46,810	52,866
#3			(dvt or vte or dvts or vtes).mp.	9,743	11,671
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	39,136	42,880
#5	**Hits of P**		**or/1-4**		90,508
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	162	293
#7			(warfarin$ or coumadin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	20,958	24,081
#8			(dabigatran or bibr 1048 or pradax*).mp.	1,428	2,173
#9			(apixaban or bms 562247 or bms562247).mp.	624	1,041
#10			(rivaroxaban or bay 597939 or xarelto).mp.	1,048	1,707
#11	**Hits of I**		**or/6-10**		22,004
#12	S	Economic	Economics/	26,863	27,421
#13			"costs and cost analysis"/	41,559	43,095
#14			Cost allocation/	1,939	1,976
#15			Cost-benefit analysis/	59,566	63,206
#16			Cost control/	20,134	20,813
#17			Cost savings/	8,634	9,189
#18			Cost of illness/	17,406	19,026
#19			Cost sharing/	1,917	2,065
#20			"deductibles and coinsurance"/	1,417	1,482
#21			Medical savings accounts/	481	487
#22			Health care costs/	26,800	29,059
#23			Direct service costs/	1,022	1,058
#24			Drug costs/	12,063	12,751
#25			Employer health costs/	1,063	1,080
#26			Hospital costs/	7,677	8,169
#27			Health expenditures/	13,573	14,390
#28			Capital expenditures/	1,942	1,968
#29			Value of life/	5,894	6,025
#30			exp economics, hospital/	19,348	20,195
#31			exp economics, medical/	13,541	13,982
#32			Economics, nursing/	3,899	4,025
#33			Economics, pharmaceutical/	2,528	2,601
#34			exp "fees and charges"/	26,928	27,925
#35			exp budgets/	12,028	12,343
#36			(low adj cost).mp.	19,931	27,629
#37			(high adj cost).mp.	7,355	8,727
#38			(health?care adj cost$).mp.	3,860	5,105
#39			(fiscal or funding or financial or finance).tw.	75,595	90,229
#40			(cost adj estimate$).mp.	1,334	1,551
#41			(cost adj variable).mp.	31	35
#42			(unit adj cost$).mp.	1,440	1,698
#43			(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	159,051	189,309
#44	**Hits of S**		**or/12-43**	42,898	42,898
#45	**Hits of P and I and S**		**5 and 11 and 44**	240	240
#46	**Limits**	**Humans**	**limit 45 to humans**	239	264
#47		**Update**	**limit 46 to updaterange="prmz[20140428-20141201235959]"**		

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ID	PICOS	Category	Search terms	Initial	Update
#48			**remove duplicates from 47**		

Cochrane

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	MeSH descriptor: [Venous Thromboembolism] this term only	400	420
#2			MeSH descriptor: [Venous Thrombosis] explode all trees	2,283	2,298
#3			MeSH descriptor: [Pulmonary Embolism] explode all trees	909	921
#4			((venous or vein) near/2 (thrombosis or thromboses or thrombus or thromboembolism)):ti,ab,kw	4,908	5,154
#5			(dvt or vte or dvts or vtes):ti,ab,kw	1,233	1,310
#6			((pulmonary or lung) near/2 (embolism* or emboli)):ti,ab,kw	1,969	2,120
#7	**Hits of P**		**(#1 or #2 or #3 or #4 or #5 or #6)**	6,257	6588
#8	I and C	Interventions and Comparators	(edoxaban or lixiana or DU-176b):ti,ab,kw	44	58
#9			(warfarin$ or coumandin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA):ti,ab,kw	2,330	2,502
#10			(dabigatran or bibr 1048 or pradax*):ti,ab,kw	220	256
#11			(apixaban or bms 562247 or bms562247):ti,ab,kw	122	161
#12			(rivaroxaban or bay 597939 or xarelto):ti,ab,kw	215	274
#13	**Hits of I and C**		**(#8 or #9 or #10 or #11 or #12)**	2,641	2865
#14	**Hits and P and I and C**		**(#7 and #13)**	609	654
#15	**Limit**	**Cochrane Database (CDSR)**	**#14 in Economic Evaluations**	34	34
#16		**Update**	**#14 Online Publication Date from May 2014 to Dec 2014, in Economic Evaluations**	-	0

Embase

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	188,020	180,233
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	103,716	99,009
#3			(dvt or vte or dvts or vtes).mp.	19,214	17,728
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	70,835	67,648
#5	**Hits of P**		or/1-4	204,252	195,817
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	993	788
#7			(warfarin$ or coumandin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	70,982	67,466
#8			(dabigatran or bibr 1048 or pradax*).mp.	6,269	5,313
#9			(apixaban or bms 562247 or bms562247).mp.	3,322	2,766
#10			(rivaroxaban or bay 597939 or xarelto).mp.	5,271	4,405
#11	**Hits of I**		or/6-10	74,441	70,422
#12	S	Economic	Socioeconomics/	110,974	108,304
#13			Cost benefit analysis/	65,668	63,974
#14			Cost effectiveness analysis/	101,453	96,535
#15			Cost of illness/	14,534	13,959

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ID	PICOS	Category	Search terms	Initial	Update
#16			Cost control/	50,100	47,939
#17			Economic aspect/	103,913	102,820
#18			Financial management/	101,610	99,969
#19			Health care cost/	132,781	127,514
#20			Health care financing/	11,532	11,387
#21			Health economics/	33,957	33,415
#22			Hospital cost/	14,270	13,630
#23			(fiscal or financial or finance or funding).tw.	109,623	103,662
#24			Cost minimization analysis/	2,562	2,445
#25			(cost adj estimate$).mp.	2,094	1,963
#26			(cost adj variable$).mp.	170	155
#27			(unit adj cost$).mp.	2,622	2,404
#28	**Hits of S**		or/12-27	680,327	658,273
#29	**Hits of P and I and S**		5 and 11 and 28	1,365	1,287

EconLit

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	TX ((venous or vein) AND (thrombosis or thromboses or thrombus or thromboembolism))	2	2
#2			TX (dvt or vte or dvts or vtes)	2	2
#3			TX ((pulmonary or lung) AND (embolism* or emboli))	5	6
#4	**Hits of P**		**or/1-3**	**8**	**9**

c. The ERG has also found a discrepancy between the number of records identified from the search in the main body of the submission and the number reported in Appendix 10. Please explain this discrepancy.

Only the results of the initial searches were reported. This has been corrected.

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C2. Regarding the search for the measurement and valuation of health effects:

a. Please explain the rationale for not searching the HTA database within the Cochrane search to identify studies on the measurement and valuation of health effects.

The specifications for our literature search included only the NHS Economic Evaluations Database [NHS EED] within the Cochrane library. This was an oversight on our part. We checked the bibliography of our literature search and found that all of the studies identified from the search strategy specified in the dabigatran submission were also identified in our searches. Therefore, this does not seem to have resulted in a material difference to the search results.

b. The ERG is unclear how Figure 24 in the main body of the submission relates to the number of records reported in Appendix 12; please clarify if this includes records identified from the initial and updated search. Please also present the number of records identified in the initial and updated search from Medline, Cochrane, Embase and Econlit separately.

The figure B24 was redesigned to account for the lack of clarity. Nevertheless the counts were correct:

From Medline, 190 + 7 = 197 references were found.

From Cochrane, 226 + 3 = 229 references were found.

From Embase, 813 + 94 = 907 references were found.

From EconLit, 8 + 1 = 9 references were found.

This makes a total of 197 + 229 + 907 + 9 = 1342. 51 additional records were identified from another source, leading to a total of 1393 references identified.

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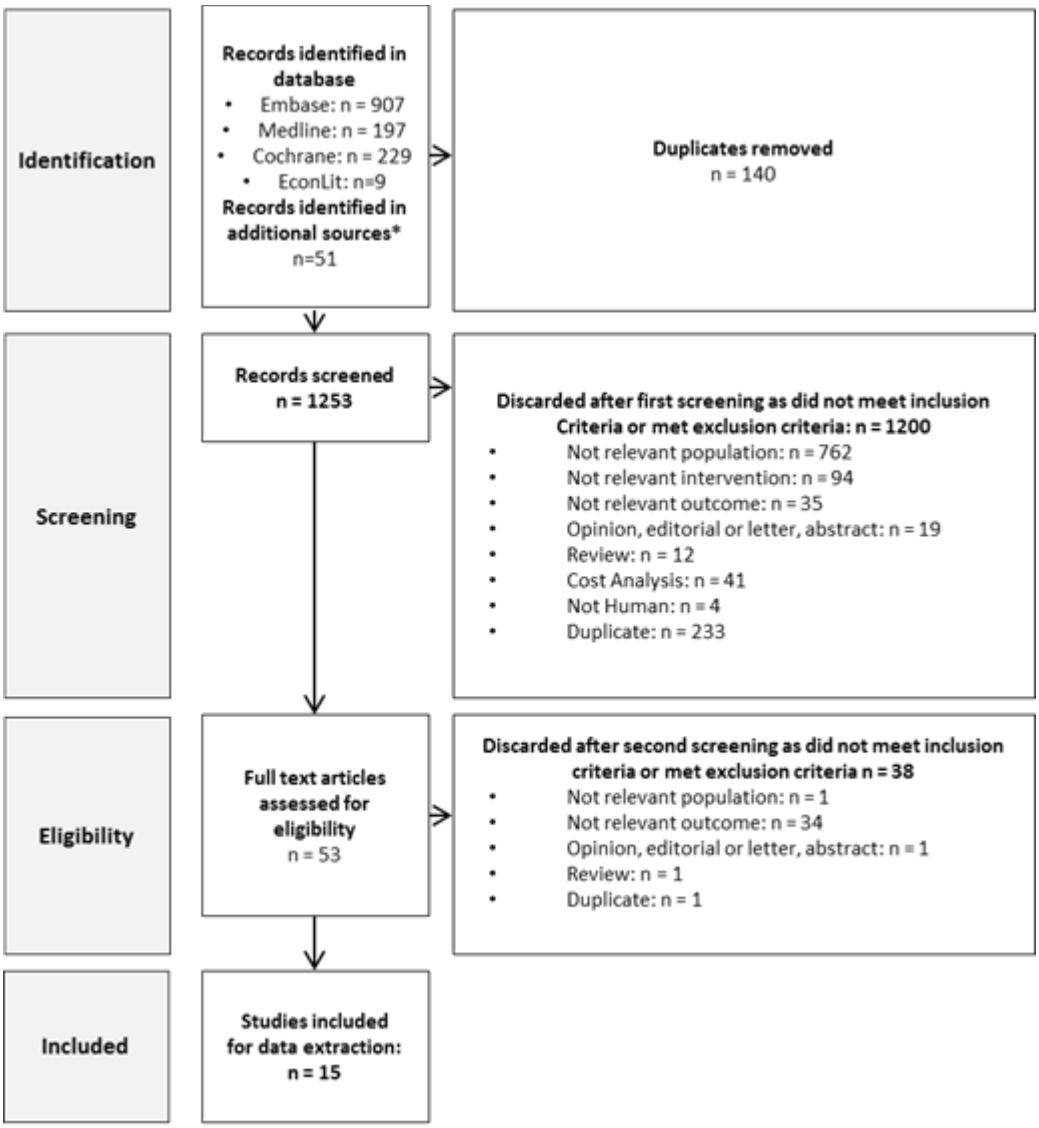
Figure B 24. Schematic for the systematic review of HRQL evidence



c. Please present the intended footnote for the * presented in Figure 24 which relates to "records identified from other sources"

When looking at bibliographies of included studies, some were found to be relevant, while not retrieved from the systematic search. This was supposed to be in the footnote. The footnote was added on figure B24 ("References retrieved from bibliographies of included studies, not retrieved from the systematic search").

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d. Please explain why the actual number of records identified from the update does not correspond to the difference in the number of records identified.

The update was performed without any limitation in dates, to ensure no publication was lost. Then, in the screening phase, all references retrieved from the initial search were removed.

This is why the number of records identified from the update does not correspond to the difference in the number of records identified.

C3. Please clarify how inputs for the model (probabilities, costs, utilities) relating to the complications associated with VTE events and the adverse effects of treatment such as stroke, major bleeding, clinically relevant non-major bleeding and HIT were intended to be captured in the searches performed as the search terms restricted the VTE population.

As stated in the answer to question B26, the literature reviews performed for the purpose of retrieving inputs for the model were probably not targeted enough. Indeed, the search terms restricted the VTE population.

This should be considered as a limitation of this submission.

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C4. Please clarify the numerical discrepancy between the number of studies included for data extraction in Figure B 1, page 39 of the company submission (n = 2 [1 trial]) and the text on page 40 of the company submission ("The only source for the edoxaban phase 3 trial is its peer-reviewed publication.").

As stated on page 40, the only source for the edoxaban phase 3 trial is its peer-reviewed publication. The second reference cited was the notification of the erratum that was published after an error in the publication was identified.

C5. Please clarify the numerical data to support the statement "...with significantly less clinically relevant bleeding in a broad spectrum of VTE subjects including high-risk subgroups (elderly, fragile and cancer subjects) as reported on page 107 of the company submission.

This statement refers to the primary safety endpoint of the Hokusai VTE study. Clinically relevant bleeding (major or non-major) occurred in 349 of 4118 patients (8.5%) in the edoxaban group and in 423 of 4122 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI, 0.71 to 0.94; P = 0.004 for superiority).

We noted that the study population included a broad spectrum of patients with VTE including the subgroups mentioned. This was primarily meant to emphasise our belief that Hokusai VTE is a trial that included a representative group of VTE patients, and furthermore, provides evidence for efficacy and safety based on a trial design that closely reflects clinical practice.

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List of additional documents

[a] A4 – WinBUGS code.zip
[b] A8 – LIFETEST Edoxaban in VTE.docx
[c] A11 – Post discontinuation treatment.rtf
[d] Hokusai VTE EQ-5D analysis European data.pdf
[e] DS internal statistical analysis - post hoc for model. PE Population.pdf
[f] Hokusai post-hoc analysis for NMA.pdf
[g] Hokusai EUR0060 Subgroup Analysis.pdf
[h] Appendices_19_20_Markov traces.xlsx
[i] Edoxaban in VTE STA updated results.docx