NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

This premeeting briefing presents:

- the key evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The average age of people across the dabigatran trials was 54 to 56 years; people in the warfarin arm of these trials spent 57 to 62% of the time within the appropriate therapeutic range. Are the characteristics of people in the dabigatran trials similar to people who would receive dabigatran in clinical practice in England?
- The duration of treatment with dabigatran for secondary prevention in RE-SONATE and RE-MEDY trials ranged from 6-36 months. What is the duration of treatment for DVT and PE in clinical practice in England?

- Would people at “clinical equipoise” such as the population in RE-SONATE be given routine anticoagulation with dabigatran in clinical practice?
- Were people in the dabigatran and rivaroxaban trials comparable in terms of the risk of recurrent venous thromboembolism and bleeding? Is the treatment effect of dabigatran independent of baseline risk?
- Given the small number of people with active cancer and the definitions used in the trials, is the limited data presented in the manufacturer’s indirect comparisons sufficient to change standard treatment with LMWH in people with active cancer who experience a DVT or PE?

Cost effectiveness

- In the manufacturer’s economic model it was assumed that the licensed dose for people aged 80 years or above (220 mg per day) had equivalent efficacy to the 300mg dose that had been assessed in the clinical trials. Is this assumption reasonable?
- The results from the manufacturer’s model are sensitive to assumptions about the decrement in utility for warfarin treatment. It was assumed that people would have a disutilty of -0.012 while taking warfarin. The same figure was applied for warfarin treatment in the cost effectiveness analysis of rivaroxaban for treating and secondary prevention of DVT/PE (Technology appraisals 261 and 287). The ERG commented that this estimate was based on a small sample size, patient preferences for health states and lack of a similar analysis for dabigatran. Is the decrement in utility of -0.012 appropriate?
- The manufacturer assumed that monitoring visits for warfarin treatment would be once a month following an initial titration period in both the acute and secondary prevention period. Is this assumption appropriate? Would the frequency of monitoring decrease with longer term treatment (that is, 3-monthly visits over the long-term) as suggested by the ERG?
- The manufacturer used NHS reference costs for follow-up visits at an anticoagulation clinic and these were weighted to take into account consultant-led and non-consultant-led appointments resulting in a weighted average cost of £27.99. The ERG considered that people visiting an anticoagulation clinic for

routine monitoring would see a nurse rather than a consultant and the average cost of a visit would be £10.61. Using the manufacturer's estimate, 1 year of monitoring visits for warfarin would cost £482.41 (assuming one initial consultant-led visit at £62.56, 4 visits while the warfarin dose is titrated and 11 further follow-up visits to the anticoagulation clinic both at a cost of £27.99). Using the ERG's estimate of £10.61, monitoring would cost £221.71 for the first year of treatment with warfarin. In technology appraisals 261 and 287 monitoring costs of £304 to £379 in the first year of treatment of were considered appropriate by Committee.

- In the manufacturer's model the proportions of recurrent VTEs that are DVT as compared to PE and fatal is dependent on the treatment received. Would this be expected in clinical practice?
- In the manufacturer's model the proportions of major or clinically relevant non major bleeds that are intracranial, extracranial and fatal are dependent on the treatment received. Would this be expected in clinical practice?
- In the manufacturer's model it is assumed that the decrement in utility associated with a major bleed lasts for 1 month (unless the bleed is an intracranial bleed resulting in disability). Is a1 month duration a reasonable assumption?
- Are the data from the manufacturer's indirect comparison sufficient to derive an accurate cost effectiveness estimate for dabigatran in the subgroup of people with active cancer?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of dabigatran etexilate within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the manufacturer	Comments from the ERG
Pop.	People with deep vein thrombosis and/or pulmonary embolism			
Int.	Dabigatran etexilate			
Com.	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • Rivaroxaban For people with cancer • Low molecular weight heparin • rivaroxaban			No comparison with fondaparinux and continued vitamin K antagonist. Clinical advisors to ERG considered use of fondaparinux limited, with LMWH being more commonly used. In RE-COVER trials 1-4% in each treatment group received fondaparinux (too small a group to do subgroup analysis). The manufacturer's approach is reasonable. No comparison between dabigatran and rivaroxaban for people with active cancer. ERG agreed with the manufacturer that there is a lack of clinical data on use of rivaroxaban in people with cancer.

Out.	The outcome measures to be considered include • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism including post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension • adverse events of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • health-related quality of life	As final scope with the exception of heart failure.	The outcome 'heart failure' was not included in the clinical trials and could thus not be modelled either. The dabiatran trials were of insufficient duration to collect meaningful comparative incidence data on post thrombotic syndrome and chronic thromboembolic pulmonary hypertension (6 months treatment duration for RE-COVER and RE-COVER 11 and up to 18 months treatment duration for RE-MEDY). Estimates of the incidence of these outcomes were derived from published literature for use in the economic model.	Given the available clinical data for dabigatran the ERG considers the outcome data presented by the manufacturer to be appropriate.

2 The technology and the treatment pathway

2.1 Dabigatran etexilate (Pradaxa, Boehringer Ingelheim) is a direct thrombin inhibitor that specifically and reversibly inhibits thrombin, a key enzyme in blood clot formation. It is administered orally.

2.2 NICE clinical guideline 144 recommends offering the choice of the parenteral treatments low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal (above knee) DVT or PE taking into account comorbidities, contraindications and drug costs, with the following exceptions:

- For people with severe renal impairment or established renal failure who should be offered unfractionated heparin (UFH) or LMWH with dose adjustments
- For people with an increased risk of bleeding for whom UFH may be considered
- For people with pulmonary embolism and haemodynamic instability in whom UFH should be offered and in who thrombolytic therapy may be considered.

The guideline states that low molecular weight heparin, fondaparinux or unfractionated heparin should be started as soon as possible and continued for at least 5 days or until the international normalised ratio (INR- adjusted by a vitamin K antagonist) is 2 or above for at least 24 hours, whichever is longer. It recommends that the vitamin K antagonist should be continued for 3 months at which point the risks and benefits of continuing the vitamin K antagonist treatment should be assessed and treatment may be continued. Clinical guideline 144 recommends at least 6 months treatment with LMWH for people with active cancer who have deep vein thrombosis or pulmonary embolism.

Technology appraisal 261 recommends rivaroxaban as an option for treating deep vein thrombosis and pulmonary embolism after a diagnosis

of acute deep vein thrombosis in adults; technology appraisal 287 recommends rivaroxaban as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

Figure 1: Treatment regimen for deep vein thrombosis and/or pulmonary embolism (based on treatment pathway outlined in CG 144 and SPCs for rivaroxaban and dabigatran)

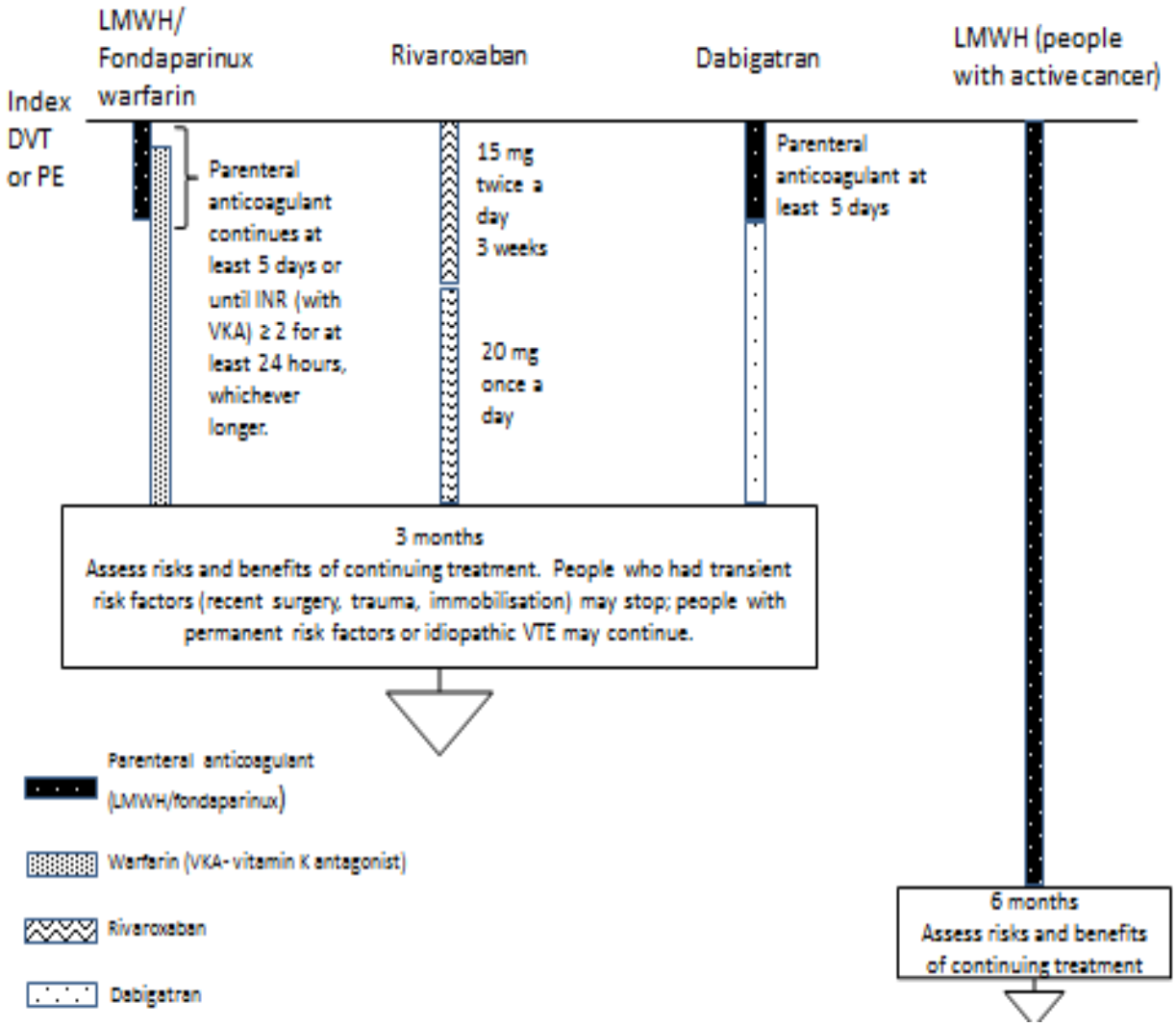


Table 2 Technology

	Intervention	Comparators		
	Dabigatran	**Rivaroxaban**	**VKA (Warfarin)**	**Low Molecular Weight Heparin**
Marketing authorisation‡	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults		Prophylaxis and treatment of venous thrombosis and pulmonary embolism	The treatment of venous thrombotic disease presenting with deep vein thrombosis, pulmonary embolism or both
Administration	Oral dabigatran 150 mg twice daily preceded by acute parenteral treatment for at least 5 days¥	Oral rivaroxaban 15 mg twice daily for 3 weeks, the 20 mg once daily	Oral Warfarin dosed to achieve a target INR of 2.0 to 3.0, preceded by acute parenteral treatment	Subcutaneous injection. Dose by body weight (dose varies by LMWH), once or twice daily
Setting	Inpatient or outpatient			
Acquisition cost/ day	£2.20*	£4.20 first 21 days £2.10 thereafter	£0.07*	£7.81 to £9.63†
Duration of treatment	At least 3 months	At least 3 months	At least 3 months	Around 5 days (if used with warfarin or dabigatran). At least 6 months for people with cancer with DVT and or PE

‡showing indications relating to DVT/PE only; * Does not include cost of initial parenteral treatment; † weighted average estimates of multiple LMWH brands and unfractionated heparin (see manufacturers submission page 323); ¥ Dose adjustment to 110 mg twice daily is recommended in people aged over 80 years and people who received concomitant verapamil and may be considered in people aged between 75 and 80 years, people with moderate renal impairment, gastritis esophagitis or gastroesophageal reflux or other people at increased risk of bleeding.

3 Comments from consultees

3.1 The professional groups agreed that initial treatment of venous thromboembolism (VTE) in clinical practice is in line with NICE clinical guideline 144 (see 2.1 above). However, there is uncertainty around the appropriate duration of anticoagulation treatment. Professional groups stated it is usually around 3 to 6 months but some people may receive life-

long anticoagulation. Continuing with anticoagulation beyond 3 months is for secondary prevention purposes, and the decision to continue or stop requires an assessment of risks and benefits. This is imprecise at the level of the individual patient, and is also dependent on whether the patient wants to continue anticoagulation. One professional group stated that although patients presenting with DVT and PE have a similar risk of recurrent VTE, patients presenting with PE are 3 fold more likely to have a PE at recurrence compared with patients who initially present with DVT. A patient with unprovoked PE may therefore be at more risk of fatal PE at recurrence and more likely to benefit from long term anticoagulation. Usual treatment for people who develop recurrent DVT or PE whilst on anticoagulant treatment is to increase the intensity of treatment with a vitamin K antagonist (to achieve an INR target of over 2.5) or swap to extended LMWH or fondaparinux.

3.2 The professional groups stated that a disadvantage of LMWH is administration of daily injections and a disadvantage of warfarin is monitoring to check that the international normalised ratio (INR) is in the therapeutic range. Dabigatran is expected to be used after initial treatment with heparin, but does not require monitoring of anticoagulation unlike warfarin, therefore may speed up hospital discharges. A patient group further explained that INR monitoring is a burden for patients as it involves frequent blood tests, visits to anticoagulation clinics, and patients (and carers) may need to take time off work. They also highlighted the lack of interaction between dabigatran and other drugs. One professional group stated that patients may favour rivaroxaban over dabigatran as rivaroxaban treatment does not require initial treatment with injections of heparin. In terms of the disadvantages of dabigatran, one professional group stated that there is overall evidence from the dabigatran trials (including those for atrial fibrillation) that the risks of coronary disease may be higher with dabigatran than vitamin K antagonists such as warfarin. The professional groups further stated that patients with impaired renal function were not represented in the trials and this group are at higher risk

of bleeding, therefore monitoring of renal function may be required in people taking dabigatran. Furthermore in most hospitals there are still no routine laboratory tests in place to monitor dabigatran levels in plasma if an overdose is suspected, and there are no definitive antidotes or protocols for rapid reversal of bleeding.

3.3 Professional groups noted that dabigatran was likely to be prescribed in both primary and secondary care, with long-term use almost entirely in primary care. The professional groups thought that dabigatran was unlikely to require additional resource due to the lack of monitoring. Training in advising patients on the relative merits of different anticoagulant interventions would be needed, but this could be carried out by the same staff dealing with venous thromboembolism at present.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The manufacturer's submission considered the marketing authorisation for dabigatran to cover 2 indications: 1) treating an acute venous thromboembolism (VTE- either a DVT or PE) and 2) the secondary prevention of a recurrent VTE. It therefore presented the clinical effectiveness results for these 2 treatment indications separately. This briefing presents a summary of the clinical effectiveness evidence on dabigatran for the whole population with deep vein thrombosis and/or pulmonary embolism The clinical evidence for dabigatran in a subgroup of people with active cancer is summarised in sections 4.27 and 4.28

4.2 The manufacturer's submission presented clinical effectiveness data from 4 phase III trials of dabigatran: RECOVER, RECOVER II, RE-MEDY (which compared dabigatran with warfarin) and RE-SONATE (which compared dabigatran with placebo) for the following two indications:

- **treating deep vein thrombosis and pulmonary embolism**: RE-COVER and RE-COVER II, were duplicate multi-centre randomised

double blind, double dummy, controlled trials which were identical in design. The trials were designed to test the non-inferiority of 150 mg twice daily dabigatran compared with adjusted dose warfarin (with a target INR of 2.0-3.0) in 5153 patients with confirmed acute symptomatic venous thromboembolism patients for whom at least 6 months of anticoagulant treatment was considered appropriate by the investigator. People received dabigatran following initial treatment (at least 5 days) with a parenteral anticoagulant. People were treated for 6 months with a 30 day follow-up after treatment had ended. People were excluded if they had: overt symptoms of VTE for longer than 2 weeks prior to enrolment or PE with at least one of the following: haemodynamic instability, in whom embolectomy or thrombolytic therapy was indicated or performed or had a suspected source of PE other than the legs. The studies also excluded: people judged by the investigators to be at an excessive risk of bleeding, people who were contraindicated, allergic to or for whom any of the study treatments were unsuitable. Please see table 26 manufacturer's submission pages 72-74 for the full list of exclusion criteria for the RE-COVER trials and examples of groups considered to be at excessive risk of bleeding.

The primary outcome was recurrent symptomatic VTE and deaths related to VTE within 6 months. VTE was defined as the composite incidence of DVT (detected by venous compression, ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography or spiral [helical] CT).

- **secondary prevention of deep vein thrombosis and pulmonary embolism:**

  RE-MEDY was a randomised double blind trial that designed to test the non-inferiority of 150 mg twice daily dabigatran compared with warfarin (target INR 2.0 to 3.0) in 2866 patients who had been successfully treated with an anticoagulant for 3 to 12 months for confirmed acute VTE. Of these people, 1016 (36%) had previously participated in the RE-

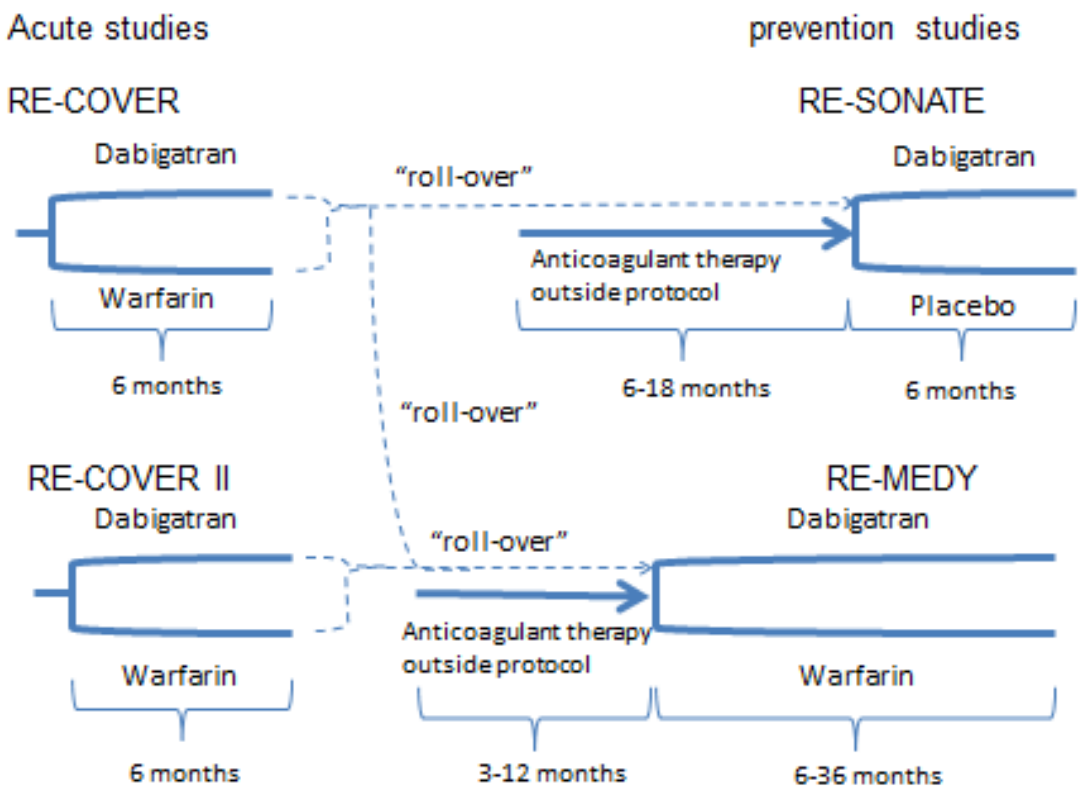
COVER trials. RE-MEDY included people who were assessed by a study investigator to have increased risk of recurrent venous thromboembolism. Risk factors for recurrent VTE included: more than 1 previous VTE; symptomatic PE as primary VTE event; time from the qualifying VTE to randomisation; active cancer; a history of non-haemorrhagic stroke; history of coronary artery disease; additional medical history/baseline conditions. People were excluded who had: symptomatic DVT or PE, a primary PE of suspected origin other than the legs, excessive risk of bleeding (as judged by investigator), or recent unstable cardiovascular disease. The manufacturer stated that the RE-MEDY trial population was a "more severely affected patient group than other trial populations". It was planned that people in RE-MEDY should receive dabigatran or warfarin for 18 months but the protocol was amended to extend the treatment period because a lower than projected event rate was observed, and people in RE-MEDY received between 6 and 36 months of treatment with a 30 day follow-up after treatment had ended. The primary outcome in RE-MEDY was recurrent symptomatic and objectively verified VTE or death associated with VTE (excluding unexplained death). Clinically suspected DVT was objectively verified using pre-specified imaging studies.

RE-SONATE was a randomised controlled trial that compared 150 mg twice daily dabigatran with placebo in 1353 people who had completed 6 to 18 months of treatment with a vitamin K antagonist for confirmed acute symptomatic VTE. Of this population, 27 (2%) had previously participated in the RE-COVER trials. RE-SONATE included people who were at "clinical equipoise" meaning that there was uncertainty with respect to the need for continued anticoagulation treatment, indicating that the risk/benefit of extended treatment was not clear. It excluded people in whom there was a clear indication that the anticoagulant treatment for their index PE or DVT should be continued, people at excessive risk of bleeding and people who needed a vitamin K

antagonist for an indication other than DVT and/or PE, people with a life expectancy of less 6 months and people with active cancer (for full inclusion/exclusion criteria see tables 25 and 26 pages 72-74 manufacturer's submission). It was intended that people should be treated for 6 months, but the number of VTE events required for the statistical analysis was reached before some people in the study had completed 6 months of treatment, therefore people included in the analysis received dabigatran or placebo for between 3 and 6 months. People in RE-SONATE were also followed-up for 30 days after treatment ended. The primary efficacy outcome in RE-SONATE was recurrent symptomatic and objectively verified VTE or death associated with VTE (including unexplained death).

The manufacturer stated that no head-to-head trials comparing dabigatran with rivaroxaban for treating or secondary prevention of VTE were identified. The rivaroxaban trials and other trials included in the indirect meta-analysis are described in sections 4.17 -4.26.

Figure 2: Summary of treatment protocols dabigatran trials (Source: dabigatran EPAR)



4.3 The baseline characteristics of people in the RE-COVER trials are shown in table 3 below. The proportions of people with risk factors for recurrent VTE are shown in table 5 below. In RE-COVER, people in the warfarin arm had an INR within the therapeutic range 59.9% of the time (21% of the time it was below and 19% of the time it was above the therapeutic range). In RE-COVER II people in the warfarin arm had an INR within the therapeutic range 56.9% of the time (24% of the time it was below and 19% of the time it was above the therapeutic range).

Table 3 baseline characteristics of patients in the RE-COVER trials (manufacturer's submission table 27 page 76)

Characteristic	RE-COVER		RE-COVER II	
	Dabigatran (n = 1,273)	**Warfarin (n = 1,266)**	**Dabigatran (n = 1,280)**	**Warfarin (n = 1,288)**
Age – mean ± SD	55.0 ± 15.8	54.4 ± 16.2	54.7 ± 16.2	55.1 ± 16.3
Female sex – n (%)	535 (42.0)	520 (41.1)	499 (39.0)	512 (39.8)
Race – n (%)				
White	1,212	1,195	993 (77.6)	999 (77.6)
Black	(95.2)	(94.4)	19 (1.5)	19 (1.5)
Asian	36 (2.8)	31 (2.4)	267 (20.9)	270 (21.0)
	25 (2.0)	40 (3.2)		
BMI – mean ± SD	28.9 ± 5.7	28.4 ± 5.5	28.4 ± 5.8	28.4 ± 5.8
Type of index event				
DVT only	880 (69.1)	869 (68.6)	877 (68.5)	873 (67.8)
PE only	270 (21.2)	271 (21.4)	298 (23.3)	297 (23.1)
DVT and PE	121 (9.5)	124 (9.8)	104 (8.1)	117 (9.1)
Neither DVT or PE	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
Cancer – n (%)	64 (5.0)	57 (4.5)	50 (3.9)	50 (3.9)
Previous VTE – n (%)	327 (25.7)	322 (25.4)	247 (19.3)	203 (15.8)
Parenteral anticoagulation				
Treatment before randomisation (days)	3.0	3.0	ND	ND
Median	2.0 - 4.0	2.0 - 4.0		
IQR				
Treatment after randomisation* (days)	6.0	6.0	6.8 ± 3.4	7.1 ± 3.7
Median	5.0 - 8.0	5.0 - 8.0		
IQR				
Unfractionated heparin – n (%)	144 (11.3)	164 (13.0)	198 (15.5)	207 (16.1)
LMW heparin – n (%)	1,138 (89.4)	1,148 (90.7)	1133 (88.5)	1147 (89.1)
Fondaparinux – n (%)	50 (3.9)	36 (2.8)	32 (2.5)	21 (1.6)

*Treatment after randomisation in the single-dummy phase.

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; LMW, low-molecular-weight; ND, no data; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

4.4 The baseline characteristics of people in RE-MEDY and RE-SONATE are shown in Table 4, and the proportions of people with risk factors for recurrent VTE are shown in Table 5 below. In RE-MEDY people receiving warfarin had an INR within the therapeutic range 61.5% of the time (it was

below the therapeutic range 21.5% of the time and above 15.2% of the time).

Table 4 Baseline characteristics of patients in the RE-MEDY and RE-SONATE trials (manufacturer's submission table 28 page 77)

Characteristic	RE-MEDY		RE-SONATE	
	Dabigatran (n = 1,430)	**Warfarin (n =1,426)**	**Dabigatran (n = 681)**	**Warfarin (n = 662)**
Age – mean ± SD	55.4 ± 15.0	53.9 ± 15.3	56.1 ± 15.5	55.5 ± 15.1
Female sex – n (%)	559 (39.1)	555 (38.9)	300 (44.1)	298 (45.0)
Race – n (%)				
White	1,288 (90.1)	1,284 (90.0)	610 (89.6)	585 (88.4)
Black	29 (2.0)	28 (2.0)	9 (1.3)	14 (2.1)
Asian	113 (7.9)	114 (8.0)	58 (8.5)	60 (9.1)
American Indian	0	0	4 (0.6)	3 (0.5)
Weight (kg) – mean ± SD	86.1 ± 19.3	86.0 ± 18.9	83.7 ± 18.0	84.0 ± 18.6
Type of index event				
DVT only	938 (65.6)	922 (64.7)	431 (63.3)	441 (66.6)
PE only	324 (22.7)	335 (23.5)	183 (26.9)	178 (26.9)
DVT and PE	167 (11.7)	168 (11.8)	47 (6.9)	35 (5.3)
Neither DVT or PE	1 (0.1)	1 (0.1)	20 (2.9)	8 (1.2)
Cancer – n (%)	60 (4.2)	59 (4.1)	1*	2*
Treatment duration before randomisation – days	198 ± 157	200 ± 117	293 ± 107	299 ± 110
Enrolled from RE-COVER study - n (%)	236 (16.5)	254 (17.8)	7 (1.0)	8 (1.2)
Dabigatran group	283 (19.8)	243 (17.0)	8 (1.2)	4 (0.6)
Warfarin group				
Enrolled from RE-COVER II study - n (%)	70 (4.9)	55 (3.9)	NA	NA
Exposure to study drug – days	473 ± 211	474 ± 206	165 ± 45	162 ± 47

*Active cancer was an exclusion criterion, and the numbers represent protocol violations.
Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; SD, standard deviation.

Table 5. Risk factors for recurrent VTE (abridged from EPAR)

	Treating		Secondary prevention	
	RE-COVER	RE-COVER II	RE-MEDY	RE-SONATE
Patients, n(%)	2539 (100.0)	2568 (100.0)	2856 (100.0)	1343 (100.)
Active cancer at any time At baseline Diagnosed during study	179 (7.1) 121 (4.8) 58 (2.3)	156 (6.1) 100 (3.9) 56 (2.2)	193 (6.8) 119 (4.2) 74 (2.6)	104 (7.7) 81 (6.0) 23 (1.7)
Previous VTE (before qualifying event)	649 (25.6)	450 (17.5)	1525 (53.4)	1341 (99.9)
Thrombophilia no test results	236 (9.3) 1611 (63.5)	172 (6.7) 1750 (68.1)	525 (18.4) 1491 (52.2)	155 (11.5) 634(37.2)
Recent prolonged immobilization Transient immobilisation Permanent immobilisation	396 (15.6) 368 (14.5) 28 (1.1)	351 (13.7) 321 (12.5) 30 (1.2)	199 (7.0) 184 (6.4) 15 (0.5)	89 (6.6) 85 (6.3) 4 (0.3)
History of venous insufficiency	492 (19.4)	405 (15.8)	-	-
Long distance travel	222 (8.7)	201 (7.8)	-	-
Recent use of oestrogens	275 (10.8)	197 (7.7)	-	-
Never smoked Ex-smoker Current smoker	1298 (51.1) 699 (27.5) 541 (21.3)	1372 (53.4) 635 (24.7) 561 (21.8)	1643 (57.5) 759 (26.6) 454 (15.9)	767 (57.1) 353 (26.3) 223 (16.6)

4.5 The manufacturer collected health-related quality of life data using the EQ-5D in the RE-COVER trials, but did not present the full results in its submission. This data is discussed in section 5.11.

ERG comments

4.6 The ERG commented on the characteristics of people in the 4 dabigatran trials. It noted that the mean baseline age was between 53 and 56 years, but its clinical advisers stated that they would expect the majority of VTE patients to be over 65 years and a proportion of people would be over 80 years (and receive the 110 mg twice daily dose). The ERG commented that few, if any, patients in the dabigatran trials were aged over 80 years and according to the trial protocols these people would be treated with the 150 mg twice daily dose. The ERG concluded that there were no clinical trial data for people over 80 years receiving 110 mg dabigatran twice daily for this indication. The ERG considered that the proportions of people in the trials with DVT and PE reflected UK clinical practice as there are higher rates of DVT than PE. The ERG noted that the 4 dabigatran trials included people with proximal DVT rather than distal DVT and its clinical

experts advised that this is appropriate because the treatment pathway for proximal DVT would not necessarily be the same as for distal DVT (NB. The marketing authorisation for dabigatran covers all DVT regardless of location). Clinical experts advising the ERG considered that the 'clinical equipoise' population in RE-SONATE is difficult to define in clinical practice but is likely be people who currently would not receive ongoing treatment for secondary prevention of VTE and can be considered a different population to that currently treated for secondary prevention in the UK.

4.7 The ERG commented on the treatment regimen in the dabigatran trials and noted that there is limited data for people treated continuously with dabigatran starting from the acute phase of VTE through to long term secondary prevention. It noted that the manufacturer had assumed equal efficacy for the different initial parenteral therapies received in both the dabigatran and warfarin arms. The ERG noted that the final scope issued by NICE specified that the analysis should consider both those who require a limited period of anticoagulation (3-6 months) and those who require long term anticoagulation (usually lifelong). It noted that the mean duration of treatment in the RE-COVER trials was 164 days and no data was available for people requiring only 3 months of anticoagulation. In the RE-MEDY AND RE-SONATE trials assessing long term secondary prevention, mean treatment duration in both was ~ 474 days (~16 months) and between 162 and 165 days (~6 months) respectively, and the ERG noted that the long term data for safety and efficacy are limited by the trial durations.

4.8 The ERG considered that assessment of renal function is already a requirement in the treatment pathway as dabigatran and rivaroxaban are contraindicated in people with severe renal impairment and warfarin dosing is dependent on renal function.

Clinical trial results

4.9 In the analyses of primary and secondary outcomes in the RE-COVER, RE-MEDY and RE-SONATE trials the manufacturer used the 'full analysis set' which included people who were randomised and had taken at least one dose of the study drug. This included 5107 of the 5153 randomised in the RE-COVER trials, 2856 of the 2866 people randomised in RE-MEDY and 1343 of the 1353 people randomised in RE-SONATE. The results for the primary outcome (recurrent venous thrombolism) are summarised in Table 6 below. Dabigatran was not associated with statistically significant differences for any of the primary or secondary efficacy outcomes in the trials comparing dabigatran with warfarin either for acute treatment or secondary prevention (RE-COVER trials and RE-MEDY). Dabigatran prevented statistically significantly more recurrent VTE events (including unexpected) deaths than placebo when taken over the long term for secondary prevention.

Table 6 Effectiveness outcomes: recurrent VTE (manufacturer's submission table 1 page 16, table 7 page 20, table 8 page 21, table 12 page 22).

Outcome	**Acute treatment**		**Secondary prevention**			
	RE-COVER trials (pooled analysis)		**RE-MEDY**		**RE-SONATE**	
	Dabigatran N =2553	**Warfarin N=2554**	**Dabigatran N=1,430**	**Warfarin N=1,426**	**Dabigatran N=681**	**Placebo N=662**
Primary outcome						
Recurrent VTE†	60(2.4%)	55(2.2%)	26(1.8%)	18(1.3%)	3(0.4%)	37 (5.6%)
Hazard ratio	HR1.09, 95% CI 0.76 to 1.57		HR 1.44, 95% CI 0.78 to 2.64		HR 0.08, 95% CI 0.02 to 0.25 (p<0.001)	
Statistical testing	RE-COVER and RE-COVER II p<0.0001 for non-inferiority		Non-inferior to warfarin p= 0.01		Dabigatran superior to placebo. P<0.0.001	
Secondary outcomes						
Symptomatic DVT	40 (1.6%)	34 (1.3)	17 (1.2%)	13 (0.9%)	2(0.3)	23(3.5)
Symptomatic non-fatal PE	18 (0.7%)	18 (0.7)	10 (0.7%)	5 (0.4)	1(0.1)	14(2.1)
Deaths related to VTE	2 (0.1%)	3 (0.1%)	1 (0.1%)	1(0.1%)		
All deaths	46 (1.8%)	46 (1.8	17 (1.2%)	19 (1.3%)	Not reported	Not reported

† includes unexplained deaths (RE-COVER, RESONATE) excludes unexplained deaths (RE-MEDY)

4.10 In the analysis of the RE-COVER trials, [redacted] (see table 51 and 52 pages 129-130 manufacturer's submission). [redacted]. The manufacturer presented results for 1323 of the 1343 people in RE-SONATE who were followed-up for 12 months after they had stopped receiving dabigatran or placebo. In this follow-up period, 6.9% of the group who had stopped dabigatran and 10.7% of the group

who had stopped placebo had a VTE event (Hazard ratio, 0.61, 95% CI 0.42 to 0.88).

ERG comments

4.11 The ERG commented that the manufacturer had used data from the full analysis set (FAS) rather than the intention to treat (ITT) population but noted that the patient numbers in both populations were similar. The ERG also commented that the results for the primary outcome in the ITT population in the RE-COVER and RE-MEDY trials (provided by the manufacturer in response to the clarification questions) were similar to the FAS population (see ERG report tables14, 15 and 40 pages 73, 74 and 102 for the ITT data).The ERG noted that less than 10% of people were lost to follow-up in any of the 4 dabigatran trials and the numbers that discontinued were well balanced between treatment groups.

Adverse effects of treatment including bleeding events

4.12 In its analysis of safety, the manufacturer used the treated set. This comprised of all randomised patients who received at least one dose of the study medication with patients assigned to the treatment group according to which drug they took (i.e. it may not have been the one they were randomised to). In total, in the RE-COVER trials, there were 1696 (66%) people in the dabigatran arms and 1772 (69%) in the warfarin arms who had an adverse event. Severe adverse events occurred in 252 (10%) people in the dabigatran arms and 254 (10%) people in the warfarin arms. Drug-related adverse events (as assessed by the investigator) occurred in 389 (15%) people in the dabigatran arm and 511 (20%) people in the warfarin arm, with the majority being bleeding events (see section 4.13). In RE-MEDY 72% of people in the dabigatran arm and 70.8% of people in the warfarin arm had an adverse event, approximately 10% in both treatment arms had a serious adverse event and 229 (16%) in the dabigatran arm and 280 (20%) of people in the warfarin arm had a drug related adverse event and 10% of people in the dabigatran arm and 9% of people in the warfarin arm discontinued their study drug because of an

adverse event. In RE-SONATE approximately 50% of people in both treatment arms experienced an adverse event, 47 (6.9%) people in the dabigatran arm and 60 (9.1%) of people in the placebo arm had a serious adverse event, 50 (7.3%) people in the dabigatran arm and 81 (12.3%) people in the placebo arm had an adverse event which led to discontinuation of the study treatment. There was a higher incidence of dyspepsia in RE-MEDY and RE-SONATE with dabigatran (1.2% in the dabigatran group and 0.4% of the warfarin group in RE-MEDY, and 4.1% of people in the dabigatran group and 1.2% of people in the placebo group in RE-SONATE experienced dyspepsia).

4.13 Rates of bleeding in the RE-COVER trials, RE-MEDY and RE-SONATE are summarised in table 7 below (please see table 33 page 80 of manufacturer's submission for definitions of bleeding outcomes). The results for RE-COVER include the period of time people were receiving the oral anticoagulant and the peranteral anticoagulant. The manufacturer also provided an analysis of bleeding outcomes covering the period when people were taking the oral anticoagulant only (see table 66 manufacturer's submission page 176).

Table 7: summary of bleeding outcomes (tables 66 page 176, 70-71 page 179-80, 76 page 187, 62 page 172 and response to clarification question A5).

Outcome	Treating		Secondary prevention			
	RE-COVER trials		RE-MEDY		RE-SONATE	
	Dabigatran	Warfarin	Dabigatran 1,430	Warfarin 1,426	Dabigatran 684	Placebo 659
Major bleeding event	37(1.4%)	51(2.0%)	13 (0.9%)	25 (1.8%)	2(0.3%)	0(0/0%)
	HR 0.73 95% CI 0.48 to 1.11		HR 0.52, 95% CI 0.27 to 1.02		-	
Major or clinically relevant bleeding	136 (5.3%)	217 (8.5%)	80 (5.6%)	145 (10.2%)	36 (5.3%)	13(2.0%)
	HR 0.62, 95% 0.50 to 0.76		HR 0.54, 95% CI 0.41 to 0.71		2.69 (1.43 to 5.07)	
Any bleeding event	411 (16.1%)	567 (22.2%)	277 (19.4%)	373 (26.2%)	10.5%	5.9%
	HR 0.70, 95% CI 0.61 to 0.79		HR 0.71, 95% CI 0.61 to 0.83 p<0.001		HR 1.82, 95% CI 1.23 to 2.68, p=0.0027	
Intracranial haemorrhage	2 (0.1%)	5 (0.2%)	2 (all cerebral)	4 (3 cerebral, 1 subdural)	None reported	
Gastrointestinal bleeding	101	68	5	8	5 (0.7%)	2 (0.3%)

4.14 The manufacturer presented the results for the number of bleeding events in the RE-COVER trials by centre grouped by the INR control of patients in the warfarin arm of the trial see table 80 manufacturer's submission page 192.

[redacted].

4.15 Across the RE-COVER trials 9 (0.3%) people in the dabigatran arms and 5 (0.2%) people in the warfarin arms had an acute coronary syndrome event. Of these, 8 (0.3%) people in the dabigatran arm and 4 (0.2%) people in the warfarin arms had a myocardial infarction. In RE-SONATE One person in each of the dabigatran and placebo groups had a

myocardial infarction. In RE-MEDY 13 (0.9%) people in the dabigatran arm and 3 (0.2%) in the warfarin arm had an acute coronary syndrome event, 9 people in the dabigatran group and 1 person in the warfarin arm had myocardial infarction and 3 people in the dabigatran group and 1 person in the warfarin group had ischaemia or unstable angina. In RE-SONATE 1 person in both the dabigatran arm and placebo arm had a myocardial infarction. Two people in the dabigatran arm had a transient ischaemic attack and 1 person in the placebo arm had an ischaemic stroke.

ERG comments

4.16 The overall adverse event and safety profile of dabigatran was generally comparable with warfarin for the outcomes reported in the manufacturer's submission. In terms of the comparison with placebo, the overall numbers of adverse events were similar for dabigatran and placebo but dabigatran was associated with statistically significantly more bleeding events. The ERG noted that the manufacturer reported a slightly higher baseline prevalence of cardiovascular risk factors in the dabigatran treatment group than in the warfarin treatment group in RE-MEDY but it was unclear whether these small differences in baseline characteristics were linked to overall incidence of ACS events in RE-MEDY.

Meta-analyses/indirect comparison/MTC

4.17 There were no head-to-head trials comparing dabigatran with rivaroxaban or comparing dabigatran to LMWH in people with cancer. The manufacturer performed a network meta-analysis but did not present the results in its submission. The manufacturer performed a direct meta-analysis to combine data from the RE-COVER trials together, and to combine data from the rivaroxaban trials of acute treatment. It performed an adjusted indirect comparison of dabigatran compared with rivaroxaban.

4.18 The manufacturer identified the following trials of rivaroxaban for treating and secondary prevention of DVT and PE.

- **Rivaroxaban for treating deep vein thrombosis and pulmonary embolism**:
  EINSTEIN-DVT and EINSTEIN-PE were open-label phase III trials that randomised patients to either rivaroxaban (15 mg twice daily for the first 3 weeks followed by 20 mg once daily) or low molecular weight heparin (enoxaparin 1mg/kg twice daily for at least 5 days) plus a VKA (warfarin or acenocoumarol), for the treatment of either recurrent symptomatic DVT or PE (people in EINSTEIN DVT had an index event of DVT, people in EINSTEIN PE has an index event of PE). Treatment duration was 3,6 or 12 months dependent on a person's risk of recurrent VTE as judged by the investigator at the start of treatment.

- **Rivaroxaban for secondary prevention of deep vein thrombosis and pulmonary embolism**:
  EINSTEIN –EXT was a phase III, randomised, placebo controlled trial designed to assess the relative efficacy and safety of rivaroxaban 20 mg in the prevention of recurrent symptomatic DVT or PE in patients who had completed 6 to 12 months of rivaroxaban or VKA treatment for an acute episode of VTE. Duration of treatment was 6-12 months

4.19 The manufacturer identified multiple sources of heterogeneity across RE-COVER and EINSTEIN trials for the acute treatment indication (see table 8).

Table 8: Differences between RE-COVER and EINSTEIN trials

	Dabigatran vs. warfarin (RE-COVER and RECOVER II)	Rivaroxaban vs VKA (EINSTEIN DVT and EINSTEIN PE)
Type of index event	Included both DVT or PE index events assessed in same study % DVT only: 68-69% % PE only: 21-23% %DVT+PE: 4-5%	EINSTEIN-DVT assessed DVT index event only, EINSTEIN PE assessed PE event only. Overall in pooled trials % DVT: 42%* % PE: 58%*
Duration of treatment and/or follow-up	6 months	3,6 or 12 months dependent on person's risk of recurrent event at start
Time in the target INR range for the warfarin/VKA arm	56.9-59.9% (across RE-COVER trials)	62.7% EINSTEIN PE* 57.7% EINSTEIN DVT*
Presence of risk factors for recurrent VTE	Not described in manufacturer's submission but duration of treatment in EINSTEIN trials was determined by patient's risk at baseline.*	

* Not described in manufacturer's submission, derived from EINSTEIN trial publications.

4.20 The main sources of heterogeneity among the secondary prevention trials identified by the manufacturer are summarised in table 9.

Table 9 Differences between RE-MEDY, RE-SONATE and EINSTEIN-EXT.

	Dabigatran vs. warfarin (RE-MEDY)	Dabigatran vs. placebo (RE-SONATE)	Rivaroxaban vs. placebo EINSTEIN-EXT
Presence of risk factors for recurrent VTE	High risk Would include people who definitely needed further anticoagulation	Clinical equipoise Would exclude people who definitely needed further anticoagulation	Clinical equipoise
Duration of 2ndary prevention and/or follow-up	6 months	6-36 months	6-12 months
Time in target INR	61.5%	n/a	n/a

4.21 The manufacturer presented data from a direct meta-analysis of the RE-COVER and RE-COVER II trials, and from a direct meta-analysis of the EINSTEIN-DVT and EINSTEIN-PE trials for recurrent VTE (including VTE related mortality) and bleeding outcomes for the treatment phase. The results of these analyses are summarised in table 10.To compare dabigatran with rivaroxaban the manufacturer performed an adjusted indirect comparison where a LMWH/vitamin K antagonist was the common comparator. The manufacturer assumed that LMWH with warfarin (the comparator in the RE-COVER trials) was equivalent to LMWH with a vitamin K antagonist (the comparator in the EINSTEIN trials). The manufacturer also presented the risk of recurrent VTE and VTE-related mortality for the subgroup of people whose index event was a PE and for the subgroup of people whose index event was a DVT.

[redacted]

Table 10 Direct and indirect comparisons acute treatment phase (data from table 54 page 142, table 55 page 143 and table 59 page 161 manufacturer's submission)

	Direct meta-analysis		Adjusted indirect comparison
	RE-COVER + RE-COVER II DBG vs. LMWH/WFN HR (95% CI)	EINSTEIN-DVT + EINSTEIN-PE RIV vs LMWH/VKA HR (95% CI)	DBG vs. RIV HR (95% CI)
VTE including VTE mortality PE subgroup DVT subgroup	[redacted] 1.09 (0.77, 1.54) 0.93 (0.53 , 1.63) 1.20 (0.78, 1.86) [redacted]	0.88 (0.54, 1.43) - -	[redacted]
Clinically relevant bleeds	0.63 (0.51, 0.77)	0.92 (0.8 , 1.06)	[redacted]
Major bleeds	0.76 (0.49, 1.18)	0.54 (0.36, 0.79)	[redacted]
Major or clinically relevant bleeds	Not reported	Not reported	[redacted]

DBG dabigatran, WFN warfarin, LMWH low molecular weight heparin, RIV rivaroxaban, HR hazard ratio, CI confidence interval

4.22 For the secondary prevention indication the manufacturer presented an adjusted indirect comparison of dabigatran compared with rivaroxaban using data from RE-SONATE and EINSTEIN-EXT as both trials compared the active treatment to placebo. The manufacturer did not include RE-MEDY as warfarin was the comparator. The hazard ratio for recurrent VTE (including VTE-related mortality) for dabigatran compared with rivaroxaban was [redacted]. The Hazard ratio for major or clinically relevant bleeds was [redacted].

ERG comments

4.23 The ERG reported the results of the manufacturer's network meta-analysis as it had been cited in one of the references cited by the manufacturer (see ERG report tables 70 on page 31 for the results of the manufacturer's network meta analysis for acute treatment and 72 page

133 for the network meta-analysis for secondary prevention). It noted that the manufacturer's network meta-analyses and adjusted indirect comparison gave similar results and there were no statistically significant differences between treatments. It also noted that the 95% confidence interval around some of the point estimates were wide, indicating a large amount of uncertainty. It also noted that the results for dabigatran compared with warfarin for secondary prevention from the adjusted indirect comparison and network meta-analysis were not consistent with the trial results from RE-MEDY.

4.24 The ERG carried out its own network meta-analyses for acute treatment and for secondary prevention based on the trials presented in the manufacturer's submission but employing different methods. For all outcomes the ERG used data assessed at the end of treatment rather than at the end of the observed period in the trial, and where possible used ITT data in the analysis. The ERG's analyses were conducted using WinBUGS and a Bayesian MCMC simulation rather than the frequentist approach using SAS undertaken by the manufacturer. The fixed effects model was preferred over the random effects model, and odds ratio was used as a summary statistic for all analyses as it has been shown to be associated with less heterogeneity in meta-analysis than risk difference or relative risk.

4.25 In its network meta-analysis for acute treatment the ERG included data from the RE-COVER trials and the EINSTEIN-DVT and PE trials (see figure 3). There were no statistically significant differences between treatment groups. The results of the ERGs network meta-analysis are presented in table 11 below.

Figure 3: Network of 4 randomised controlled trials informing the NMA conducted by the ERG for the acute treatment of VTE (figure 8 ERG report page 135)

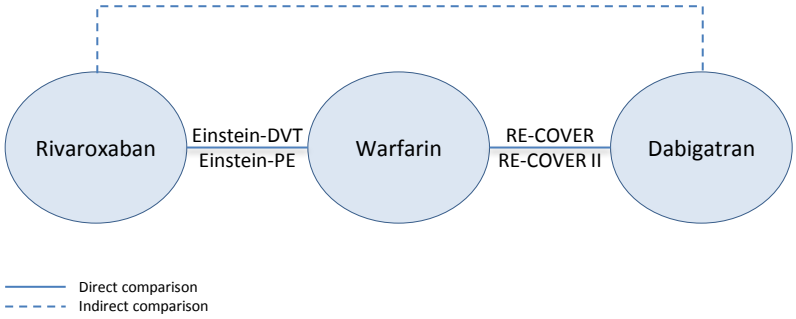


Table 11: Results from the NMA conducted by the ERG for the acute treatment of VTE using dabigatran as a baseline (OR <1 favours comparator; OR >1 favours dabigatran) (table 75 ERG report page 136).

Outcome	Mean Odds Ratio	95% Credible Interval	
		Lower	Upper
VTE			
Warfarin vs dabigatran	0.921	0.636	1.281
Rivaroxaban vs dabigatran	0.837	0.516	1.299
Major bleed			
Warfarin vs dabigatran	1.369	0.860	2.061
Rivaroxaban vs dabigatran	0.763	0.402	1.320
CRNMB			
Warfarin vs dabigatran*	1.647	1.310	2.035
Rivaroxaban vs dabigatran*	1.647	1.234	2.114

*Statistically significant at the 5% level.

Abbreviations used in table: CRNMB, clinically relevant non-major bleed; VTE, venous thromboembolism; vs, versus.

4.26 In the ERG's meta-analysis for secondary prevention, data were included from RE-MEDY, RE-SONATE , EINSTEIN-EXT and 4 trials that had compared warfarin with placebo. The ERG noted that the manufacturer had concerns about the comparability of RE-MEDY and RE-SONATE,

however after comparing the inclusion/exclusion criteria and the available demographics for the patient populations the ERG considered them similar enough to be included in the same network. It noted that this assumption is conditional on the relative treatment effect being consistent in patients at different baseline risk (people in RE-MEDY were considered at high risk of a recurrent event, people in RE-SONATE were at equipoise meaning that there was not a clear indication for continued treatment as they were at lower risk of a recurrent event). See figure 4. The results showed a statistically significant increase in risk of a major bleed and clinically relevant non major bleeds with warfarin compared with dabigatran, and a statistically significant increase in clinically relevant non major bleeds with dabigatran compared with placebo alongside a decreased risk of recurrent VTE. There were no further statistically significant differences between treatments. See table 12 for results.

Figure 4: network of 7 RCTs informing the NMA conducted by the ERG for the secondary prevention of VTE (figure 10 ERG report)

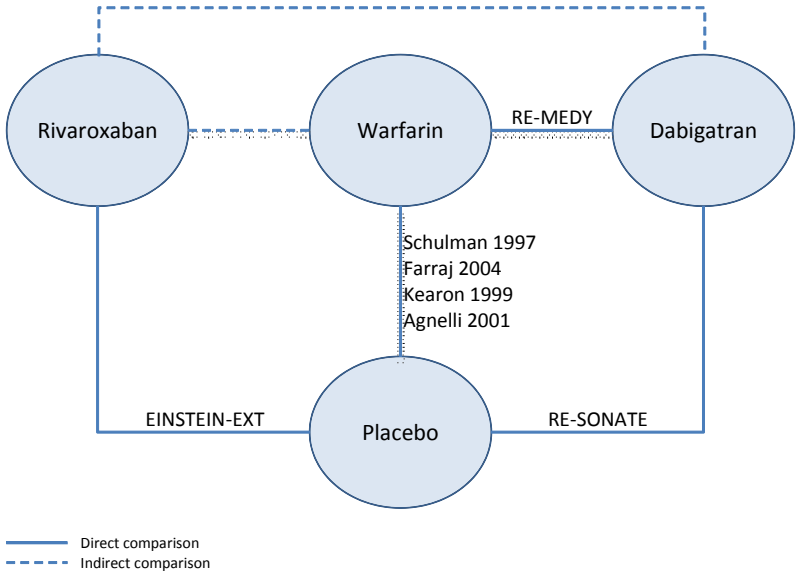


Table 12: Results from the NMA conducted by the ERG for the secondary prevention of VTE using dabigatran as a baseline (OR <1 favours comparator; OR >1 favours dabigatran) (table 75 page 139 ERG report)

Outcome	Mean Odds Ratio	95% Credible Interval	
		Lower	Upper
VTE			
Warfarin vs dabigatran	0.948	0.509	1.616
Rivaroxaban vs dabigatran	1.744	0.510	4.388
Placebo vs dabigatran*	9.670	4.469	19.140
Major bleed†			
Warfarin vs dabigatran*	2.039	1.007	3.759
Rivaroxaban vs dabigatran	42	0.329	113
Placebo vs dabigatran	0.726	0.232	1.704
CRNMB			
Warfarin vs dabigatran*	1.849	1.358	2.472
Rivaroxaban vs dabigatran	2.133	0.681	5.303
Placebo vs dabigatran*	0.387	0.205	0.643

*As zero events occurred for placebo in EINSTIEN-EXT[28] and RE-SONATE[48], a single major bleed had to be added to placebo to establish a link between dabigatran and rivaroxaban using these studies. This may result in an underestimate of risk of major bleed in for these two treatments.

†Statistically significant at the 5% level.

Abbreviations used in table: CRNMB, clinically relevant non-major bleed; VTE, venous thromboembolism; vs, versus.

Clinical effectiveness of dabigatran, LMWH and rivaroxaban for treating and preventing recurrent VTE in the subgroup of people with active cancer

4.27 The RE-COVER trials and RE-MEDY included a small number of people with active cancer at baseline (~4%). In the RE-COVER trials 10 out of the 173 people (5.8%) in the dabigatran arms with active cancer and 12/162 (7.4%) people in the warfarin arm had VTE or death related to VTE). The manufacturer did not present the rate of recurrent VTE for people with active cancer in RE-MEDY. The Summary of Product Characteristics for dabigatran states that the efficacy and safety [of dabigatran] have not been established for DVT/PE patients with active cancer. There were no trial data for dabigatran compared with LMWH or rivaroxaban for people with active cancer. The manufacturer presented a direct meta-analysis of 5 trials of LMWH compared with VKA in people with active cancer for the treatment phase and the results of analysis of LMWH compared with VKA in people with active cancer in the secondary prevention phase (Cancer –DACUS extension study, Siragusa et al 2011). The results are summarised below.

Table 13 rates of recurrent VTE and major bleeding in people with active cancer treated with LMWH compared with a vitamin K antagonist (data from table 99 page 240-241 manufacturer's submission)

	Recurrent VTE	Major bleeding
Treatment phase LMWH vs. VKA	RR 0.49, 95% CI 0.34 to 0.70	RR 1.05, 95% CI 0.53 to 2.10
Secondary prevention phase	RR 0.63 95% CI 0.34 to 1.18	RR 2.58, 95% CI 0.51 to 13.06

ERG comments

4.28 The ERG commented on the cancer subgroup in the clinical trials and it noted that the definition of active cancer used in the RE-COVER trials and RE-MEDY included some people who may have been in remission for nearly 5 years who would not usually be considered to have active cancer in UK clinical practice. It noted in the RE-COVER and RE-MEDY trials that

people in the control arm who had active cancer received parenteral anticoagulant followed by warfarin rather than continued LMWH as is clinical practice in England. The ERG noted that the number of patients with active cancer were small and the event rates low. No data was presented for the use of rivaroxaban in people with active cancer. The ERG carried out a network meta-analysis for acute treatment in a population with active cancer including data from the EINSTEIN DVT/PE trials, the RE-COVER Trials and the 5 trials comparing warfarin with LMWH. The ERG noted that there was no data for clinically relevant non major bleeds for any of the comparisons and for major bleeding events in the rivaroxaban compared with dabigatran comparison. There were no statistically significant results in this analysis (see figure 9 and table 74 pages 136 and 137 for a diagram of the network and results table). The ERG stated that there was insufficient data to perform an analysis of secondary prevention of VTE in patients with active cancer. The ERG considered that limited conclusions can be made for the subgroup of people with cancer.

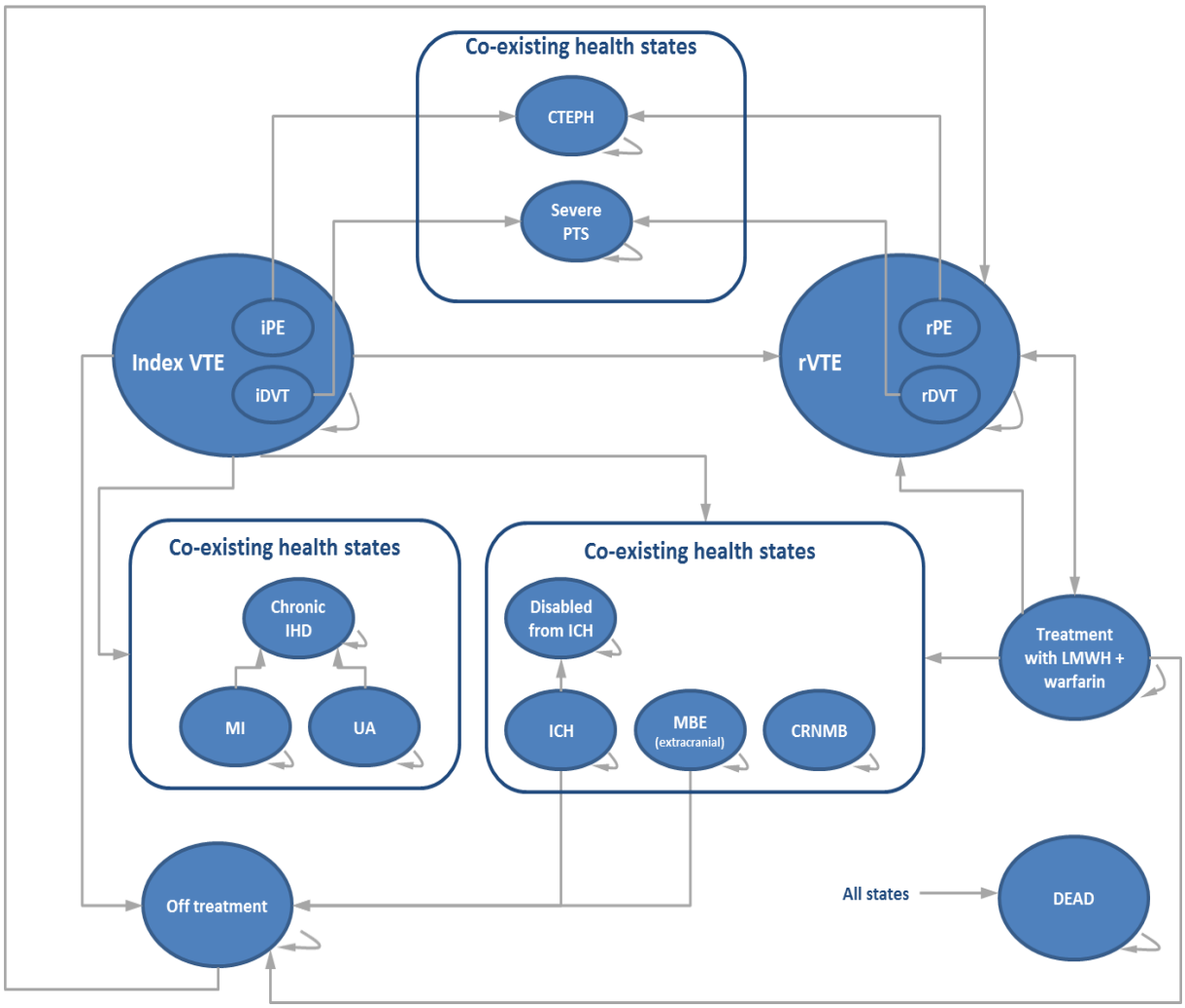
5 Cost-effectiveness evidence

Model structure

5.1 The manufacturer developed a Markov model, with a 1 month (30 days) cycle length and a lifetime time horizon (60 years). A 3.5% discount rate was applied for costs and consequences and the model was the perspective of the NHS/PSS. Patients entered the model after an index VTE event and received treatment. If people had a recurrent DVT or PE they stopped treatment and received a 6 month treatment with LMWH followed by warfarin (regardless of their initial treatment) and they did not receive continued anticoagulation for secondary prevention. Treatment was stopped completely if there was an intracranial haemorrhage, major bleeding event, or for other reasons (such as end of planned treatment duration, other pre-existing conditions or adverse events other than

bleeding). In the ‘off treatment’ health state people were assumed to have no risk of bleeding but were at continued risk of recurrent VTE. In the model people could have up to 2 recurrent VTE events. People who had a pulmonary embolism (either the index event or a recurrent PE) could develop chronic thromboembolic pulmonary hypertension (CTEPH -the risk of this complication remained for 2 years after the PE). People who had a DVT (either the index event or a recurrent DVT) could develop post thrombotic syndrome (PTS -the risk remained for 5 years after their DVT). The model only included people with severe PTS because the manufacturer stated that mild PTS had little detrimental effect on quality of life. People could from die from any cause while in any of the health states. Age and gender specific UK mortality rates were used (2010 Office National Statistics). The cardiovascular health states (myocardial infarction and unstable angina) and a health state for dyspepsia were only modelled in the sensitivity analyses (see section 5.28).

Figure 5: Model structure (figure 29 manufacturer's submission page 230)



MI = myocardial infarction; UA = unstable angina and IHD = Chronic ischemic heart disease apply to sensitivity analyses only.
Index VTE = index venous thromboembolism; iDVT = index deep vein thrombosis; iPE = index pulmonary embolism; CTEPH = Chronic thromboembolic pulmonary hypertension; PTS = post thrombotic syndrome; rVTE = recurrent venous thromboembolism; rPE = recurrent pulmonary embolism; rDVT = recurrent deep vein thrombosis; MBE = major bleeding events; CRNMB = Clinically relevant non-major bleeds; ICH = intracranial haemorrhage.
Note: The coexisting health states shown within the pale blue panel may occur concurrently with any other health state (they are not mutually exclusive).

5.2 In the model the average age of the cohort at baseline was 55 years, 69% of people entered the model with an initial DVT, and 31% entered the model with an initial PE (data from pooled RE-COVER trials). The manufacturer modelled two scenarios: acute treatment of VTE only and treating and long term secondary prevention of VTE. In the acute treatment scenario specifically people only received acute treatment for

initial or recurrent DVT/PE and did not receive further treatment if they had a recurrent VTE. In the treatment and secondary prevention scenario people received acute treatment and secondary prevention for initial DVT/PE and acute treatment only (with LMWH/warfarin) for recurrent DVT/PE.

5.3 The manufacturer modelled the risk of the composite outcome of recurrent VTE and related death and then split this risk by the proportion that was attributable to DVT, fatal PE and non-fatal PE. Likewise it modelled the risk of the composite outcome of major or clinically relevant non-major bleeds and split this total incidence by the proportion attributable to extracranial major bleeding events, intracranial major bleeding events, fatal major bleeding events and clinically relevant non-major bleeding events.

5.4 The manufacturer used clinical data from the pairwise comparisons in the clinical trials and did not use the adjusted indirect comparisons or data from a network meta-analysis in its model. For the acute treatment phase the manufacturer assumed the baseline risk of each VTE and bleeding composite outcome was the incidence observed in the warfarin arm in the RE-COVER trials. It multiplied these baseline risks by the hazard ratio from RE-COVER to derive incidence of each outcome with dabigatran, or multiplied these baseline risks by the hazard ratio for warfarin compared with rivaroxaban from the pooled EINSTEIN DVT/PE trials to derive the incidence of each outcome with rivaroxaban. To derive the proportion of people experiencing each type of recurrent VTE event or bleeding event it applied the proportions observed in the warfarin arm of the RE-COVER trial, the dabigatran arm in the RE-COVER trials and the rivaroxaban arm of the pooled EINSTEIN DVT/PE trials. For the risks of these outcomes during secondary prevention the manufacturer used a similar approach. However as the rivaroxaban secondary prevention trial EINSTEIN EXT compared rivaroxaban with placebo, the manufacturer took the baseline risk to be that observed on placebo in RE-SONATE and multiplied by the

hazard ratios from RE-SONATE and EINSTEIN-EXT for the risk of these outcomes while taking dabigatran and rivaroxaban respectively. The manufacturer modelled the risk of these outcomes for dabigatran compared with warfarin based on the treatment effect and baseline risks observed in RE-MEFY. As a consequence of this approach the risks of recurrent VTE or bleeding with dabigatran during long term treatment for secondary prevention differ depending on whether rivaroxaban or warfarin is the comparator. It also affects other assumptions in the model, for example duration of dabigatran treatment compared with warfarin treatment for secondary prevention was 18 months (reflecting treatment length in RE-MEDY), and 6 months for dabigatran compared with rivaroxaban for secondary prevention (reflecting treatment length in RE-MEDY). The duration of acute treatment was 6 months in all comparisons. When the comparator was LMWH (for the cancer population) duration of treatment was 6 months. The risks of each event for each comparison and the source of data used are summarised in tables 14 and 15 below. The manufacturer derived the risks of non-fatal PE, Proximal DVT, VTE-related death and distal DVT after therapy discontinuation from Pradoni et al 2007.

Table 14 summary or risk of recurrent VTE and major or clinically relevant bleeds in the model (data from table 107 manufacturer's submission page 253)

	Baseline risk of event			Treatment effect			
				Dabigatran		Rivaroxaban	
	Trial pop.	Treatment arm	Value	Trial pop.	Treatment effect	Trial pop.	Treatment effect
Treatment phase							
Incidence rVTE	Pooled RE-COVER	LMWH/ warfarin	2.43%	Pooled RE-COVER ITT analysis includes 30 d post- tx	HR 1.09 (0.77,1.54) **Incidence: 2.65%**	Pooled EINSTEIN DVT/PE ITT 3,6,12 month treatment group	HR 0.89 (0.66, 1.19) **Incidence: 2.16**
Incidence MCRB	Pooled RE-COVER	LMWH/ warfarin	7.68%	Pooled RE-COVER Treated	HR 0.62 (0.5 to 0.76) **Incidence: 5.27%**	Pooled EINSTEIN DVT/PE ITT	HR 0.93 (0.81, 1.06) **Incidence: 7.90%**
Secondary prevention phase comparison with rivaroxaban							
Incidence rVTE	RE-SONATE	Placebo	5.59%	RE-SONATE FAS as randomised	HR 0.08 (0.02, 0.25) **Incidence: 0.45%**	EINSTEIN EXT ITT	HR 0.18 (0.09, 0.39) **Incidence: 1.01%**
Incidence MCRB	RE-SONATE	Placebo	1.97%	RE-SONATE FAS as treated	HR 2.69(2.30, 11.70) **Incidence: 5.31%**	EINSTEIN EXT safety	HR 5.19 (2.30, 11.70) **Incidence 10.24%**
Secondary prevention phase comparison with warfarin							
Incidence rVTE	RE-MEDY	warfarin	1.26%	RE-MEDY FAS as randomised	HR 1.44 (0.78, 2.64) **Incidence: 1.82%**	No data available for rivaroxaban vs. warfarin	
Incidence MCRB	RE-MEDY treated set	warfarin	10.17%	RE-MEDY FAS as treated	HR 0.55 (0.41, 0.72) **Incidence: 5.59%**		

Table 15 Proportion of recurrent DVT and PE, and bleeding events by treatment, applied within the acute and secondary prevention treatment periods. ERG report tables 85 and 86 (page 178) and 92 and 93 (page 193)

Type of recurrent VTE	Dabigatran	Warfarin	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
Acute treatment					
Recurrent DVT (proximal)	63%	61%	42%	63%	58%
Recurrent PE (non-fatal)	34%	34%	55%	34%	39%
Recurrent PE (fatal)	3%	5%	3%	3%	3%
Source	Pooled RE-COVER		Pooled EINSTEIN-PE/DVT	Pooled RE-COVER cancer subgroup	Average of other presented data
Secondary prevention					
Type of recurrent VTE	**Dabigatran**	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Dabigatran (population with cancer)**	**LMWH (population with cancer)**
Recurrent DVT (proximal)	62%	72%	67%	71%	67%	58%
Recurrent PE (non-fatal)	35%	22%	33%	29%	33%	39%
Recurrent PE (fatal)	4%	6%	0%	0%	0%	3%
Source	RE-MEDY	RE-MEDY	RE-SONATE	EINSTEIN-EXT	RE-SONATE	As acute period
Abbreviations used in table: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.						
Acute treatment						

Type of bleeding event	Dabigatran	Warfarin	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
MBE (ICH)	1%	2%	1%	2%	1%
MBE (extra-cranial)	26%	21%	9%	34%	11%
CRNMB	73%	76%	90%	65%	88%
Source	Pooled RE-COVER	Pooled RE-COVER	Pooled EINSTEIN-PE/DVT	Pooled RE-COVER, cancer subgroup	Pooled trial data
Secondary prevention					
Type of bleeding event	**Dabigatran**	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Dabigatran (population with cancer)**	**LMWH (population with cancer)**
MBE (ICH)	2.5%	2.8%	0.0%	0.0%	0.0%	1.6%
MBE (extra-cranial)	13.8%	14.5%	5.6%	11.1%	5.6%	13.1%
CRNMB	83.8%	82.8%	94.4%	88.9%	94.4%	85.3%
Source	RE-MEDY	RE-MEDY	RE-SONATE	EINSTEIN-EXT	RE-SONATE	Pooled trial data
Abbreviations used in table: CRNMB, clinically relevant non-major bleed; ICH, intracranial haemorrhage; LMWH, low-molecular-weight heparin; MBE, major bleeding event.						

5.5 During the acute treatment period the risk of a recurrent VTE or bleeding was assumed to decrease over time. This was based on the results of the dabigatran trials in which the rates of recurrent VTE and bleeds were higher in the first months after the index event and gradually declined thereafter. To model the decrease in risk over time manufacturer applied a log-normal distribution with respect to time to the hazard ratios/relative risk from trials of treating VTE (RE-SOLVE, EINSTEIN-DVT, EINSTEIN-PE). The risk of recurrent VTE and bleeding events was assumed to be constant over the secondary prevention treatment period and in the post-treatment period. Probabilities of events other than VTE or bleeding in the model were assumed to remain constant over time.

5.6 CTEPH is a complication of PE and is associated with considerable morbidity and mortality. The probability of CTEPH in the model was taken from Pengo et al. 2004. Post thrombotic syndrome was not reported in the trials. The incidence of PTS was assumed to be the same for all comparators. The incidence of severe PTS was based on data from Pradoni et al 1997.

ERG comments

5.7 The ERG had concerns about a number of the assumptions in the model relating to how people would be treated in clinical practice. In the manufacturer's analyses the duration of acute treatment was 6 months. The ERG's clinical experts considered this to reasonably reflect clinical practice; however, the ERG acknowledges that more recently, and following publication of CG144, acute treatment duration of 3 months is increasingly common. The ERG noted that in the model people received treatment for secondary prevention for 6-18 months (dependent on the comparator) whereas its clinical advisors stated that some people may receive life-long anticoagulation treatment. The ERG noted that in the model people experiencing a recurrent VTE did not receive secondary prevention, rather they received only acute treatment. Based upon clinical advice the ERG considered it more likely that a patient experiencing

multiple VTE events would receive life-long secondary prevention unless precluded by the balance of risk of bleeding. The ERG also disagreed that the only anticoagulation treatment option for a recurrent VTE would be LMWH/warfarin. It thought that some people may receive rivaroxaban and people with cancer would receive LMWH. In the model people experiencing a major bleeding event stop treatment permanently and the ERG considered this to mean that people would not re-start anticoagulation treatment if they had a recurrent VTE which may not reflect UK clinical practice. It noted that in technology appraisals 261 and 287 (rivaroxaban for treating and secondary prevention of DVT and PE respectively) people with experiencing a major bleeding event could restart anticoagulation treatment after 1 to 3 months.

5.8 The ERG stated that it was appropriate to exclude cardiovascular health states from the base case as these are not of direct relevance to the condition of interest for this appraisal, but it felt that dyspepsia should be included in base case as an important side effect associated with dabigatran treatment.

5.9 The ERG stated that the average age of patients entering the model was underestimated by the manufacturer and resulted in longer time horizon than necessary (60 years). The ERG considered that 50 years would be sufficient as 99.9% of the modelled cohort would have died by 50 years. The ERG stated that it could not find the source of age dependent all-cause mortality used by the manufacturer and used 2013 data from Office of National statistics in its own sensitivity analyses

5.10 The ERG noted that the synthesis of data was not carried out using a network meta-analysis; instead the manufacturer used a series of head-to-head and indirect comparisons. The limitation of this approach for the secondary prevention analyses was that the data for dabigatran varied in each comparison, resulting in a lack of comparability across assessed scenarios. The ERG did not consider that duration of treatment would

differ by intervention. The ERG also noted that discontinuation on dabigatran for secondary prevention also varied based on what the comparator was.

5.11 The ERG noted that the proportion of people experiencing each type of recurrent VTE event (DVT or PE); type of bleeding event (major bleeding event [intracranial haemorrhage]; major bleeding event [extracranial] and clinically relevant non-major bleed) and whether a major bleed was fatal differed by treatment arm (table 97 ERG report page 200). This was because the proportions of people experiencing each outcome were taken directly from observations in each separate clinical trial. The ERG consulted with clinical experts about whether a difference in these outcomes was expected and was advised that there was no clinical basis for such a difference. The clinical experts said that the number of deaths may be expected to differ in clinical practice if the rates of gastrointestinal MBEs differed, but the ERG considered the rates of GI bleeds to be similar across trials.

Model details - utility values

5.12 The manufacturer used baseline age and gender specific utility values in its model, and adjusted for decreases in quality of life associated with treatment and each health state (see table 16). The duration of the decrement in utility with a recurrent DVT or PE was assumed to be 6 weeks. For any type of bleeding event (intracranial haemorrhage, major bleeding event or clinically relevant non-major bleeding event) a 1 month decrement in utility was assumed. An additional decrement in utility was applied for a person's lifetime if they were disabled as a consequence of an intracranial haemorrhage. People who were not receiving treatment and had an acute episode of chronic thromboembolic pulmonary embolism were assumed to have reduced utility for 1 month. People who experienced severe post-thrombotic syndrome while of treatment were assumed to have a reduced utility for their remaining lifetime.

Table 16: Utility values used in the manufacturer's model (table 113 manufacturer's submission page 300)

Baseline utility is the estimates for the general population in England according to age and gender see table 113 page 300 manufacturers submission for age and gender breakdown. Mean of modelled cohort age 54.7 years utility value 0.85 (Prescott-Clarke P et al The health survey for England 1996)			
Health state	Mean disutility [95% CI]	Duration of disutility	Source and rationale
Initial and recurrent DVT	-0.25 [-0.24 to -0.26]	6 weeks	EQ-5D collected in RE-COVER trials at day 1, 3 months and 9 months. There were no differences between treatment arms so data was pooled. There was an increase in utility value of 0.25 after 3 months from the baseline of 0.58 (immediately after the index event)
Initial and recurrent PE	-0.25 [-0.23 to 0.27]	6 weeks	
During active warfarin treatment	-0.012 [-0.008 to -0.016]	Time on warfarin	Marchetti et al. 2001. Time trade off survey of 48 patients attending an anticoagulation clinic
During active LMWH treatment	-0,008 [-0.005 to -0.011]	Time on LMWH	
Severe PTS	-0.07 [-0.048 to -0.092]	Remaining lifetime after onset	Lenert et al 1997 Survey of 30 healthy volunteers and 30 physicians about using standard gamble methods
Major bleed: ICH with a resulting disability	-0.5 [-0.502 to -0.598]	Remaining lifetime after bleed	Wolowacz et al 2009
Major bleed: MBE (includes people with ICH who are not disabled by it)	-0.13 [-0.105 to -0.155]	Applied in month of event	EQ-5D data collected in RE-COVER trials. Difference in change in mean EQ5D score from baseline to 6 months between people without a MBE and people with a MBE and between people without a CRNMB and people with a CRNMB
Non-major bleed: CRNMB	-0.04 [-0.032 to -0.048]	Applied in month of event	
Myocardial infarction	-0.063 [-0.050 to -0.075]	Applied in month of	Sullivan et al 2011. EQ-5D questionnaire (US), with UK preference values applied.

(sensitivity analysis)		event	
Unstable angina*	-0.085 [-0.069 to -0.102]	Applied in month of event	
CTEPH	-0.12 [-0.08 to -0.120]	Remaining lifetime	79,80 Keogh et al 2007 (subtracted the mean utility value in Keogh 0.73 from the age/gender weighted baseline utility value)
Dyspepsia (sensitivity analysis)	-0.04 [-0.032 to 0.048]	Applied during duration of treatment	Gerson et al 2005 Time trade off. Disutility calculated mean rating of patients off medication 0.9 – mean rating of patients on therapy for reflux 0.94

ERG comments

5.15 The ERG noted that the decrement in utility associated with DVT and PE, derived from EQ-5D data collected in the RE-COVER trials, was the same figure used in the manufacturer's model (-0.25). It noted that this was surprising as PE is a more serious condition which might be expected to be associated with a larger decrease in quality of life compared with DVT. It further noted that in TA 261 and 287 the utility values estimated for PE and DVT were 0.63 and 0.84 respectively. The ERG commented however that it was appropriate to use EQ-5D data collected from the RE-COVER trials within the model, rather than other published estimates of utility.

5.16 The ERG noted that the decrement in utility assumed for a patient taking warfarin was based on data from a study of 48 patients. It estimated that the value of -0.012 may not be robust as it was derived from a small sample of people which may limit the generalizability of the results and it used patient preferences to value the health states. Furthermore there was not a similar analysis provided for dabigatran. The ERG noted that a head-to-head comparison of warfarin and dabigatran from RE-LY (a trial of stroke prevention in people with atrial fibrillation) indicated that there was no long term difference in the EQ-5D scores for patients receiving warfarin and dabigatran. The ERG noted however that the utility decrement used by the manufacturer in the current submission was the same as that used by the manufacturer of rivaroxaban in TA 261 and TA 287. It also noted that in the model people taking warfarin were assumed to be within the appropriate INR 58% of the time. The ERG did not consider that this assumption was unreasonable for the acute treatment period but expected that INR control would be likely to increase once patients are stable on treatment, during secondary prevention, to a level of 60% or higher. The ERG concluded that whilst there may be a difference in utility associated with warfarin, the disutility is likely to be small and may reduce over time as people become used to their

treatment regimen. However, the ERG notes that there is a great degree of uncertainty around estimates of disutility while on warfarin.

Model details- resource assumptions

5.17 The drug costs used in the manufacturer's model are outlined in table 17 below.

Table 17 Drug costs per day (taken from MIMS 2014) MS table 115 pg 322 and 116 page 323

Treatment	Cost per day	
Dabigatran (150 mg twice daily)	£2.20	
Warfarin (generic, 4 mg per day	£0.07	
Rivaroxaban • 15 mg twice daily (first 21 days of treatment) • 20 mg once daily (remainder of treatment and secondary prevention)	 £4.20 £2.10	
LMWH or UFH Enoxaparin (1.5 mg/kg/day SC) Dalteparin (200 IU/kg/ day SC) Dalteparin (100IU/kg twice daily SC) Tinzaparin (175 IU/kg/day) UFH (5,000U (IV) followed by 1000-2000 U/hr) UFH (5,000 U (IV) followed by 15,000 U twice daily (SC) Weighted average cost/day	% DVT patients 24.75% 24.75% 24.75% 24.75% 0.5% 0.5% £9.63	% PE patients 90% 0.5% 0.5% £7.81

5.18 It was assumed that people receiving warfarin would have 1 initial anticoagulation clinic visit with a consultant at a cost of £62.56 (NHS reference costs 2012/13), 4 anticoagulation clinic visits during the warfarin titration period, and follow-up visits (one per month) while on treatment with warfarin. The cost of a visit to the anticoagulation clinic was assumed to be £27.99 based on NHS reference costs 2012/13 and weighted to take into account consultant-led and non-consultant-led appointments. People receiving dabigatran or rivaroxaban were assumed to visit an anticoagulation clinic once. Warfarin monitoring costs over the first year

of treatment were £482.41 (assuming one consultant-led visit and 15 further follow-up visits to the anticoagulation clinic).

5.19 The manufacturer assumed that 52% of people with an acute proximal DVT and 90% of people with an acute PE would be admitted to hospital (based on the hospitalisation records from the EINSTEIN trial), and that the length of stay in hospital would be the same for people receiving rivaroxaban (with no parenteral treatment) and dabigatran and warfarin (who also received parenteral treatment). Costs for an inpatient stay and mean length of stay were estimated from NHS reference costs (2012/13). An in-patient stay following a DVT was assumed to be 5.68 days on average at a total cost of £955.69 (cost per day £168.28). An in-patient stay following a PE was assumed to be 6.09 days on average at a total cost of £1,520.67 (cost per day £249.69). The manufacturer assumed that if people were discharged from hospital before they had completed the course of LMWH injections, most people (87%) would be able to self-inject at home with no additional costs. However 6% of people would need a nurse visit at a cost of £39.18 per day and 7% of people would need to attend a daily clinic visit for their injection at a cost of £27.99 per day. The costs of a recurrent DVT or PE were assumed to be the same as the index event, with the addition of diagnosis costs totalling £158.14 for a recurrent DVT and £291.78 for a recurrent PE (see manufacturer's submission table 120 page 325 for full break down of diagnosis costs).

5.20 The costs of bleeds and other adverse events are summarised in table 18 below.

Table 18 costs of adverse events in the manufacturer's model (manufacturer's submission table 122 page 328)

Cost element (%) assumed proportion of population	Amount	Source
MCRB ICH: initial acute management ICH: annual cost of long term care Other major bleed Hospitalised CRNMB (30%) Outpatient visit CRNMB (70%)	 £10,182 £3,011 £2,357 £1,102 £93	 Youman et al 2003 Youman/ RE-COVER NHSRC 2012/13 NHSRC 2012/13 NHSRC 2012/13
Severe post-thrombotic syndrome Year 1: 1 x vascular surgery, outpatient 1st visit 2x vascular surgery, outpatient follow-up visit Year 2+: GP appointments, 2x per year	 £168 £274 £92	 NHSRC 2012/13 NHSRC 2012/13 PSSRU
Myocardial infarction Acute management Long-term care (60%) per month	 £4,724 £34	 Ara et al 2012* Ara et al 2012
Unstable angina Acute management Long term care (60%) per month	 £4,588 £34	 Ara et al 2012 Ara et al 2012
CTEPH Pulmonary endarterectomy (50.5 %) Ongoing management (per month)	 £7,447 £1,365	 NHSRC 2012/13 NICE CG92
Dyspepsia Management with NSAIDs	 £46	 Latimer et al 2009

* study evaluating cost effectiveness of treatment with high dose versus low dose statins for individuals with acute coronary syndrome.

ERG comments

5.21 The ERG noted that for patients experiencing an index VTE who are treated with dabigatran, rivaroxaban or LMWH monotherapy, the manufacturer has not included an initial appointment where people are prescribed treatment and receive any training on how to take their medication. By contrast all patients receiving warfarin were assumed to have an initial anticoagulation appointment at which treatment would be initiated, even those who have been admitted to hospital for their index VTE. The ERG was therefore considered that the manufacturer both overestimated the number of appointments for admitted patients who

received warfarin (as they will not require an initial anticoagulation visit), but also underestimated the number of appointments required for dabigatran, rivaroxaban or LMWH monotherapy, as non-hospitalised patients will require an initial appointment. Consequently the ERG considered that the cost of administering dabigatran compared with warfarin may be underestimated.

5.22 The ERG noted that the manufacturer assumed that after an initial titration period in the first month, people taking warfarin would visit an anticoagulation clinic once a month for the remainder of treatment. The ERG heard from clinical experts that whilst this frequency of monitoring visits may be appropriate for initial acute treatment, but if people continued to take warfarin long-term for secondary prevention, monitoring would be carried out less frequently, typically once every 3 months. The ERG's clinical experts considered the monitoring schedule for dabigatran and rivaroxaban to be reasonable but noted that patients receiving either of these drugs may return to their GP annually. The ERG noted that the manufacturer's estimated cost for follow-up visits to an anticoagulation clinic (£27.99) took into account that some visits would be consultant-led. The clinical experts advised that in clinical practice, it is typical for nurses to provide the majority of contact at follow-up visits. Such visits were assumed to cost £10.61 by the ERG.

Manufacturer's base case results

5.23 The manufacturer presented base case results for the cost effectiveness of dabigatran compared with low molecular weight heparin followed by warfarin for treating VTE only and for both treating and secondary prevention of VTE. In the treating and secondary prevention base case, the manufacturer presented 2 pairwise comparisons: one for dabigatran compared with low molecular weight heparin followed by warfarin, and 1 for dabigatran compared with rivaroxaban. It did not present a fully incremental analysis. The deterministic results are shown in tables 19-20 below. The probabilistic results were comparable to the deterministic

results for the acute treatment-only base case. The probabilistic ICER for dabigatran compared with warfarin was £1,016 per QALY gained and dabigatran remained dominant to rivaroxaban (was less costly and more effective). In the acute treatment and secondary prevention base case, the probabilistic ICERs were again comparable to the deterministic results (for dabigatran compared with warfarin the probabilistic ICER was £8,319 per QALY gained, dabigatran remained dominant to rivaroxaban). See manufacturer's submission page 356 for probabilistic results.

Table 19: deterministic base case treating VTE (table 145 manufacturer's submission page 356)

Treatment	Total costs	Total LY	Total QALYs	Inc. costs	Inc. QALYS	ICER
Warfarin	7,482	16.159	12.428	-	-	-
Dabigatran	7,503	16.170	12.452	21	0.0239	£862
Rivaroxaban	7,523	16.170	12.451	20	-0.0003	Dominated by dabigatran

Table 20: deterministic base case results treatment followed by secondary prevention (table 146 manufacturer's submission page 356+ model)

Treatment	Total costs	Total LY	Total QALYs	Inc. costs	Inc. QALYS	ICER
Comparison dabigatran with warfarin						
Warfarin	7,861	16.262	12.464			
Dabigatran	8,319	16.242	12.519	£458	0.0551	£8,319
Comparison dabigatran with rivaroxaban						
Dabigatran	7,785	16.206	12.480			
Rivaroxaban	7,852	16.208	12.478	£67	-0.002	Dominated by dabigatran

5.24 The manufacturer presented deterministic and probabilistic base case results for the subgroup of people with active cancer. See tables 21 and 22 below.

Table 21 deterministic base case treatment of VTE for people with active cancer (table 145 MS page 356)

Treatment	Total costs	Total LY	Total QALYs	Inc. costs	Inc. QALYS	ICER
LMWH/ warfarin	5,522	7.491	5.817	-	-	-
Dabigatran	£4,152*	-	£5.805*	-£1370	-0.0124	Dabigatran is less expensive and less effective £110,742 (SW)

* from model as not presented in manufacturer's submission

Table 22: deterministic base case treatment and secondary prevention for people with active cancer (table 146 MS page 356)

Treatment	Total costs	Total LY	Total QALYs	Inc. costs	Inc. QALYS	ICER
LMWH	11,161	16.194	12.451	-	-	-
Dabigatran	£7,821*	-	£12.471	-3,342	0.0226	LMWH is dominated bv dabigatran

* from model as not presented in manufacturer's submission

ERG comments

5.25 The ERG commented that in the acute treatment deterministic base case analysis, costs varied between all three treatment strategies by £40 and QALYs varied by approximately 0.02 per patient across treatment arms. In particular, for dabigatran compared with rivaroxaban, the estimated total QALYs differed by 0.0003. Therefore, whilst dabigatran was found to dominate rivaroxaban in the manufacturer's base case for acute treatment, the average total costs and QALYs estimated by the manufacturer imply that these treatments result in very similar costs and consequences.

5.26 The manufacturer did not present a fully incremental analysis for the treatment and secondary prevention base case The ERG stated that the key disadvantage of using alternative model parameters for dabigatran is that the results arising from each analysis cannot be compared because the costs and QALYs associated with dabigatran will differ in each case. The ERG stated that although dabigatran dominated rivaroxaban in the

acute treatment and secondary prevention base case there was a QALY difference of less than 0.002 per patient over their life-time and a cost difference of £67 implying that these treatments are similar.

5.27 The ERG stated that it had identified 16 potential errors in the manufacturer's model (see page 265 ERG report for a description of these errors and table 133 and 134 on page 270 for how these corrections affected the manufacturer's base case analyses). It presented the manufacturer's base case analysis with these errors corrected and stated that there was a modest difference in the resulting ICERs. For the acute treatment base casethis resulted in an ICER of £1,813 per QALY gained for dabigatran compared with warfarin; an ICER of £770 per QALY gained for dabigatran compared with rivaroxaban (south-west quadrant, dabigatran less costly and less effective) and an ICER of £88,793 for dabigatran compared with LMWH in the subgroup of people with cancer (south-west quadrant, dabigatran less costly and less effective). For the acute treatment and secondary prevention base case the ICER for dabigatran compared with warfarin was £9,398 per QALY gained; the ICER for dabigatran compared with rivaroxaban was £898 per QALY gained (south-west quadrant, dabigatran less costly and less effective); dabigatran was dominant when compared with LMWH in the subgroup of people with active cancer

Manufacturer's scenarios

5.28 In response to a request from the ERG the manufacturer presented the results of its univariate sensitivity analyses in tables 1-3 on pages 49-55 of the manufacturer's response to clarification. However it did not state how much it varied each parameter by in each of the analyses. Furthermore, the manufacturer did not provide sufficient information to determine the direction of change in costs and QALYs. For example by only providing an ICER it was not possible to determine for a positive ICER whether dabigatran was more costly and more effective than its comparator or less costly and less effective than its comparator.

5.29 The manufacturer's scenario analyses are described in tables 23 and 24 below. The adjustment for time in therapeutic range was based on analysis of the relationship between time spent in an INR range of 2.0 to 3.0 and the incidence of recurrent VTE and bleeding using the General Practice Research Database Hospital Episode data. A 1% decrease in time in the international normalised ratio range was associated with an increase in the risk of recurrent VTE (HR 1.011 95% CI 1.003, to 1.019) and a marginal increase in the risk of bleeding (HR 1.016, 95% CI 0.999 to 1.033).

Table 23: Manufacturer's scenario analyses treatment phase only (combination of tables 123 page 332 and table 148 page 358 manufacturer's submission)

Mfr. #	Base case assumption	scenario	ICER DBG vs. WFN	ICER DBG vs. RIV
	Base case		£862	DBG dominant
1	No adjustment for time in therapeutic range	Adjustment made for TTR	£778	DBG dominant
2	People in rivaroxaban arm do not receive LMWH	People in rivaroxaban arm receive LMWH for 1.1 days if have DVT and 1.4 days if have PE as observed in EINSTEIN DVT and PE trials	n/a	DBG dominant
3	Utility decrement of 0.012 applied while taking warfarin	No utility decrement applied while taking warfarin	£1,217	n/a
4	Costs and utility decrement of dyspepsia not included	Costs and utility of dyspepsia included	£911	n/a
5	Time horizon lifetime (60 years)	Time horizon 6 months	£5,317	£46,274 (Δcost £15; Δ QALY 0.0003)
6	Time horizon lifetime (60 years)	Time horizon 1 year	£4,963	£44,142 (Δcost £15; Δ QALY 0.003)
8	Included bleeds occurring whilst on LMWH in dabigatran and warfarin arms	Only counted bleeds occurring while on dabigatran or warfarin after stopped LMWH	£1,435	DBG less expensive and less effective
9	Costs and utility decrement of myocardial infarction and unstable angina not included	Costs and utility decrement of myocardial infarction and unstable angina included	£1,390	DBG dominant
	Data for rivaroxaban came from pooled results of people treated for 3,6 and 12 months	Data for rivaroxaban from 6 month treatment duration only	n/a	DBG dominant

DBG: dabigatran; WFN warfarin; RIV: rivaroxaban

Table 24: Manufacturer's scenario analyses treatment and secondary prevention (combination of tables 123 page 332 and table 149 page 361 manufacturer's submission)

Mfr #	Base case assumption	scenario	ICER DBG vs. WFN	ICER DBG vs. RIV
	Base case		£8,319	DBG dominant
1	No adjustment for time in therapeutic range	Adjustment made for TTR	£8,160	DBG dominant
2	People in rivaroxaban arm do not receive LMWH	People in rivaroxaban arm receive LMWH for 1.1 days if have DVT and 1.4 days if have PE as observed in EINSTEIN DVT and PE trials	n/a	DBG dominant
3	Utility decrement of 0.012 applied while taking warfarin	No utility decrement applied while taking warfarin	£14,947	n/a
4	Costs and utility decrement of dyspepsia not included	Costs and utility decrement of dyspepsia included	£8,556	n/a
7	Time horizon lifetime (60 years)	Time horizon 1 year	£12,905	DBG dominant
8	Included bleeds occurring whilst on LMWH in dabigatran and warfarin arms	Only counted bleeds occurring while on dabigatran or warfarin after stopped LMWH	£8,350	DBG dominant
9	Costs and utility decrement of myocardial infarction and unstable angina not included	Costs and utility decrement of myocardial infarction and unstable angina included	£9,425	DBG dominant
11	Data for rivaroxaban came from pooled results of people treated for 3,6 and 12 months	Data for rivaroxaban from 6 month treatment duration only	n/a	DBG dominant
10	Unexplained deaths from trial not included in model	Unexplained deaths included in model	£7,427	n/a

DBG: dabigatran; WFN warfarin; RIV: rivaroxaban

ERG exploratory analyses

5.30 The ERG carried out 42 scenario analyses. These are described on pages 267 to 269 of the ERG report. The impact of these scenarios on the manufacturer's deterministic base case results for acute treatment are presented in table 135 (ERG report page 272-274) and the impact of these scenarios on the manufacturer's deterministic base case results for acute treatment and secondary prevention are presented in table 136 (ERG report pages 276-278).

5.31 To derive its exploratory base cases the ERG combined 16 of its scenarios (with the exception of 4 for the acute treatment exploratory base case as these were only relevant to the secondary prevention treatment phase). Please see table 25 below for a description of these scenarios.

Table 25: ERG scenarios included in its exploratory base case

	Acute treatment		Acute treatment and secondary prevention	
Dabigatran vs.	warfarin	rivaroxaban	warfarin	rivaroxaban
Base case ICER (deterministic)	£862	Dabigatran dominant	£8,319	Dabigatran dominant
B6 (50% MBEs return to treatment rather than 0%)	£861	Dabigatran dominant	£8,389	Dabigatran dominant
B8 (extending secondary prevention to lifelong from 6-18 months)	NA	NA	£6,868	£157
B9 (50 year time horizon rather than 60 years)	£862	Dabigatran dominant	£8,319	Dabigatran dominant
B10 (ERG NMA results for VTE)	£913	Dabigatran dominant	£7,800	Dabigatran dominant
B11 (consistent proportion of VTE event type across treatments)	£1,032	£21,055	£9,293	Dabigatran dominant
B13 (ERG NMA results for bleeding)	£646	Dabigatran dominant	£9,281	Dabigatran dominant
B14 (consistent proportion of bleeding event type across treatments)	£2,244	Dabigatran dominant	£11,394	Dabigatran dominant
B16 (rate of death from ICH set at 39.5%)	£404	Dabigatran dominant	£6,381	Dabigatran dominant
B17 (ERG probability of death and change in model cohort age to 65 years)	£1,256	Dabigatran dominant	£9,405	Dabigatran dominant
B20 (disutility associated with PE set to 0.265)	£862	Dabigatran dominant	£8,320	Dabigatran dominant
B21 (disutility associated with DVT and PE applied for 30 days)	£862	Dabigatran dominant	£8,309	Dabigatran dominant
B34 (initial anticoagulation appointment for warfarin removed)	£3,345	Dabigatran dominant	£9,395	Dabigatran dominant
B35 (warfarin monitoring appointments in the secondary prevention period reduced to once every three months from once a month)	NA	NA	£12,859	Dabigatran dominant
B37 (non-consultant led follow-up visits)	£6,212	Dabigatran dominant	£14,867	Dabigatran dominant
B38 (cost of severe stroke £14,777)	£642	Dabigatran dominant	£8,126	Dabigatran dominant
B42 (secondary prevention discontinuation rates)	NA	NA	NA	Dabigatran dominant
Combined (ERG exploratory base case)	£18,240	Dabigatran dominant	£35,768	Rivaroxaban extendedly dominated by dabigatran

5.32 In the ERG's exploratory base case for acute treatment, dabigatran was associated with an incremental cost of £223 compared with warfarin and 0.012 more QALYs (ICER £18,240 per QALY gained). Dabigatran dominated rivaroxaban (it cost £3 less per patient for an additional 0.0018 QALYs). In the ERG's exploratory base case for acute treatment and secondary prevention dabigatran was associated with an additional cost of £3,331 per patient and 0.093 additional QALYs compared with warfarin (ICER £35,768 per QALY gained). Rivaroxaban was extendedly dominated by dabigatran (compared with warfarin, rivaroxaban had incremental costs of £2,710 and incremental QALYs of 0.020; compared with rivaroxaban, dabigatran had incremental costs of £620 and 0.073 incremental QALYs). The total and incremental costs and QALYs for each scenario incorporated in the ERG's exploratory base cases are presented in tables 139-142 pages 281-288.

5.33 The ERG commented that for its exploratory acute treatment base case analysis the key driver increasing the ICER for dabigatran compared with warfarin relative to the manufacturer's base case was the reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led. The cost of a warfarin monitoring appointment was also a key driver in the exploratory base case for acute treatment and secondary prevention, as was the assumed frequency of warfarin monitoring in the secondary prevention period (3 monthly rather than once monthly). The ERG commented that a scenario analysis carried out by the manufacturer in which there was no utility decrement associated with warfarin showed that warfarin disutility was a key driver in the manufacturer's model. The ERG noted that if, in addition to the assumptions in its exploratory base case, it also assumed no disutility with warfarin in the secondary prevention period, the ICER for dabigatran compared with warfarin would be £90,000 per QALY gained. This would have a particularly large effect on the ICER because the ERG's model incorporating its preferred scenarios is increasingly sensitive to changes in QALYs.

5.34 Although the ERG carried out sensitivity analyses for the population with active cancer it did not present an exploratory base case analysis for this subgroup. This was because it had concerns over the reliability of the data and therefore the applicability of the findings for this group. In particular the ERG considered it unclear whether the population in RE-COVER trials with active cancer reflected the populations with cancer in clinical practice and because there were no data on bleeding events in the population with cancer.

6 Equalities issues

6.1 One professional group noted that the lack of need for monitoring may benefit patients with limited mobility who no longer have to attend hospital/GP clinics. This issue was also raised during consultation on the scope for this appraisal, but was not considered to be an equalities issue. The manufacturer and the ERG did not raise any equalities issues.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500169948.pdf