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Single Technology Appraisal (STA)

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID483]

Dear [redacted]

The Evidence Review Group, **BMJ Group**, and the technical team at NICE have now had an opportunity to take a look at the submission received on the **29th May 2014** by **Boehringer Ingelheim**. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

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

We request you to provide a written response to this letter to the Institute by **5pm** on **4th July 2014**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

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

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

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

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

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data (A1-23)

Section B: Clarification on cost-effectiveness data (B1-12)

Section C: Textual clarifications and additional points (C1-7)

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Section A: Clarification on effectiveness data

A1. Priority Question: Please clarify how dabigatran will be used in clinical practice, including:

- Whether there will be any overlap with LMWH treatment;

For the treatment of patients with DVT or PE, there will not be an overlap of dabigatran with LMWH treatment in clinical practice. The start of dabigatran treatment is following the cessation of the LMWH therapy. The Summary of Product Characteristics for dabigatran provides the following relevant guidance to healthcare professionals:

4.2 Posology and method of administration
The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days.

Switching (SPAF, DVT/PE)

Parenteral anticoagulants to Pradaxa
Discontinue the parenteral anticoagulant and start dabigatran etexilate 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)).

- The expected duration of secondary prevention after acute treatment for people presenting with a) DVT and b) PE, and how this is determined. If a range of expected treatment durations exist, please describe these and confirm the typical duration;

According to recommendations from the British Committee for Standards in Haematology, at least 3 months of anticoagulant treatment is required to prevent extension of thrombus and recurrence in patients with proximal DVT (i.e. involvement of popliteal vein or above) and/or PE:

- Patients with proximal DVT or PE should be treated for at least 3 months (1A)
- If a diagnostic strategy that identifies isolated calf vein DVT is employed, treatment of such clots can be restricted to 6 weeks (1A)
- Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose LMWH rather than warfarin (1A).
- The BCSH recommendations on long-term VKA therapy are as follows:
- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by surgery (1B)

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- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by non-surgical transient trigger factors (1B)

- Patients with unprovoked proximal DVT or PE should be considered for long-term anticoagulation, taking into account information that may help predict risk of recurrence and risk of bleeding in the individual patient (2B)

- Long-term anticoagulant therapy is not recommended in patients with VTE confined to the calf (i.e. not extending into the popliteal vein) (1A).

Data from the VERITY registry conducted in the United Kingdom shows that the intended duration of warfarin treatment for treatment of DVT/PE was up to 6 months in 80% of patients, whilst 20% of patients were intended to receive warfarin for more than 6 months.

The decision to continue long-term anticoagulation for secondary prevention of recurrent DVT and PE is a clinical decision taking into account the reduction in risk of venous thromboembolism versus the risk of bleeding. In the dabigatran clinical trial programme, two cohorts of patients were enrolled in trials of 'secondary prevention'. In the RE-SONATE trial, patients were considered to be at "equipoise" with regard to the benefit/risk balance of continued anticoagulation – these patients were randomised to six months treatment with either dabigatran 150mg bid or placebo. In the RE-MEDY trial, patients considered to be at "high-risk" for recurrent VTE, for whom continued anticoagulation was clinically indicated, were randomised to 18 months treatment with either dabigatran 150mg bid or warfarin (INR 2-3).

- whether dabigatran would be prescribed for acute treatment at recurrence of DVT or PE

Anticoagulation remains the mainstay of treatment for venous thromboembolism. Existing treatment guidelines for the treatment of venous thromboembolism do not specify that the choice of treatment for index and recurrent VTE events are expected to be different. The use of dabigatran for treatment of recurrent VTE is expected to be a clinical decision by the treating physician. In the RE-COVER trials, approximately one-third of patients enrolled in the trials had a history of previous VTE.

A2. Please provide an updated version of Table 19 in the submission to include the rationale for deviating from the NICE final scope in relation to:

- Comparison with fondaparinux;

As stated in Section 2.6 of the manufacturer's submission, fondaparinux is an alternative to LMWH or UFH for the initial treatment of DVT. However, it is not approved for long-term prophylaxis of VTE

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and therefore is not considered a relevant comparator for dabigatran for the treatment and long-term secondary prevention of VTE.

For analyses of treatment of DVT and PE, fondaparinux is included as an option for initial parenteral treatment prior to adjusted-dose warfarin treatment. In the RE-COVER trial, 2.8% of patients received initial fondaparinux prior to adjusted-dose warfarin. This is applied in the base case analysis of the economic model (please see cell **'Input data!F1283'** in the economic model). The data from the RE-COVER trial Clinical Study Report is provided below:

Table 11.2.7.3: 1 Parenteral therapy administered for the treatment of the index event /TS

	Dabigatran (n/%)	Warfarin (n/%)	Total (n/%)
Treated patients	1273 (100.0)	1266 (100.0)	2539 (100.0)
Patients with any parenteral therapy	1272 (99.9)	1265 (99.9)	2537 (99.9)
LMWH	1138 (89.4)	1148 (90.7)	2286 (90.0)
UH	144 (11.3)	164 (13.0)	308 (12.1)
Fondaparinux	50 (3.9)	36 (2.8)	86 (3.4)
Patients with more than 1 parenteral therapy	120 (9.4)	133 (10.5)	253 (10.0)
Patients without parenteral therapy	1 (0.1)	1 (0.1)	2 (0.1)

Abbreviations: TS Treated Set; LMWH Low-Molecular Weight Heparin; UH Unfractionated Heparin

- Comparison with rivaroxaban in relation to the subgroup of patients with active cancer.

In a previous NICE Technology Appraisal of rivaroxaban for the treatment and secondary prevention of recurrent VTE (TA 261), the Appraisal Committee made the following conclusion in relation to the use of rivaroxaban in the subgroup of patients with active cancer:

"Given the lack of clinical evidence for this group of patients, the Committee was unable to make specific recommendations on the use of rivaroxaban in people with cancer but recognised the disadvantages of the currently available treatment, which involves regular injections, and which some patients might choose to decline."

Given this opinion from the Appraisal Committee, rivaroxaban was not considered to be a relevant treatment option in this subgroup and was therefore not included as a comparator to dabigatran for this subgroup in the submission.

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Furthermore, LMWH monotherapy is considered to be standard treatment for DVT and PE in this subgroup. The British Committee for Standards in Haematology makes the following recommendation:

- Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose LMWH rather than warfarin (1A).

It was therefore considered most appropriate to only include a comparison of dabigatran with LMWH monotherapy in the subgroup of patients with cancer.

Dabigatran trials

A3. Priority Question: Please provide details of the percentage time in therapeutic range (TTR) by warfarin treatment group for the individual geographic regions evaluated for the full randomised (ITT), full analysis and per protocol populations of RE-COVER I, RE-COVER II, and REMEDY.

Please see Appendix A3 Clarification Letter document as attached. As stated in a telephone conversation with NICE on 10/07/14, BI does not have the ITT analyses requested in A3 to A5. However, we do have the FDA-requested ITT analysis for efficacy. This has also been appended for your information. In order to generate the ITT results requested for A3 to A5, our trial statisticians would be required to analyse patient level data. This could take months. The data we have provided should be sufficient and robust enough to answer the proceeding questions.

A4. Priority Question: Please complete the following table for RE-COVER I, RE-COVER II, REMEDY, and RESONATE for the listed subgroups in the full randomised, full analysis and per protocol populations (that is, 16 tables):

a. Western Europe region;

b. INR control as measured by percentage time in therapeutic range (TTR) for centres in the warfarin group with TTR <60%;

c. INR control as measured by percentage time in therapeutic range (TTR) for centres in the warfarin group with TTR ≥60%.

Please see Appendix A4 Clarification Letter document as attached.

A5. Priority Question: Please complete the table below to provide details on the number of events (n) and number of people analysed (N) for the outcomes of headache and gastrointestinal bleeding for the full randomised, full analysis and per protocol populations of RE-COVER I, RE-COVER II, REMEDY, and RESONATE (3 tables). Please also provide a reference to where this data is available in the clinical study reports for these trials.

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Please see Appendix A5a and A5b Clarification Letter documents as attached. Gastrointestinal (GI) bleeding events are defined as any bleeding event with a GI bleeding site, including major bleeding events (MBE) clinically relevant non-major bleeding events (CRNMBE) and minor GI bleeds. The results presented in Appendix A5a. When only MBE are counted for GI bleeds, dabigatran is associated with a lower number of GI bleeds, as shown in Appendix A5b.

A6. Please provide the definition of active cancer used in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately).

The definitions of active cancer used in RE-COVER, RE-COVER II and REMEDY are shown in the table below. In RESONATE, patients with active cancer were excluded and no specific definition of active cancer was provided in the clinical trial report.

Definitions of active cancer used in RE-COVER, RE-COVER II, RESONATE and REMEDY

Trial	Definition of Active Cancer Used	Source
RE-COVER	Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment; any treatment for cancer within 5 years before enrolment; or recurrent or metastatic cancer.	P68, section 9.4.1.2 of the RE-COVER CTR
RE-COVER II	Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment; any treatment for cancer within 5 years before enrolment; or recurrent or metastatic cancer.	P57, section 9.4.1.2 of the RE-COVER II CTR
RESONATE	Patients with active cancer were excluded. No definition specified in the CTR	
REMEDY	Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before the enrolment; any treatment for cancer within 5 years; or recurrent or metastatic cancer.	P64, section 9.4.1.2 of the REMEDY CTR

A7. Please complete the table below to provide a breakdown of the patients with cancer at baseline in RE-COVER I, RE-COVER II, and REMEDY for the randomised population:

	Dabigatran		**Warfarin**	
	n	**N**	**N**	**N**
Cancer under active treatment or with ≤1year remission				
RE-COVER I				
RE-COVER II				
REMEDY				

It is unfortunately not possible to provide this analysis as the data captured in the CRF of the clinical trials did not include the date of the “active cancer” event.

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A8. Please provide a definition for "equipoise" as used in RESONATE and details of inclusion/exclusion criteria specifically pertaining to "equipoise". Please clarify whether the reasons for inclusion in the trial were similar across treatment groups.

Equipoise is a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Equipoise as used in RESONATE refers to the fact that there is uncertainty with respect to the need for continued anticoagulation, indicating that the risk/benefit of extended treatment is not clear.

In light of the definition above, the inclusion criteria were chosen to admit a broad sample of the target population into the study. On the other hand, the choice of exclusion criteria aimed to limit the risk to patients of participation in the study. Therefore, the specific inclusion/exclusion criteria which specifically pertain to equipoise are the following two exclusions:

- Indication for Vitamin K antagonist other than DVT and/or PE.
- Patients in whom anticoagulation treatment for their index PE or DVT should have been continued.

In addition, the reasons for inclusion in the trial were similar across treatment groups.

A9. Please provide a definition for "high risk" as used in REMEDY and details of inclusion/exclusion criteria specifically pertaining to "high risk". Please clarify whether the reasons for inclusion in the trial were similar across treatment groups.

A "high risk" patient group was identified as patients who are at an increased risk of recurrent venous thromboembolism on the basis of the site investigator's assessment. In REMEDY, the list of risk factors included:

- More than 1 previous VTE (yes, no)
- Symptomatic PE as primary VTE event (yes, no)
- Time from the qualifying VTE to randomisation (<3, 3 to <6, 6 to <9, 9 to <12, ≥12 months)
- Active cancer (yes, no)
- History of non−haemorrhagic stroke (yes, no)
- History of coronary artery disease (yes, no)
- Additional medical history/baseline conditions as recorded on the CRF

The main inclusion criterion specifically pertains to this high risk population (i.e. patients at an increased risk of recurrent VTE), which is stated as the following:

- Objectively confirmed symptomatic uni- or bilateral DVT of the leg involving proximal veins or PE, treated with an approved anticoagulant therapy or with study drug taken during participation in the RE-COVER and RE-COVER II trials for 3 to 12 months at the time of screening, in patients considered at increased risk of recurrent VTE (proximal veins are: trifurcation area, popliteal, superficial femoral, deep femoral, common femoral and iliac vein).

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All reasons for inclusion in the trial were similar across treatment groups.

A10. Please clarify how many UK centres participated in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) and how many patients from the UK were randomised in each trial.

Details regarding the number of UK centres and number of patients from the UK randomised into RE-COVER, RE-COVER II, RESONATE and REMEDY are illustrated in the table below. The United Kingdom did not participate in the RESONATE trial and therefore, there were no centres or patients from the UK included in this trial.

Number of UK centres and number of patients from the UK participating in RE-COVER, RE-COVER II, RESONATE and REMEDY

Trial	Number of sites initiated	Number of sites recruited	Dabigatran n (%)	Warfarin n (%)	Total n (%)
Treated			1,273 (100.0)	1,266 (100.0)	2,539 (100.0)
RE-COVER	10	7	49 (3.8)	48 (3.8)	97 (3.8)
RE-COVER II	6	5	32 (2.5)	35 (2.7)	67 (2.6)
RESONATE	-	-	-	-	-
REMEDY	8	5	23 (1.8)	17 (1.3)	40 (1.6)

A11. Please provide details of the randomised population (ITT) treatment discontinuation rates by treatment group for RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) for: 1) the whole trial population and 2) centre's with TTR ≥60%. Please provide reasons for treatment discontinuation, with total number of patients discontinuing in each group for that reason. If this information is available in the CSRs, please also provide the page and table numbers.

Table 1.1.1.2, Table 1.1.1.3, Table 1.1.1.4 and Table 1.1.1.5 show the discontinuation rates by treatment group for RE-COVER, RE-COVER II, REMEDY and RESONATE, respectively, for the whole trial population. In addition, Table 1.4.1, Table 1.4.2 and table 1.4.3 show the patient disposition at the end of treatment in the centre with TTR ≥60% for RE-COVER, RE-COVER II and REMEDY, respectively.

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Table 1.1.1.2 Patient disposition at the end of treatment for study 1160.53 (RE-COVER) - All patients

	DE N (%)	W N (%)	Total N (%)
Enrolled			2630
Not entered/randomized			66
Entered/randomized	1281	1283	2564
Not treated	7	18	25
Treated	1274 (100.0)	1265 (100.0)	2539 (100.0)
Not prematurely discontinued from study medication	1069 (83.9)	1083 (85.6)	2152 (84.8)
Prematurely discontinued from study medication	205 (16.1)	182 (14.4)	387 (15.2)
Adverse event	127 (10.0)	101 (8.0)	228 (9.0)
AE: worsening of disease under study*	35 (2.7)	25 (2.0)	60 (2.4)
AE: worsening of other pre-existing disease	15 (1.2)	12 (0.9)	27 (1.1)
AE: other (including bleeding events)	77 (6.0)	64 (5.1)	141 (5.6)
Bleeding events^	15 (1.2)	21 (1.7)	36 (1.4)
Other than bleeding event$	62 (4.9)	43 (3.4)	105 (4.1)
Non compliant with protocol	21 (1.6)	35 (2.8)	56 (2.2)
Lost to follow-up	9 (0.7)	6 (0.5)	15 (0.6)
Patient refused to continue medication§	39 (3.1)	36 (2.8)	75 (3.0)
Other	9 (0.7)	4 (0.3)	13 (0.5)

*: i.e. symptomatic DVT or PE based on investigator's assessment

^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication

$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding

§: Patients could decide to continue study without taking study medication or to withdraw from study permanently

All information is based on investigator assessment in eCRF pages.

Table 1.1.1.3 Patient disposition at the end of treatment for study 1160.46 (RE-COVER II) - All patients

	DE N (%)	W N (%)	Total N (%)
Enrolled			2701
Not entered/randomized			112
Entered/randomized	1293	1296	2589
Not treated	14	7	21
Treated	1279 (100.0)	1289 (100.0)	2568 (100.0)
Not prematurely discontinued from study medication	1092 (85.4)	1106 (85.8)	2198 (85.6)
Prematurely discontinued from study medication	187 (14.6)	183 (14.2)	370 (14.4)
Adverse event	102 (8.0)	101 (7.8)	203 (7.9)
AE: worsening of disease under study*	28 (2.2)	23 (1.8)	51 (2.0)
AE: worsening of other pre-existing disease	22 (1.7)	15 (1.2)	37 (1.4)
AE: other (including bleeding events)	52 (4.1)	63 (4.9)	115 (4.5)
Bleeding events^	10 (0.8)	19 (1.5)	29 (1.1)
Other than bleeding event$	42 (3.3)	44 (3.4)	86 (3.3)
Non compliant with protocol	39 (3.0)	37 (2.9)	76 (3.0)
Lost to follow-up	6 (0.5)	3 (0.2)	9 (0.4)
Patient refused to continue medication§	33 (2.6)	38 (2.9)	71 (2.8)
Other	7 (0.5)	4 (0.3)	11 (0.4)

*: i.e. symptomatic DVT or PE based on investigator's assessment

^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication

$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding

§: Patients could decide to continue study without taking study medication or to withdraw from study permanently

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All information is based on investigator assessment in eCRF pages.

Table 1.1.1.4 Patient disposition at the end of treatment for study 1160.47 (RE-MEDY) - All patients

	DE N (%)	W N (%)	Total N (%)
Enrolled			2918
Not entered/randomized			52
Entered/randomized	1435	1431	2866
Not treated	5	5	10
Treated	1430 (100.0)	1426 (100.0)	2856 (100.0)
Not prematurely discontinued from study medication	1154 (80.7)	1145 (80.3)	2299 (80.5)
Prematurely discontinued from study medication	276 (19.3)	281 (19.7)	557 (19.5)
Adverse event	147 (10.3)	129 (9.0)	276 (9.7)
AE: worsening of disease under study*	19 (1.3)	19 (1.3)	38 (1.3)
AE: worsening of other pre-existing disease	18 (1.3)	21 (1.5)	39 (1.4)
AE: other (including bleeding events)	110 (7.7)	89 (6.2)	199 (7.0)
Bleeding events^	20 (1.4)	34 (2.4)	54 (1.9)
Other than bleeding event$	90 (6.3)	55 (3.9)	145 (5.1)
Non compliant with protocol	23 (1.6)	34 (2.4)	57 (2.0)
Lost to follow-up	2 (0.1)	6 (0.4)	8 (0.3)
Patient refused to continue medication§	64 (4.5)	58 (4.1)	122 (4.3)
Other	40 (2.8)	54 (3.8)	94 (3.3)

*: i.e. symptomatic DVT or PE based on investigator's assessment

^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication

$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding

§: Patients could decide to continue study without taking study medication or to withdraw from study permanently

All information is based on investigator assessment in eCRF pages.

Table 1.1.1.5 Patient disposition at the end of treatment for study 1160.63 (RE-SONATE) - All patients

	DE N (%)	P N (%)	Total N (%)
Enrolled			1366
Not entered/randomized			13
Entered/randomized	685	668	1353
Not treated	4	6	10
Treated	681 (100.0)	662 (100.0)	1343 (100.0)
Not prematurely discontinued from study medication	610 (89.6)	563 (85.0)	1173 (87.3)
Prematurely discontinued from study medication	71 (10.4)	99 (15.0)	170 (12.7)
Adverse event	50 (7.3)	81 (12.2)	131 (9.8)
AE: worsening of disease under study*	4 (0.6)	49 (7.4)	53 (3.9)
AE: worsening of other pre-existing disease	4 (0.6)	4 (0.6)	8 (0.6)
AE: other (including bleeding events)	42 (6.2)	28 (4.2)	70 (5.2)
Bleeding events^	11 (1.6)	4 (0.6)	15 (1.1)
Other than bleeding event$	31 (4.6)	24 (3.6)	55 (4.1)
Non compliant with protocol	9 (1.3)	5 (0.8)	14 (1.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Patient refused to continue medication§	12 (1.8)	13 (2.0)	25 (1.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)

*: i.e. symptomatic DVT or PE based on investigator's assessment

^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication

$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding

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§: Patients could decide to continue study without taking study medication or to withdraw from study permanently
All information is based on investigator assessment in eCRF pages.

Table 1.4.1 Patient disposition at the end of treatment in centres with TTR >=60% for study 1160.53 (RE-COVER) - All patients

	DE N (%)	W N (%)	Total N (%)
Enrolled			1480
Not entered/randomized			26
Entered/randomized	716	738	1454
Not treated	4	11	15
Treated	712 (100.0)	727 (100.0)	1439 (100.0)
Not prematurely discontinued from study medication	612 (86.0)	646 (88.9)	1258 (87.4)
Prematurely discontinued from study medication	100 (14.0)	81 (11.1)	181 (12.6)
Adverse event	65 (9.1)	53 (7.3)	118 (8.2)
AE: worsening of disease under study*	20 (2.8)	17 (2.3)	37 (2.6)
AE: worsening of other pre-existing disease	6 (0.8)	5 (0.7)	11 (0.8)
AE: other (including bleeding events)	39 (5.5)	31 (4.3)	70 (4.9)
Bleeding events^	6 (0.8)	9 (1.2)	15 (1.0)
Other than bleeding event$	33 (4.6)	22 (3.0)	55 (3.8)
Non compliant with protocol	9 (1.3)	11 (1.5)	20 (1.4)
Lost to follow-up	1 (0.1)	1 (0.1)	2 (0.1)
Patient refused to continue medication§	19 (2.7)	15 (2.1)	34 (2.4)
Other	6 (0.8)	1 (0.1)	7 (0.5)

*: i.e. symptomatic DVT or PE based on investigator's assessment
^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication
$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding
§: Patients could decide to continue study without taking study medication or to withdraw from study permanently
All information is based on investigator assessment in eCRF pages.

Table 1.4.2 Patient disposition at the end of treatment in centres with TTR >=60% for study 1160.46 (RE-COVER II) - All patients

	DE N (%)	W N (%)	Total N (%)
Enrolled			1177
Not entered/randomized			28
Entered/randomized	571	578	1149
Not treated	8	3	11
Treated	563 (100.0)	575 (100.0)	1138 (100.0)
Not prematurely discontinued from study medication	490 (87.0)	509 (88.5)	999 (87.8)
Prematurely discontinued from study medication	73 (13.0)	66 (11.5)	139 (12.2)
Adverse event	40 (7.1)	36 (6.3)	76 (6.7)
AE: worsening of disease under study*	12 (2.1)	12 (2.1)	24 (2.1)
AE: worsening of other pre-existing disease	6 (1.1)	3 (0.5)	9 (0.8)
AE: other (including bleeding events)	22 (3.9)	21 (3.7)	43 (3.8)
Bleeding events^	4 (0.7)	7 (1.2)	11 (1.0)
Other than bleeding event$	18 (3.2)	14 (2.4)	32 (2.8)
Non compliant with protocol	15 (2.7)	18 (3.1)	33 (2.9)
Lost to follow-up	2 (0.4)	2 (0.3)	4 (0.4)
Patient refused to continue medication§	11 (2.0)	7 (1.2)	18 (1.6)
Other	5 (0.9)	3 (0.5)	8 (0.7)

*: i.e. symptomatic DVT or PE based on investigator's assessment

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^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication
$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding
§: Patients could decide to continue study without taking study medication or to withdraw from study permanently
All information is based on investigator assessment in eCRF pages.

Table 1.4.3 Patient disposition at the end of treatment in centres with TTR >=60% for study 1160.47 (RE-MEDY) - All patients

	DE N (%)	W N (%)	Total N (%)
Enrolled			1620
Not entered/randomized			22
Entered/randomized	797	801	1598
Not treated	3	1	4
Treated	794 (100.0)	800 (100.0)	1594 (100.0)
Not prematurely discontinued from study medication	642 (80.9)	654 (81.8)	1296 (81.3)
Prematurely discontinued from study medication	152 (19.1)	146 (18.3)	298 (18.7)
Adverse event	90 (11.3)	75 (9.4)	165 (10.4)
AE: worsening of disease under study*	9 (1.1)	6 (0.8)	15 (0.9)
AE: worsening of other pre-existing disease	11 (1.4)	9 (1.1)	20 (1.3)
AE: other (including bleeding events)	70 (8.8)	60 (7.5)	130 (8.2)
Bleeding events^	9 (1.1)	21 (2.6)	30 (1.9)
Other than bleeding event$	61 (7.7)	39 (4.9)	100 (6.3)
Non compliant with protocol	12 (1.5)	16 (2.0)	28 (1.8)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Patient refused to continue medication§	26 (3.3)	19 (2.4)	45 (2.8)
Other	24 (3.0)	36 (4.5)	60 (3.8)

*: i.e. symptomatic DVT or PE based on investigator's assessment
^: Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study medication
$: This line only counts patients who discontinued due to another AE but who did not discontinue due to bleeding
§: Patients could decide to continue study without taking study medication or to withdraw from study permanently
All information is based on investigator assessment in eCRF pages.

A12. Please complete the table below to provide a breakdown of the types and frequency of adverse event that led to treatment discontinuation in each of the RE-COVER I treatment groups for the ITT population. Please complete similar tables for RE-COVER II, REMEDY and RESONATE. If this information is available in the CSRs, please also provide the page and table numbers.

Please see Appendix A12 Clarification Letter document as attached.

A13. Please provide details of any protocol amendments made in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) and give the reasons for any amendments

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RE-COVER

In RE-COVER, the original trial protocol (dated 18 November 2005) was amended globally on 4 occasions, these were Protocol Amendment 1 (dated 27 March 2006), Protocol Amendment 2 (dated 11 February 2008), Protocol Amendment 3 (dated 18 July 2008), and Protocol Amendment 4 (dated 2 March 2009). The following sections summarise important changes implemented by the 4 global protocol amendments, changes to the analyses as described in the TSAP, as well as changes that were implanted after finalisation of the TSAP and unblinding of the trial.

1. Protocol Amendment 1 (dated 27 March 2006):

As per original trial protocol, INR measurements during the study were to be performed using a POC device provided by the sponsor. The POC device provide an encrypted INR; the study site personnel had to obtain an unencrypted INR value by calling into an IVRS system (true INR for patients randomised to warfarin / sham INR for patients randomised to warfarin placebo). Protocol Amendment 1 allowed alternative means of INR monitoring if use of the POC device was not feasible. In such cases, the INR could be measured in an unblended manner by authorised personnel who then forwarded the unblinded INR value to the IVRS, while strictly maintaining the blinded status of all study site personnel involved in the conduct of the study (other than those assessing INRs in an unblinded manner). Details of this alternative procedure were provided in the ISF.

It was clarified that for patients who decided to participate in the RE-MEDY trial, Visit 9 was the last visit in RE-COVER, and no Visit 10 was required in these patients. It was also clarified that for roll-over patients, participation in RE-COVER was concluded with the last intake of trial medication. For roll-over patients, Visit 9 of the RE-COVER trial could be combined with Visits 1 and 2 of the RE-MEDY trial. However, for the analyses presented in this CTR, 'end of treatment' for patients rolling over from RE-COVER to RE-MEDY was defined as the day following the last intake of warfarin; 'end of trial' was defined as last intake of warfarin plus 1 day or date of Visit 9, whichever came later. For patients rolling over to the RE-SONATE trial, end of treatment and end of trial were defined accordingly. However, roll-over patients could have received dabigatran / dabigatran placebo from a medication kit of RE-COVER during the roll-over period and later than last intake of warfarin plus 1 day.

A number of clarifications were made with regard to the documentation of blood transfusions and concomitant medications on the CRF.

It was clarified that the forms for expedited reporting of MBEs and CRBEs, LFT abnormalities, and suspected ACS events (i.e. Safety fax, Liver fax, ACS fax, respectively) were to be sent by the site to the sponsor, who had to forward the forms to the DSMB. In case of suspected ACS, the form was additionally to be forwarded to the ACS / AC.

As per the original trial protocol, the HRP had to forward its assessments of LFT increases to the sponsor; it had also to inform - in a blinded manner - the DSMB about LFT increases that were considered to be drug-related by the HRP. Similarly, the ACS/AC was to inform the sponsor about the adjudication outcomes of ACS events, and it was also to inform - in a blinded manner - the DSMB

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about cases of ACS considered to be drug-related. Protocol Amendment 1 (dated 27 March 2006) clarified that results of all central assessments by the HRP and ACS / AC were to be provided to the DSMB as soon as the adjudication results were available; the restriction on drug-related cases was removed. Also, direct communication between the HRP or ACS/AC and the DSMB was no longer to occur based on Protocol Amendment 1. Since Protocol Amendment 1 was issued before the first patient was enrolled (7 Apr 2006), the communication of adjudication results for LFT increases and ACS events followed the specifications made in this amendment.

Protocol Amendment 1 removed the rule that a time window of 2 hours was allowed for the intake of dabigatran / dabigatran placebo capsules in the morning and evening.

2. Protocol Amendment 2 (dated 11 February 2008):

The main purpose of Protocol Amendment 2 was to contraindicate the concomitant administration of quinidine; this was based on the results of the early terminated BI trial 1160.75. It was added to the exclusion criteria that patients with an anticipated need of quinidine were barred from participation in this trial. Quinidine was also added to the list of medications whose concomitant use was prohibited during the trial.

A warning was added with regard to the potential role of P-glycoprotein inhibition on dabigatran plasma levels and subsequent tolerability. Investigators were alerted to the concomitant administration of moderate to strong P-glycoprotein inhibitors due to a potential risk of higher plasma levels of dabigatran and consequent exaggerated pharmacodynamics effects of dabigatran (especially a potentially higher risk for bleeding events). Concomitant use of P-glycoprotein inhibitors was not prohibited (with the exception of quinidine). However, the investigators were advised to use P-glycoprotein inhibitors with caution or, at investigator discretion, to switch patients to a suitable alternative. If a moderate to strong Pglycoprotein inhibitor was to be concomitantly administered, it was recommended to separate the administration of dabigatran and the P-glycoprotein inhibitor by several hours. A list of Pglycoprotein inhibitors was added to the ISF.

The DSMBs of all concerned trials were alerted to this potential interaction, especially with respect to assessment of bleeds. The DSMBs were to provide independent evaluation across all phase II / III trials with dabigatran etexilate in addition to ongoing sponsor scrutiny of the safety database with regard to all ongoing and planned trials with this substance.

3. Protocol Amendment 3 (dated 18 July 2008)

Additional guidance was provided regarding the management of patients who required surgery or invasive procedures during the treatment period. Regarding the discontinuation of dabigatran before surgery it was recommended to check serum creatinine 1 to 2 weeks before surgery and to calculate the creatinine clearance using the Cockroft-Gault formula. In patients with a creatinine clearance of ≥50 mL/min to 80 mL/min, dabigatran / dabigatran placebo was to be discontinued 2 to 3 days before surgery if a high risk of bleeding was anticipated, or 24 hours before surgery, if a standard risk of bleeding was anticipated. In patients with a creatinine clearance of ≥30 mL/min to <50 mL/min, dabigatran / dabigatran placebo was to be discontinued 4 days before surgery in case of a high risk of bleeding, or at least 48 hours before surgery in case of a standard risk of bleeding; the time periods were >5 days and 2 to 5 days, respectively, in patients with a creatinine clearance of <30 mL/min. Other risk factors were to be considered as specified in the Protocol Amendment.

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It was outlined that a high risk of bleeding was associated with types of surgery such as cardiac surgery, neurosurgery, abdominal surgery, and surgery involving a major organ, but also with procedures such as spinal anaesthesia. In patients at high risk of bleeding, including patients with severe renal dysfunction (i.e. creatinine clearance <30 mL/min), the anticoagulation status was to be assessed 6 to 12 hours before surgery. A persistently prolonged thrombin clotting time that was not due to the use of heparin, fibrin / fibrinogen degradation products, or high concentrations of serum proteins (e.g. myeloma) indicated persistently elevated blood dabigatran concentrations in the patient. In this case, delaying surgery was to be considered.

If elective surgery or invasive procedure could not be delayed until after the trial period, it was recommended to stop both warfarin / warfarin placebo and dabigatran / dabigatran placebo at least 24 hours before the procedure in patients with a creatinine clearance >50 mL/min and at least 48 hours before the procedure in patients with a creatinine clearance of 30 to 50 mL/min. Vitamin K (1 mg orally or 0.5 mg intravenously) was to be administered 24 hours before the procedure, if required. A local, unblinded INR was to be obtained a few hours before the procedure. After the procedure, warfarin / warfarin placebo was to be restarted as soon as allowed for by the type of surgery. UFH or LMWH as bridging therapy were to be started in the evening of the day of the procedure, or later if the risk of bleeding was too high. INR monitoring was to be performed daily using the POC device / IVRS until an INR value in the therapeutic range, at least an INR of 2.0, had been reached. At this time point, heparin was to be discontinued, dabigatran / dabigatran placebo was to be restarted, and warfarin / warfarin placebo was to be continued.

In case of emergency surgery, study medication was to be discontinued. As per Protocol Amendment 3, it was recommended to postpone the surgery until at least 24 hours after the last oral intake of dabigatran / dabigatran placebo in patients with a creatinine clearance >50 mL/min and at least 48 hours after the last oral intake of dabigatran / dabigatran placebo in patients with a creatinine clearance of 30 to 50 mL/min. It was mentioned that dabigatran could be removed by dialysis, however, that the fraction cleared is low and the potential clinical utility is unknown. Use of fresh frozen plasma, activated prothrombin complex concentrates, or recombinant Factor VIIa was to be considered to achieve haemostasis in patients who were still anticoagulated at the time of surgery.

Clarifications were made regarding the discontinuation of study treatment for patients with severe renal dysfunction. As per original trial protocol, the creatinine clearance was to be calculated using the Cockroft-Gault formula in patients who were found to have clinically significant increases of serum creatinine. Protocol Amendment 3 clarified that for patients with a calculated creatinine clearance of >30 mL/min but <50 mL/min the creatinine clearance was to be calculated at each study visit. For patients with a calculated creatinine clearance of ≤30 mL/min, the measurement of serum creatinine had to be repeated immediately. Patients had to be withdrawn from treatment if the creatinine clearance was ≤30 mL/min, unless repeated testing demonstrated a creatinine clearance of >30 mL/min.

4. Protocol Amendment 4 (dated 2 March 2009)

Protocol Amendment 4 provided guidance on the concomitant administration of verapamil, based on the results of the BI trial 1160.74. If initiation of therapy with verapamil was considered necessary, it was recommended to administer verapamil 2 hours after administration of study drug

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for the first 2 to 3 days. Thereafter, patients could use verapamil concurrently with study drug. For patients at an increased risk of bleeding it was recommended to continue to administer verapamil 1 to 2 hours after study drug intake. Therapy with an alternative to verapamil was to be considered for patients at a high risk of bleeding or unable to comply with the recommended dosing of verapamil 1 to 2 hours after dabigatran. Patients at high risk of bleeding for whom no acceptable alternative to verapamil could be identified and patients who were assumed to be not reliably compliant with the specified dosing interval were to be removed from treatment with study drug. This amendment also provided an updated list of drugs for which no clinically relevant interaction with dabigatran has been revealed in drug-drug interaction studies.

RE-COVER II

In RE-COVER II, the original trial protocol (dated 8 October 2007) was amended globally on 6 occasions, these were Protocol Amendment 1 (dated 26 October 2007), Protocol Amendment 2 (dated 12 February 2008), Protocol Amendment 3 (dated 18 July 2008), Protocol Amendment 4 (dated 6 March 2009), Protocol Amendment 5 (dated 28 January 2010), and Protocol Amendment 6 (dated 4 February 2010). The following sections summarise important changes implemented by the global protocol amendments, changes to the analyses as described in the TSAP, as well as changes that were implanted after finalisation of the TSAP and unblinding of the trial.

1. Protocol Amendment 1 (dated 26 October 2007)

The protocol amendment clarified that the haematology and biochemistry variables needed to assess the patient's eligibility to participate in the study (serum creatinine, haemoglobin, platelet count, ALT, and AST) were to be obtained from a local laboratory. The results were to be documented on the CRF. This amendment became effective before the first patient was enrolled into the study on 17 June 2008.

2. Protocol Amendment 2 (dated 12 February 2008)

The main purpose of Protocol Amendment 2 was to contraindicate the concomitant administration of quinidine; this was based on the results of the early terminated BI trial 1160.75. It was added to the exclusion criteria that patients with an anticipated need of quinidine were barred from participation in this trial. Quinidine was also added to the list of medications whose concomitant use was prohibited during the trial.

A warning was added with regard to the potential role of P-glycoprotein inhibition on dabigatran plasma levels and subsequent tolerability. Investigators were alerted to the concomitant administration of moderate to strong P-glycoprotein inhibitors due to a potential risk of higher plasma levels of dabigatran and consequent exaggerated pharmacodynamics effects of dabigatran (especially a potentially higher risk for bleeding events). Concomitant use of P-glycoprotein inhibitors was not prohibited (with the exception of quinidine). However, the investigators were advised to use P-glycoprotein inhibitors with caution or, at investigator discretion, to switch patients to a suitable alternative. If a moderate to strong Pglycoprotein inhibitor was to be concomitantly administered, it was recommended to separate the administration of dabigatran etexilate and the P-glycoprotein inhibitor by several hours. A list of P-glycoprotein inhibitors was added to the ISF.

3. Protocol Amendment 3 (dated 18 July 2008)

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Additional guidance was provided regarding the management of patients who required surgery or invasive procedures during the treatment period. Regarding the discontinuation of dabigatran etexilate before surgery it was recommended to check serum creatinine 1 to 2 weeks before surgery and to calculate the creatinine clearance using the Cockroft-Gault formula. In patients with a creatinine clearance of ≥50 mL/min to 80 mL/min, dabigatran etexilate / dabigatran etexilate placebo was to be discontinued 2 to 3 days before surgery if a high risk of bleeding was anticipated, or 24 hours before surgery, if a standard risk of bleeding was anticipated. In patients with a creatinine clearance of ≥30 mL/min to <50 mL/min, dabigatran etexilate / dabigatran etexilate placebo was to be discontinued 4 days before surgery in case of a high risk of bleeding, or at least 48 hours before surgery in case of a standard risk of bleeding; the time periods were >5 days and 2 to 5 days, respectively, in patients with a creatinine clearance of <30 mL/min. Other risk factors were to be considered as specified in the Protocol Amendment.

It was outlined that a high risk of bleeding was associated with types of surgery such as cardiac surgery, neurosurgery, abdominal surgery, and surgery involving a major organ, but also with procedures such as spinal anaesthesia. In patients at high risk of bleeding, including patients with severe renal dysfunction (i.e. creatinine clearance <30 mL/min), the anticoagulation status was to be assessed 6 to 12 hours before surgery. A persistently prolonged thrombin clotting time that was not due to the use of heparin, fibrin / fibrinogen degradation products, or high concentrations of serum proteins (e.g. myeloma) indicated persistently elevated blood dabigatran concentrations in the patient. In this case, delaying surgery was to be considered.

If elective surgery or invasive procedure could not be delayed until after the trial period, it was recommended to stop both warfarin / warfarin placebo and dabigatran etexilate / dabigatran etexilate placebo at least 24 hours before the procedure in patients with a creatinine clearance >50 mL/min and at least 48 hours before the procedure in patients with a creatinine clearance of 30 to 50 mL/min. Vitamin K (1 mg orally or 0.5 mg intravenously) was to be administered 24 hours before the procedure, if required. A local, unblinded INR was to be obtained a few hours before the procedure. After the procedure, warfarin / warfarin placebo was to be restarted as soon as allowed for by the type of surgery. UFH or LMWH as bridging therapy were to be started in the evening of the day of the procedure, or later if the risk of bleeding was too high. INR monitoring was to be performed daily using the POC device / IVRS until an INR value in the therapeutic range, at least an INR of 2.0, had been reached. At this time point, heparin was to be discontinued, dabigatran etexilate / dabigatran etexilate placebo was to be restarted, and warfarin / warfarin placebo was to be continued.

In case of emergency surgery, study medication was to be discontinued. As per Protocol Amendment 3, it was recommended to postpone the surgery until at least 24 hours after the last oral intake of dabigatran etexilate / dabigatran etexilate placebo in patients with a creatinine clearance >50 mL/min and at least 48 hours after the last oral intake of dabigatran etexilate / dabigatran etexilate placebo in patients with a creatinine clearance of 30 to 50 mL/min. It was mentioned that dabigatran could be removed by dialysis, however, that the fraction cleared is low and the potential clinical utility is unknown. Use of fresh frozen plasma, activated prothrombin complex concentrates, or recombinant Factor VIIa was to be considered to achieve haemostasis in patients who were still anticoagulated at the time of surgery.

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Clarifications were made regarding the discontinuation of study treatment for patients with severe renal dysfunction. As per original trial protocol, the creatinine clearance was to be calculated using the Cockroft-Gault formula in patients who were found to have clinically significant increases of serum creatinine. Protocol Amendment 3 clarified that for patients with a calculated creatinine clearance of >30 mL/min but <50 mL/min the creatinine clearance was to be calculated at each study visit. For patients with a calculated creatinine clearance of ≤30 mL/min, the measurement of serum creatinine had to be repeated immediately. Patients had to be withdrawn from treatment if the creatinine clearance was ≤30 mL/min, unless repeated testing demonstrated a creatinine clearance of >30 mL/min.

4. Protocol Amendment 4 (dated 6 March 2009)

Protocol Amendment 4 provided guidance on the concomitant administration of verapamil, based on the results of the BI trial 1160.74. If initiation of therapy with verapamil was considered necessary, it was recommended to administer verapamil 2 hours after administration of study drug for the first 2 to 3 days. Thereafter, patients could use verapamil concurrently with study drug. For patients at an increased risk of bleeding it was recommended to continue to administer verapamil 1 to 2 hours after study drug intake. Therapy with an alternative to verapamil was to be considered for patients at a high risk of bleeding or unable to comply with the recommended dosing of verapamil 1 to 2 hours after dabigatran etexilate. Patients at high risk of bleeding for whom no acceptable alternative to verapamil could be identified and patients who were assumed to be not reliably compliant with the specified dosing interval were to be removed from treatment with study drug. This amendment also provided an updated list of drugs for which no clinically relevant interaction with dabigatran has been revealed in drug-drug interaction studies.

5. Protocol Amendment 5 (dated 28 January 2010)

Through Protocol Amendment 5, the systemic use of the P-gp inhibitor ketoconazole was contraindicated and updated guidance was provided regarding co-administration of the P-gp inducer rifampicin; it was based on the drug-drug interaction study 1160.101. Systemic use of ketoconazole was added to the list of concomitant therapies prohibited in this trial. Investigators were advised to avoid co-administration of rifampicin, or to use it with caution and only when no suitable alternative was available, as it may result in underexposure to dabigatran. The amendment also provided an updated list of substances tested in drug-drug interaction studies with dabigatran etexilate. Further guidance for administration of strong P-gp-inducers was provided, stating that rifampicin and other strong P-gp inhibitors, such as carbamazepine and St. John'sWort, were to be used with caution and only when no suitable alternative is available.

6. Protocol Amendment 6 (dated 4 February 2010)

Following Protocol Amendment 6, the recruitment period was extended by 5 months, thereby changing the planned end of trial date from February 2011 to July 2011. The reason for the change was a slower recruitment than expected.

REMEDY

In REMEDY, the original trial protocol (dated 20 January 2006) was amended globally on 9 occasions; these were Protocol Amendment 1 (dated 10 April 2006), Protocol Amendment 2 (15 March 2007),

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Protocol Amendment 3 (dated 21 January 2008), Protocol Amendment 4 (dated 14 February 2008), Protocol Amendment 5 (dated 23 July 2008), Protocol Amendment 6 (dated 12 December 2008), Protocol Amendment 7 (dated 3 March 2009), Protocol Amendment 8(dated 20 January 2010), and Protocol Amendment 9 (dated 26 January 2010). The following sections summarise important changes implemented by these amendments, changes to the analyses as described in the TSAP, as well as changes that were implanted after finalisation of the TSAP and unblinding of the trial.

1. Protocol Amendment 1 (dated 10 April 2006)

As per original trial protocol, INR measurements during the study were to be performed using a sponsor-supplied POC device, which provided an encrypted INR. Study site personnel had to obtain an unencrypted INR value by calling into an IVRS system (true INR for patients randomised to warfarin / sham INR for patients randomised to warfarin placebo). Protocol Amendment 1 allowed alternative means of INR monitoring if use of the POC device was not feasible. In such cases, the INR could be measured in an unblinded manner by authorised personnel who then forwarded the unblinded INR value to the IVRS, while strictly maintaining the blinded status of all study site personnel involved in the conduct of the study (other than those assessing INRs in an unblinded manner). Details of this alternative procedure were provided in the ISF.

In addition, Amendment 1 introduced several clarifications and corrections of minor errors. AEs were also to be assessed on Visit 1. The process of recording transfusion details on the CRF was clarified. It was clarified that the forms for expedited reporting of MBEs and CRBEs, LFT abnormalities, and suspected ACS events (i.e. Safety fax, Liver fax, ACS fax, respectively) were to be sent by the site to the sponsor, who had to forward the forms to the DSMB. In case of suspected ACS, the form was additionally to be forwarded to the ACS/AC. As per the original trial protocol, the HRP had to forward its assessments of LFT increases to the sponsor; it also had to inform - in a blinded manner - the DSMB about LFT increases that were considered to be drug-related by the HRP. Similarly, the ACS/AC was to inform the sponsor about the adjudication outcomes of ACS events, and it was to inform - in a blinded manner - the DSMB about cases of ACS considered to be drug-related. Amendment 1 clarified that results of all central assessments by the HRP and ACS/AC were to be provided to the DSMB as soon as the adjudication results were available; removing the restriction to drug-related cases. Also, direct communication between the HRP or ACS/AC and the DSMB was no longer to occur. Since Amendment 1 was issued before the first patient was enrolled (26 July 2006), the communication of adjudication results for LFT increases and ACS events followed the specifications made in this amendment. Amendment 1 removed the rule that a time window of 2 h was allowed for the intake of dabigatran etexilate / dabigatran etexilate placebo capsules in the morning and evening.

2. Protocol Amendment 2 (dated 15 March 2007)

The required time period of previous anticoagulant therapy prior to entry into the RE-MEDY trial was extended from 3 to 6 months to 3 to 12 months. This change follows the guidelines of the 7th ACCP Consensus Conference on Antithrombotic Therapy, which state that for patients at highest risk of recurrent VTE, a minimum of 6 to 12 months therapy is recommended. Based on reported rates of VTE recurrence in patients on treatment for varying durations, it was not expected that the recurrence rate would be substantially different in patients entered into the study after 12 months of prior therapy vs. 6 months of prior therapy.

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Secondly, the investigator was given the option of using bridging therapy with LMWH for patients who had just completed participation in RE-COVER or RE-COVER II and were beginning participation in RE-MEDY. The rationale for this change was that bridging therapy could have been desirable for some patients entering RE-MEDY from RE-COVER or RECOVER II, because of the potential switch from dabigatran etexilate therapy in RE-COVER or RE-COVER II to warfarin therapy in RE-MEDY. It was assumed to take several days for warfarin to attain a therapeutic effect in these patients. It was thought that for many patients the risk of recurrent VTE after having received 6 months of treatment was low enough so that bridging therapy was not needed. Nonetheless, the option to include bridging therapy was provided to allow safe participation of even the highest-risk patients in RE-MEDY. Since both of these trials were double-blind, the investigator was not to know which patients were transitioning from dabigatran etexilate to warfarin. However, since about ¼ of all patients rolling over between the 2 trials were making this transition, the investigator was cautioned that this was a possibility for any patient.

3. Protocol Amendment 3 (dated 21 January 2008)

Following Protocol Amendment 3, the recruitment period was extended by 7 months, thereby changing the planned end of trial date from December 2009 to July 2010. The reason for this was that recruitment was slower than expected.

The schedule of Liver Function Test (LFT) Monitoring was changed, with Mandatory Visits 5, 7 and 8 being replaced by mandatory phone calls. The changes were made following the DSMB's and Steering Committee's recommendations. The DSMB stated that after inclusion of more than 1200 patients in RE-COVER and more than 600 patients in RE-MEDY, no concerns had been raised regarding elevations of Liver FTs. Per protocol, testing was necessary in monthly intervals during the first year in RE-MEDY, and the DSMB recommended to instead test only after 1, 3, 6, 9, 12, 15 and 18 months. The Steering Committee recommended that Visits 5, 7, and 8 be replaced by phone call to check whether symptoms of new or recurrent VTE or bleeding events were present. A visit with physical examination and blood drawn were to be performed only every 3 months during the whole study to conform to standard medical practices.

4. Protocol Amendment 4 (dated 14 February 2008)

The main purpose of Protocol Amendment 4 was to contraindicate the concomitant administration of quinidine; this was based on the results of the prematurely terminated BI trial 1160.75. Anticipated need of quinidine treatment was introduced as an exclusion criterion for this trial, and quinidine was added to the list of medications whose concomitant use was prohibited during the trial. A warning was added regarding the potential role of P-glycoprotein (P-gp) inhibition on dabigatran etexilate plasma levels and subsequent tolerability. Investigators were alerted about the concomitant administration of moderate to strong P-gp inhibitors given the potential risk of higher dabigatran etexilate plasma levels and thus exaggerated pharmacodynamic dabigatran etexilate effects (especially a potentially higher risk of bleeding events). Concomitant use of P-gp inhibitors was not prohibited (with the exception of quinidine), but investigators were advised to use P-glycoprotein inhibitors cautiously or, at their discretion, to use a suitable alternative treatment. If a moderate to strong P-gp inhibitor was to be concomitantly administered, it was recommended to separate the administration of dabigatran etexilate and the P-gp inhibitor by several hours. A list of P-gp inhibitors were added to the ISF.

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The DSMBs of all concerned trials were alerted to this potential interaction, especially with respect to assessment of bleeds. The DSMBs were to provide independent evaluation across all phase II / III trials with dabigatran etexilate in addition to ongoing sponsor scrutiny of the safety database with regard to all ongoing and planned trials with this substance.

5. Protocol Amendment 5 (dated 23 July 2008)

Additional guidance was provided regarding the management of patients who required surgery or invasive procedures during the treatment period. Regarding the discontinuation of dabigatran etexilate before surgery it was recommended to check serum creatinine 1 to 2 weeks before surgery and to calculate the creatinine clearance using the Cockroft-Gault formula. In patients with a creatinine clearance of ≥50 mL/min to 80 mL/min, dabigatran etexilate / dabigatran etexilate placebo was to be discontinued 2 to 3 days before surgery in case of a high risk of bleeding or 24 h before surgery in case of a standard risk of bleeding. In patients with a creatinine clearance of ≥30 mL/min but <50 mL/min, dabigatran etexilate / dabigatran etexilate placebo was to be discontinued 4 days before surgery in case of a high risk of bleeding, or at least 48 h before surgery in case of a standard risk of bleeding; the time periods were >5 days and 2 to 5 days, respectively, in patients with a creatinine clearance of <30 mL/min. Other risk factors were to be considered as specified in the Protocol Amendment.

It was outlined that a high risk of bleeding was associated with types of surgery such as cardiac surgery, neurosurgery, abdominal surgery, and surgery involving a major organ, but also with procedures such as spinal anaesthesia. In patients at high risk of bleeding, including patients with severe renal dysfunction (i.e. creatinine clearance <30 mL/min), the anticoagulation status was to be assessed 6 to 12 h before surgery. A persistently prolonged thrombin clotting time that was not due to the use of heparin, fibrin / fibrinogen degradation products, or high concentrations of serum proteins (e.g. myeloma) indicated persistently elevated blood dabigatran etexilate concentrations in the patient. In this case, delaying surgery was to be considered.

If elective surgery or invasive procedure could not be delayed until after the trial period, it was recommended to stop both warfarin / warfarin placebo and dabigatran etexilate / dabigatran etexilate placebo at least 24 h before the procedure in patients with a creatinine clearance >50 mL/min and at least 48 h before the procedure in patients with a creatinine clearance of 30 to 50 mL/min. Vitamin K (1 mg orally or 0.5 mg intravenously) was to be administered 24 h before the procedure, if required. A local, unblinded INR was to be obtained a few hours before the procedure. After the procedure, warfarin / warfarin placebo was to be restarted as soon as the type of surgery allowed. UFH or LMWH as bridging therapy were to be started in the evening of the day of the procedure, or later if the risk of bleeding was too high. INR monitoring was to be performed daily using the POC device / IVRS until an INR value in the therapeutic range (at least an INR of 2.0) had been reached. Heparin was then to be discontinued, dabigatran etexilate / dabigatran etexilate placebo to be restarted, and warfarin / warfarin placebo to be continued.

In case of emergency surgery, study medication was to be discontinued. As per Protocol Amendment 5, it was recommended to postpone the surgery until at least 24 h after the last oral intake of dabigatran etexilate / dabigatran etexilate placebo in patients with a creatinine clearance >50 mL/min and at least 48 h after the last oral intake of dabigatran etexilate / dabigatran etexilate placebo in patients with a creatinine clearance of 30 to 50 mL/min. It was mentioned that dabigatran

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etexilate could be removed by dialysis, but that the fraction cleared using that method is low and the potential clinical utility unknown. Use of fresh frozen plasma, activated prothrombin complex concentrates, or recombinant Factor VIIa was to be considered to achieve haemostasis in patients who were still anticoagulated at the time of surgery.

Clarifications were made regarding the discontinuation of study treatment for patients with severe renal dysfunction. As per original trial protocol, creatinine clearance was to be calculated using the Cockroft-Gault formula in patients who were found to have a clinically significant increase of serum creatinine. Protocol Amendment 5 clarified that for patients with a calculated creatinine clearance of >30 mL/min but <50 mL/min the creatinine clearance was to be calculated at each study visit. For patients with a calculated creatinine clearance of ≤30 mL/min, the measurement of serum creatinine had to be repeated immediately. Patients had to be withdrawn from treatment if the creatinine clearance was ≤30 mL/min, unless repeated testing demonstrated a creatinine clearance of >30 mL/min.

6. Protocol Amendment 6 (dated 12 December 2008)

The planned treatment duration was changed from 18 months to 6 to 36 months, and the number of patients to be recruited was increased, with recruitment to occur through no later than 31st of December 2009. Based on the protocol-specified review of the overall primary endpoint event rate, this amendment was undertaken to ensure a power of 80 %.The trial protocol had specified that an analysis should be undertaken when approximately 80% of the planned patients had been entered into the study. Accordingly, a cut-off date of 30 Sept 2008 was used for this analysis, when 1600 patients had been entered, and approximately 45% of the planned total patient exposure had accrued. The total hazard rate observed was 1.2% over 18 months. With events occurring at this rate, a power of only 66% to prove non-inferiority was projected. Therefore, to achieve a sufficient number of primary endpoint events, patients still receiving blinded study medication in the study at the time of amendment implementation were invited to re-consent to stay on study treatment through the scheduled last patient completion date at the end of July 2010. As a result, 3 'cohorts' of patients were included in the study. First, patients who completed the trial prior implementation of this amendment or those not willing to consent to participate as per this amendment; such patients had a planned treatment duration of 18 months. Second, patients who were randomised prior to implementation of this amendment and who consented to trial participation as per this amendment; such patients had a planned treatment duration of between 18 and 36 months. Third, patients randomised after implementation of this amendment but enrolled within 18 months of the planned study close-out; these patients had a planned treatment duration of 6 to <18 months.

Based on simulations, a combined number of about 1000 patients either additionally recruited or consenting to prolong study therapy was deemed necessary to achieve a power of 80%. Six hundred ongoing patients were expected to re-consent and prolong study therapy, and 400 additional patients were planned to be recruited. Consequently, 1400 patients were anticipated to be in the first patient cohort, about 600 patients in the second cohort and 400 in the third cohort. Furthermore, a constant hazard rate was assumed in all 3 patient cohorts (according to the information available from the blinded analysis that identified the need for this amendment), and a 20% drop-out rate over each 18 month period. Under these assumptions, it was concluded that a total of 2400 patients would provide adequate power to claim non-inferiority.

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Because of the changes in planned trial duration and patient recruitment, the visit schedule was changed. In the original protocol, 13 visits plus a follow-up visit were planned. Protocol Amendment 6 clarified that after Visit 9, subsequent treatment period follow-up visits were to be scheduled at 3-month intervals, with the end-of-treatment visit being the last visit of the study treatment period. Additional clarifications were made concerning the scheduling of the end-of-treatment visit and the follow-up visit. Furthermore, the schedule of supply dispensation and collection was changed to accommodate the change in trial duration.

Protocol Amendment 6 specified the statistical methods to be used for non-inferiority and superiority testing in this trial given the changes in the planned treatment duration and patient recruitment. Per original protocol, risk differences were to be calculated using the Kaplan-Meier (KM) estimates of the cumulative risk at month 18. Amendment 6 specified that the risk difference at month 18 would not consider the additional events after the originally planned treatment period of 18 months. Patients not attaining 18 months of treatment without having an event qualifying for the primary endpoint were to be censored accordingly. It was further specified that a lower event rate would increase the power for the risk difference assuming a point estimator of the between-group difference of close to zero. It was therefore concluded that it may have been acceptable to risk observing fewer than expected events for the risk difference comparison. Consequently, the focus of the medical interpretation of the results was to be based on the analyses of the hazard ratio, while the risk difference was to be used to benchmark this interpretation.

Concerning the primary analyses of the primary endpoint it was specified that the different patient cohorts introduced by Amendment 6 were to be handled like sub-trials. Pooling of the results was to be done applying meta-analyses techniques, and the weight for the 3 patient cohorts was to be the inverse variance for the respective point estimator, i.e., hazard ratio or risk difference. The additionally observed events in the cohort for the longer treatment period was to be considered in the hazard ratio, based on the Cox proportional hazard model. However, the risk difference based on the Kaplan-Meier estimators at month 18 was not to consider the additional events after the originally planned treatment period of 18 months. Concerning the method of obtaining the estimate and confidence interval for the overall risk difference, it was added that the 3 patient cohorts were to be pooled using meta-analysis techniques. Concerning the estimate and confidence interval for the hazard ratio, it was added that meta-analysis techniques were to be used for the 3 patient cohorts. The use of meta-analysis techniques was also added to the methods to compare the time to first occurrence of the primary endpoint.

The second major change introduced by Protocol Amendment 6 was to allow inclusion of patients of RE-COVER II (study 1160.46), a replicate trial of RE-COVER. Thirdly, clarifications regarding physical examination requirements were provided.

7. Protocol Amendment 7 (dated 3 March 2009)

Protocol Amendment 7 provided guidance on the concomitant administration of the P-glycoprotein inhibitor verapamil, as based on the results of the BI trial 1160.74. If initiation of therapy with verapamil was considered necessary, it was recommended to administer verapamil 2 h after the study drug for the first 2 to 3 days. Thereafter, verapamil and study drug could be used concurrently. For patients with increased risk of bleeding, it was recommended to continue administering verapamil 1 to 2 h after study drug intake. A suitable alternative to verapamil was to be considered

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for patients with a high risk of bleeding or those unable to comply with the recommended dosing of verapamil 1 to 2 h after dabigatran etexilate. Patients with a high risk of bleeding and for whom no suitable alternative to verapamil could be identified and patients who were considered unreliably compliant with the specified dosing interval were to be removed from treatment with study drug. This amendment also provided an updated list of drugs for which no clinically relevant interaction with dabigatran etexilate has been revealed in drug-drug interaction studies.

8. Protocol Amendment 8 (dated 20 January 2010)

Through Protocol Amendment 8, the systemic use of the P-gp inhibitor ketoconazole was contraindicated and updated guidance was provided regarding co-administration of the P-gp inducer rifampicin; it was based on the drug-drug interaction study 1160.101. Systemic use of ketoconazole was added to the list of concomitant therapies prohibited in this trial. Investigators were advised to avoid co-administration of rifampicin, or to use it with caution and only when no suitable alternative was available, as it may result in under-exposure to dabigatran etexilate. The amendment also provided an updated list of substances tested in drug-drug interaction studies with dabigatran etexilate.

9. Protocol Amendment 9 (dated 26 January 2010)

Protocol Amendment 9 provided update guidance for administration of strong P-gp-inducers, stating that rifampicin and other strong P-gp inhibitors, such as carbamazepine and St. John's Wort, were to be used with caution and only when no suitable alternative is available.

RESONATE

In RESONATE, there were 7 global amendments to the trial protocol. Of these, Protocol Amendment 2 (dated 30 May 2008) required prior IEC / IRB approval. Protocol Amendment 1 (dated 11 February 2008), Protocol Amendment 3 (dated 18 July 2008), Protocol Amendment 4 (dated 09 March 2009), Protocol Amendment 6 (dated 22 January 2010), and Protocol Amendment 7 (dated 03 February 2010) were implemented immediately, and the IECs / IRBs were in parallel notified of the changes and their approval was requested. Protocol Amendment 5 (dated 21 July 2009) introduced changes related to logistic and administrative aspects and was implemented without prior IEC / IRB approval. There were also 3 local amendments (2 in Germany and 1 in Sweden).

1. Protocol Amendment 1 (dated 11 February 2008)

The main purpose of Protocol Amendment 1 was to contraindicate the concomitant administration of quinidine; this was based on the results of the early-terminated BI trial 1160.75. Since this amendment addressed a safety issue, it was implemented immediately and the IECs / IRBs were in parallel notified of the changes and their approval was requested. The exclusion criteria were amended to exclude patients with an anticipated need of quinidine or other restricted medication during the treatment period from participation in the trial. Quinidine was added to the list of restricted medications. In addition, text was added to alert investigators about the concomitant use of moderate to strong P-gp inhibitors and the potential exaggerated effects of dabigatran etexilate (particularly with respect to bleeding risk). Concomitant use of such drugs was not prohibited in this study per se (except quinidine), but they were to be used with caution or, at investigator' discretion,

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switched to a suitable alternative. If a moderate to strong P-gp inhibitor was co-administered, investigators were advised it might be helpful to separate the timing of administration of dabigatran etexilate and the P-gp inhibitor by several hours.

2. Protocol Amendment 2 (dated 30 May 2008)

Protocol Amendment 2 required prior IEC / IRB approval. It was introduced to amend the study design by extending the follow-up period after completion or discontinuation of study medication to 12 months to determine whether or not there was an increase in VTE recurrence following discontinuation of study treatment over this period. In addition, following a DSMB recommendation, the monitoring frequency for LFTs was reduced and samples were no longer to be collected at Visits 5, 7, and 8 (at 2, 4, and 5 months).

The eligibility criteria for the trial were amended to allow patients to roll-over into the RE-SONATE trial after participation in RE-COVER (BI study 1160.53). They were also amended to exclude patients known to have active cancer. Changes in the protocol were also introduced to clarify patients' eligibility if bridging therapy was given during the previous 6 to 18 months of oral VKA therapy and to clarify the timing of initiation of study medication relative to patients' last dose of VKA.

In addition, Protocol Amendment 2 introduced corrections of minor typographical errors.

3. Protocol Amendment 3 (dated 18 July 2008)

Protocol Amendment 3 provided updated guidance regarding management of patients who require surgery or invasive procedures during the treatment period. Since this amendment addressed a safety issue, it was implemented immediately and the IECs / IRBs were in parallel notified of the changes and their approval was requested.

It was recommended that if surgery could not be delayed until completion of the treatment period, CrCl should be checked 2 weeks before the planned surgery. Recommendations for discontinuation of study medication prior to surgery were provided for all patients and for those found to have renal dysfunction. Post procedure, study treatment could be resumed at the discretion of the investigator. Conditions for the use of UFH or LMWH as bridging therapy were described.

For emergency surgery, study medication was to be discontinued. Surgery was to be postponed if possible until at least 24 h after the last oral intake of dabigatran/ dabigatran placebo in patients with a CrCl >50 mL/min and for at least 48 h in patients with a CrCl of 30 to 50 mL/min.

4. Protocol Amendment 4 (dated 9 March 2009)

The purpose of Protocol Amendment 4 was to provide updated guidance regarding the concomitant administration of verapamil; this was based on the results of the drug-drug interaction study, BI trial 1160.74. Since this amendment addressed a safety issue, it was implemented immediately and the IECs / IRBs were in parallel notified of the changes and their approval was requested.

Verapamil was not added to the list of restricted medications. However, if required as a concomitant medication, investigators were advised that it should be administered 2 h after RE-SONATE study medication for the first 2 to 3 days of verapamil co-administration.

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5. Protocol Amendment 5 (dated 21 July 2009)

Protocol Amendment 5 introduced changes related to logistic and administrative aspects of the trial. It was implemented without prior IEC / IRB approval. The changes included a change in the trial Coordinating Investigator and other administrative changes and corrections of minor typographical errors or inconsistencies.

6. Protocol Amendment 6 (dated 22 January 2010)

The main purpose of Protocol Amendment 6 was to contraindicate the concomitant administration of ketoconazole and to provide updated guidance regarding the concomitant administration of rifampicin. This was based, respectively, on the results of the BI drug-drug interaction studies 1160.100 and 1160.101. Since this amendment addressed a safety issue, it was implemented immediately and the IECs / IRBs were in parallel notified of the changes and their approval was requested.

Systemic use of ketoconazole was added to the list of restricted medications. In addition, text was added to alert investigators about the concomitant use of rifampicin. Investigators were advised that because the P-gp inducer rifampicin had been shown to decrease exposure to dabigatran it should be used with caution and only when no suitable alternative was available.

7. Protocol Amendment 7 (dated 3 February 2010)

The main purpose of Protocol Amendment 7 was to provide guidance regarding the concomitant administration of strong P-gp inducers. Since this amendment addressed a safety issue, it was implemented immediately and the IECs / IRBs were in parallel notified of the changes and their approval was requested.

Investigators had been advised (in Protocol Amendment 6) that rifampicin should be used with caution and only when no suitable alternative was available. This was amended to advise that other strong P-gp inducers (e.g. carbamazepine and St. John's wort) also should be used with caution and only when no suitable alternative was available.

8. Local Protocol Amendments

a. Local Amendments in Germany

Local Protocol Amendment 1 in Germany (dated 24 October 2007) required prior IEC / IRB approval. At the request of the German Competent Authority, for safety reasons, an exclusion criterion was added to exclude patients with a contraindication to systemic anticoagulation.

Local Protocol Amendment 2 in Germany (dated 26 June 2008) required prior IEC / IRB approval. It was introduced to amend the exclusion criteria regarding excessive risk of bleeding (because of anticipated need for quinidine), to allow previous study medication from the RE-COVER trial to have been used, and to exclude patients with active cancer. These changes were to ensure the protocol was consistent with the changes introduced with the global clinical trial Protocol Amendments 1 (11 February 2008) and 2 (30 May 2008)

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b. Local Amendments in Sweden

Local Protocol Amendment 1 in Sweden (dated 15 October 2007) required prior IEC / IRB approval. At the request of the Swedish Health Authority (MPA), exclusion criterion 11 was amended because combined systemic hormonal contraceptives were contraindicated in Sweden for women with a history of venous thromboembolism. The permitted methods of contraception therefore included consistent and correct use of hormone containing implants and injectables, hormone containing intrauterine devices, surgical sterilisation, sexual abstinence, and vasectomy, and excluded combined oral contraceptives. Combined oral contraceptives were added to the list of restricted concomitant medications. The concomitant use of gestagen-only systemic hormonal contraception required a risk benefit assessment by the investigator.

A14. The NICE final scope lists post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension as important outcome measures to be considered in the STA. Please clarify the rationale for not including data on these outcomes from the dabigatran trials included in the submission. Where possible, for these outcomes, please provide the number of events (n) and the number of people analysed in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) for the full randomised, full analysis and per protocol populations.

The design of the RE-COVER and RE-COVER II trials, including endpoints and methodology, were consistent with the guidance of the European Medicines Agency (EMA) on clinical investigation of medicinal products for the treatment of VTE. The EMA guidance indicates that recurrent venous thromboembolism and bleeding are the principal relevant outcomes to be assessed for treatments for treatment and prevention of recurrent VTE.

The following outcomes are stated as relevant for confirmatory trials in the *Committee for Proprietary Medicinal Products Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of venous thromboembolic disease*:

Confirmatory trials

Phase III trials should primarily address clinical outcomes in the form of:

- Recurrent, symptomatic VTE (nonfatal DVT and/or nonfatal PE)
- Deaths
- Bleeding episodes

The number of events for respective outcomes stated in Question A.14 could not be derived from available clinical trials reports for a number of reasons. Patients with acute right heart failure were not enrolled in the clinical trials based on exclusion criteria: PE complicated with haemodynamic instability. Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension constitute long-term complications of venous thromboembolism. The dabigatran trials were of

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insufficient duration to collect meaningful comparative incidence data on these outcomes (6 months treatment duration for RE-COVER and RE-COVER II and up to 18 months treatment duration for RE-MEDY). It was therefore inappropriate to include these outcomes in the dabigatran trials.

Despite this, the outcomes were considered relevant to the appraisal given that the time horizon for the economic model was 'lifetime', in line with the NICE Reference Case:

Element of health technology appraisal	Reference Case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared

Therefore, for the purpose of the appraisal, it was considered appropriate to model the long-term occurrence of these outcomes using data from literature sources.

A15. Please clarify the rationale for conducting analyses by centre TTR using quintiles rather than quartiles.

The purpose of categorisation of the time in therapeutic ranges was to evaluate whether the quality of warfarin control has an impact on the estimated treatment effect. In the literature, quartiles and quintiles of the centre TTR are used for this purpose. We decided to focus on quintiles, since this provides more granularity in the assessment and the exclusion of the extreme categories allows still an assessment of a relevant spectrum of INR control reflecting the expected real world situation. Furthermore, using quintiles provide a balance between the number of events per category and the intended granularity.

A16. Please present the data in tables 51, 52, 82 and 83 broken down by centre TTR using quartiles.

Please see A16 Clarification Letter document as attached.

Meta analyses

A17. Priority Question: Please provide the inclusion/exclusion criteria and the patient characteristics for all studies included in the meta-analyses discussed in the submission. Please also provide all Review Manager files for these meta-analyses.

As per the systematic literature review, only information from publically available sources was extracted for inclusion in the Meta-Analysis, with the exception of the Clinical Trial Reports for the four Boehringer Ingelheim trials (RE-COVER, RE-COVER II, REMEDY and RESONATE). Therefore, we do not have access to the requested information for all the trials included in the meta-analysis. Both

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the inclusion/exclusion criteria and patient characteristics are shown below for RE-COVER, RE-COVER II, EINSTEIN-DVT and EINSTEIN-PE. However, the inclusion/exclusion criteria were not publically available for the 6 trials comparing warfarin versus LMWH (5 for treatment and 1 for secondary prevention). Nevertheless, the patient characteristic information available from the respective trial publications are provided below.

Please refer to Appendix A17a and Appendix A17b for the Review Manager files as attached.

RE-COVER

Inclusion criteria
Patients could be included in the study if the following criteria were fulfilled:

1. Acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins, and / or PE confirmed by definitive objective clinical test in patients for whom at least 6 months of anticoagulant therapy was considered appropriate by the investigator [proximal veins are: trifurcation area, popliteal, superficial femoral, deep femoral, common femoral, and iliac veins]
2. Male or female, being 18 years of age or older
3. Written informed consent for study participation

Exclusion criteria
If any of the following criteria applied (as defined in the original trial protocol) patients were barred from entering this study:

1. Overt symptoms of VTE for longer than 2 weeks prior to enrolment
2. PE satisfying at least one of the following criteria:
   - Haemodynamic instability
   - Embolectomy indicated or performed
   - Thrombolytic therapy indicated or performed
   - Suspected source of PE other than the legs
3. Actual or anticipated use of vena cava filter
4. Contraindications to anticoagulant therapy including contraindications to heparins or other alternate approved therapy used for initial treatment, and warfarin
5. Patients who in the investigator's opinion should not be treated with warfarin
6. Allergy to heparins (including history of heparin induced thrombocytopenia) or other alternate approved therapy used for initial treatment, warfarin or dabigatran, or to one of the excipients included in these medications
7. Patients who in the investigator's judgement were perceived as having an excessive risk of bleeding, for example because of:
   - Haemorrhagic disorder or bleeding diathesis
   - Trauma or major surgery within the last month or as long as an excessive risk of bleeding persisted after these events, or planned major surgery
   - Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm.
   - History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intraarticular bleeding
   - Gastrointestinal haemorrhage within the past 3 months

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−Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
−Treatment with thrombolytic agents within 14 days before enrolment
−Anticipated need of restricted medication during the treatment period
−Known thrombocytopenia (platelet count <100·109/L)

8. Known anaemia (haemoglobin <100 g/L)
9. Need of anticoagulant treatment for disorders other than VTE
10. Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis, or history of myocardial infarction within the last 3 months
11. Elevated AST or ALT >2 x ULN based on the local laboratory results obtained at screening and prior to randomisation (or central screening laboratory results if available on time)
12. Liver disease expected to have any potential impact on survival (e.g. acute hepatitis, possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery)
13. Patients who had developed transaminase elevations upon exposure to ximelagatran
14. Severe renal impairment (estimated creatinine clearance ≤30 ml/min)
15. Women who were pregnant, nursing, or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study (A negative pregnancy test had to be obtained for any woman of childbearing potential prior to entry into the study.)
16. Participation in another clinical trial with an investigational drug during the last 30 days or previous participation in this study
17. Patients considered unsuitable for inclusion by the investigator, e.g. because considered unreliable to comply with the requirements for follow-up during the study and/or compliance with study drug administration, had a life expectancy less than the expected duration of the trial due to concomitant disease, or had any condition which in the opinion of the investigator would not allow safe participation in the study (e.g. drug addiction, alcohol abuse)
18. In case of anticipated study-related diagnostic procedures requiring contrast medium (e.g. contrast venography or pulmonary angiography):
−Elevated serum creatinine, which in the investigator's opinion contraindicated these examinations
−Known allergy to radio opaque contrast media or iodine, which in the investigator's opinion contraindicated these examinations

With Protocol Amendment 2 (dated 11 February 2008) it was added to the exclusion criteria that patients with an anticipated need of quinidine were barred from participation in this trial.

Demographic data / TS

	Dabigatran	Warfarin	Total
Patients, n (%)	1273 (100.0)	1266 (100.0)	2539 (100.0)
Sex, n (%)			
Male	738 (58.0)	746 (58.9)	1484 (58.4)
Female	535 (42.0)	520 (41.1)	1055 (41.6)
Age, mean (SD) [years]	55.0 (15.8)	54.4 (16.2)	54.7 (16.0)

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Age categories, n (%)			
18 to <40 years	240 (18.9)	247 (19.5)	487 (19.2)
40 to <50 years	234 (18.4)	239 (18.9)	473 (18.6)
50 to <65 years	394 (31.0)	395 (31.2)	789 (31.1)
65 to <75 years	269 (21.1)	231 (18.2)	500 (19.7)
≥75 years	136 (10.7)	154 (12.2)	290 (11.4)
Race, n (%)			
White	1212 (95.2)	1195 (94.4)	2407 (94.8)
Black	36 (2.8)	31 (2.4)	67 (2.6)
Asian	25 (2.0)	40 (3.2)	65 (2.6)
Geographical region, n (%)			
Western Europe[1]	394 (31.0)	399 (31.5)	793 (31.2)
Central Europe[2]	390 (30.6)	369 (29.1)	759 (29.9)
North America[3]	215 (16.9)	226 (17.9)	441 (17.4)
Latin America[4]	70 (5.5)	86 (6.8)	156 (6.1)
Asia[5]	17 (1.3)	27 (2.1)	44 (1.7)
Other[6]	187 (14.7)	159 (12.6)	346 (13.6)
Weight, mean (SD) [kg][7]	85.5 (19.2)	84.2 (18.3)	84.9 (18.7)
BMI, mean (SD) [kg/m^2][8]	28.9 (5.7)	28.4 (5.5)	28.6 (5.6)
Creatinine clearance, mean (SD)[9]	105.8 (40.7)	104.4 (39.9)	105.1
Creatinine clearance categories, n (%)[9]			
<30 mL/min	5 (0.4)	8 (0.6)	13 (0.5)
30 to <50 mL/min	59 (4.6)	61 (4.8)	120 (4.7)
50 to <80 mL/min	275 (21.6)	276 (21.8)	551 (21.7)
≥80 mL/min	923 (72.5)	910 (71.9)	1833
Smoking history, n (%)[10]			
Never smoked	662 (52.0)	636 (50.2)	1298
Ex-smoker	342 (26.9)	357 (28.2)	699 (27.5)
Current smoker	269 (21.1)	272 (21.5)	541 (21.3)

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RE-COVER II

Inclusion criteria

Patients could be included in the study if the following criteria were fulfilled:

1.) Acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins and / or PE confirmed by definitive objective clinical test in patients for whom at least 6 months of anticoagulant therapy was considered appropriate by the investigator [proximal veins are: trifurcation area, popliteal, superficial femoral, deep femoral, common femoral, and iliac veins]

2.) Male or female, being 18 years of age or older

3.) Written informed consent for study participation

Exclusion criteria

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If any of the following criteria applied (as defined in the original trial protocol) patients were barred from entering this study:

1.) Overt symptoms of VTE for longer than 2 weeks prior to enrolment
2.) PE satisfying at least 1 of the following criteria:
- Haemodynamic instability
- Embolectomy indicated or performed
- Thrombolytic therapy indicated or performed
- Suspected source of PE other than the legs

3.) Actual or anticipated use of vena cava filter
4.) Contraindications to anticoagulant therapy including contraindications to heparins or other alternate approved therapy used for initial treatment, and warfarin
5.) Patients who in the investigator's opinion should not be treated with warfarin
6.) Allergy to heparins (including history of heparin induced thrombocytopenia) or other alternate approved therapy used for initial treatment, warfarin or dabigatran etexilate, or to one of the excipients included in these medications
7.) In case of anticipated study-related diagnostic procedures requiring contrast medium (e.g. contrast venography or pulmonary angiography):
- Elevated serum creatinine, which in the investigator's opinion contraindicated these examinations
- Known allergy to radio opaque contrast media or iodine, which in the investigator's opinion contraindicated these examinations

8.) Patients who in the investigator's judgement were perceived as having an excessive risk of bleeding, for example because of:
- Haemorrhagic disorder or bleeding diathesis
- Trauma or major surgery within the last month or as long as an excessive risk of bleeding persisted after these events, or planned major surgery
- Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm
- History of intracranial, intraocular, spinal, retroperitoneal, or a traumatic intraarticular bleeding
- Gastrointestinal haemorrhage within the past 3 months
- Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
- Treatment with thrombolytic agents within 14 days before enrolment
- Anticipated need of restricted medication during the treatment period
- Known thrombocytopenia (platelet count <100·109/L)

9.) Known anaemia (haemoglobin <100 g/L)
10.) Need of anticoagulant treatment for disorders other than VTE
11.) Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis, or history of myocardial infarction within the last 3 months
12.) Elevated AST or ALT >3 x ULN based on the local laboratory results obtained at screening and prior to randomisation (or central screening laboratory results if available on time)
13.) Known liver disease expected to have any potential impact on survival (e.g. acute hepatitis, possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery)

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14.) Severe renal impairment (estimated creatinine clearance ≤30 ml/min)
15.) Women who were pregnant, nursing, or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study (A negative pregnancy test had to be obtained for any woman of childbearing potential prior to entry into the study.)
16.) Patients considered unsuitable for inclusion by the investigator, e.g. because considered unreliable to comply with the requirements for follow-up during the study or compliance with study drug administration, had a life expectancy less than the expected duration of the trial due to concomitant disease, or had any condition which in the opinion of the investigator would not allow safe participation in the study (e.g. drug addiction, alcohol abuse)
17.) Participation in another clinical trial with an investigational drug during the last 30 days or previous participation in this study or in RE-COVER (BI trial 1160.53) With Protocol Amendment 2 (dated 12 February 2008) it was added to the exclusion criteria that patients with an anticipated need of quinidine or other restricted medication during the treatment period were barred from participation in this trial.

Demographic data / TS

	Dabigatran etexilate		Warfarin		Total	
Patients, n (%)	1280	(100.0)	1288	(100.0)	2568	(100.0)
Sex, n (%)						
Male	781	(61.0)	776	(60.2)	1557	(60.6)
Female	499	(39.0)	512	(39.8)	1011	(39.4)
Age, mean (SD) [years]	54.7 (16.19)		55.1 (16.26)		54.9 (16.22)	
Age categories, n (%)						
18 to <40 years	256	(20.0)	253	(19.6)	509	(19.8)
40 to <50 years	216	(16.9)	220	(17.1)	436	(17.0)
50 to <65 years	431	(33.7)	392	(30.4)	823	(32.0)
65 to <75 years	225	(17.6)	262	(20.3)	487	(19.0)
≥75 years	152	(11.9)	161	(12.5)	313	(12.2)
Race, n (%)[1]						
White	993	(77.6)	999	(77.6)	1992	(77.6)
Black	19	(1.5)	19	(1.5)	38	(1.5)
Asian	267	(20.9)	270	(21.0)	537	(20.9)
Geographical region, n (%)						

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Central Europe[2]	422	(33.0)	421	(32.7)	843	(32.8)
Asia[3]	255	(19.9)	258	(20.0)	513	(20.0)
Western Europe[4]	218	(17.0)	228	(17.7)	446	(17.4)
North America[5]	197	(15.4)	207	(16.1)	404	(15.7)
Other[6]	181	(14.1)	167	(13.0)	348	(13.6)
Latin America[7]	7	(0.5)	7	(0.5)	14	(0.5)
Weight, mean (SD) [kg]	83.2 (19.7)		82.9 (19.6)		83.1 (19.6)	
BMI, mean (SD) [kg/m^2]	28.4 (5.8)		28.4 (5.8)		28.4 (5.8)	
Creatinine clearance, mean (SD) [mL/min]	108.2 (43.7)		107.1 (41.1)		107.7 (42.4)	
Creatinine clearance categories, n (%)						
<30 mL/min	7	(0.5)	3	(0.2)	10	(0.4)
30 to <50 mL/min	57	(4.5)	63	(4.9)	120	(4.7)
50 to <80 mL/min	266	(20.8)	285	(22.1)	551	(21.5)
≥80 mL/min	939	(73.4)	929	(72.1)	1868	(72.7)
Missing	11	(0.9)	8	(0.6)	19	(0.7)
Smoking history, n (%)						
Never smoked	685	(53.5)	687	(53.3)	1372	(53.4)
Ex-smoker	316	(24.7)	319	(24.8)	635	(24.7)
Current smoker	279	(21.8)	282	(21.9)	561	(21.8)

EINSTEIN-DVT

Inclusion criteria

1. Confirmed acute symptomatic proximal DVT without symptomatic PE , or
2. Written informed consent

Exclusion criteria

1. Legal lower age limitations (country specific)
2. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE
3. Other indication for VKA than DVT and/or PE
4. More than 48 hours pre-randomisation treatment with therapeutic dosages of (LMW) Heparin/fondaparinux or more than a single dose of VKA prior to randomisation. More than 36 hours pre-randomisation treatment with therapeutic dosages of (LMW) Heparin/fondaparinux or more than a single dose of VKA prior to randomisation
5. Participation in another pharmacotherapeutic study within 30 days
6. Creatinine clearance < 30 ml/min,
7. Significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALAT > 3 x ULN
8. Bacterial endocarditis
9. Life expectancy <3 months
10. Active bleeding or high risk for bleeding contraindicating treatment with enoxaparin or VKA

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11. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
12. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
13. Any other contraindication listed in the local labeling of warfarin, acenocoumarol, or enoxaparin
14. Concomitant use of strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole) or CYP 3A4 inducers like rifampicin.

Demographic and Clinical Characteristics

Demographic and Clinical Characteristics of Patients with Deep-Vein Thrombosis, According to the Study and the Assigned Group.*				
Characteristic	**Acute DVT Study**		**Continued Treatment Study**	
	Rivaroxaban (N=1731)	Standard Therapy† (N=1718)	Rivaroxaban (N=602)	Placebo (N=594)
Age — yr	55.8±16.4	56.4±16.3	58.2±15.6	58.4±16
Male sex — no. (%)	993 (57.4)	967 (56.3)	354 (58.8)	339 (57.1)
Weight — no. (%)				
≤50 kg	37 (2.1)	49 (2.9)	10 (1.7)	5 (0.8)
>50–100 kg	1443 (83.4)‡	1422 (82.8)‡	491 (81.6)‡	488 (82.2)‡
>100 kg	245 (14.2)‡	246 (14.3)‡	85 (14.1)‡	87 (14.6)‡
Missing data	6 (0.3)	1 (<0.1)	16 (2.7)	14 (2.4)
Creatinine clearance — no. (%)				
<30 ml/min	6 (0.3)	9 (0.5)	0	5 (0.8)
30–49 ml/min	115 (6.6)	120 (7.0)	37 (6.1)	44 (7.4)
50–79 ml/min	393 (22.7)	399 (23.2)	134 (22.3)	122 (20.5)
≥80 ml/min	1193 (68.9)	1170 (68.1)	373 (62.0)	373 (62.8)
Missing data	24 (1.4)	20 (1.2)	58 (9.6)	50 (8.4)
Initial diagnosis — no.				
DVT	1708	1697 (only 1 distal)	386	356
PE	12	11	216	238
Time from onset of symptoms to randomisation — days				
Median	5	5	204	206
Interquartile range	3–10	3–10	188–302	189–307
Cause of DVT or PE — no. (%)				
Unprovoked	1055 (60.9)	1083 (63.0)	440 (73.1)	441(74.2)
Recent surgery or trauma	338 (19.5)	335 (19.5)	21 (3.5)	28 (4.7)
Immobilisation	265 (15.3)	260 (15.1)	89 (14.8)	77 (13.0)
Estrogen therapy	140 (8.1)	115 (6.7)	23 (3.8)	22 (3.7)
Active cancer	118 (6.8)	89 (5.2)	28 (4.7)	26 (4.4)
Puerperium	6 (0.3)	11 (0.6)	1 (0.2)	0
Known thrombophilic condition — no. (%)	107 (6.2)	116 (6.8)	49 (8.1)	48 (8.1)
Previous VTE — no. (%)	336 (19.4)	330 (19.2)	108 (17.9)	84 (14.1)

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EINSTEIN-PE

Inclusion criteria

1. Confirmed acute symptomatic PE with or without symptomatic DVT
2. Written informed consent

Exclusion criteria

1. Legal lower age limitations (country specific)
2. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE
3. Other indication for VKA than DVT and/or PE
4. More than 48 hours pre-randomisation treatment with therapeutic dosages of (LMW) Heparin/fondaparinux or more than a single dose of VKA prior to randomisation. More than 36 hours pre-randomisation treatment with therapeutic dosages of (LMW) Heparin/fondaparinux or more than a single dose of VKA prior to randomisation
5. Participation in another pharmacotherapeutic study within 30 days
6. Creatinine clearance < 30 ml/min,
7. Significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALAT > 3 x ULN
8. Bacterial endocarditis
9. Life expectancy <3 months
10. Active bleeding or high risk for bleeding contraindicating treatment with enoxaparin or VKA
11. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
12. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
13. Any other contraindication listed in the local labeling of warfarin, acenocoumarol, or enoxaparin
14. Concomitant use of strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole) or CYP 3A4 inducers like rifampicin.

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Deitcher et al (2006)

TABLE 1. Baseline Demographic Characteristics and Index Venous Thromboembolism Diagnosis: Safety Sample

Characteristic	Enoxaparin 1.0 mg/kg (n = 31)	Enoxaparin 1.5 mg/kg (n = 36)	Warfarin (n = 34)	Total (N = 101)
Age				
Mean ± SD	62.7 ± 13.4	64.0 ± 10.7	64.1 ± 12.4	63.7 ± 12.0
Range	35-80	36-79	40-87	35-87
Age category (%)				
≤50 years	6 (19.4)	3 (8.3)	7 (20.6)	16 (15.8)
51-60 years	6 (19.4)	11 (30.6)	2 (5.9)	19 (18.8)
61-70 years	8 (25.8)	9 (25.0)	15 (44.1)	32 (31.7)
>70 years	11 (35.5)	13 (36.1)	10 (29.4)	34 (33.7)
Race (%)				
Caucasian	25 (80.6)	29 (80.6)	32 (94.1)	86 (85.1)
Black	5 (16.1)	4 (11.1)	2 (5.9)	11 (10.9)
Asian	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.0)
Hispanic	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.0)
Other	1 (3.2)	1 (2.8)	0 (0.0)	2 (2.0)
Index VTE (%)				
PE	12 (38.7)	17 (47.2)	15 (44.1)	44 (43.6)
DVT	24 (77.4)	29 (80.6)	31 (91.2)	84 (83.2)
PE and DVT	7 (22.6)	10 (27.8)	13 (38.2)	30 (29.7)

SD = standard deviation; VTE = venous thromboembolic event; PE = pulmonary embolism; DVT = deep venous thrombosis.

Hull et al (2006)

Clinical Characteristics of Cancer Patients with Proximal-Vein Thrombosis Treated with Long-Term Low-Molecular-Weight Heparin or Oral Anticoagulant Therapy

Characteristic	No. of Patients Low-Molecular-Weight Heparin n = 100	Intravenous heparin/warfarin n = 100
Age (years <60, >60	38, 62	24, 76
Sex (M, F)	52, 48	50, 50
Status at entry		
Symptomatic deep-vein thrombosis	90 (92)	94 (94)
Symptoms of pulmonary embolism	21 (21)	21 (21)
Previous venous thromboembolism	18 (18)`	20 (20)
Factor V Leiden gene mutation	10 (10)	8 (8)
Clinical measures at entry		
Surgery or trauma in past 6 months	53 (53)	49 (49)
Coronary heart disease	16 (16)	29 (29)
Diabetes	15 (15)	14 (14)
Chronic obstructive pulmonary disease	8 (8)	10 (10)
Peripheral vascular disease	9 (9)	3 (3)
Congestive heart disease	8 (8)	8 (8)

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Leg paralysis	7 (7)	3 (3)
Liver disease	5 (5)	6 (6)
High risk of bleeding	49 (49)	52 (52)
Cancer		
Solid tumour		
Nonmetastatic	43	51
Metastatic	47	36
Hematologic	10	13

Lee et al (2003)

Base-Line Characteristics of the Patients*		
Characteristic	**Dalteparin**	**Oral Anticoagulant**
	(N = 338)	**(N = 338)**
Mean age (yr)	62 ± 12	63 ± 13
Female sex (no. of patients)	179	169
ECOG performance Score (no. of patients)		
0	80	63
1	135	150
2	118	122
3†	5	3
Hospitalization status (no. of patients)		
Outpatient	169	156
Inpatient	169	182
Hematologic cancer (no. of patients	40	30
Solid tumor		
No clinical evidence of disease	36	33
Localized disease	39	43
Metastatic disease	223	232
Antineoplastic treatment (no. of patients)‡	266	259
Current smoker (no. of patients)	33	42
History of DVT or PE (no. of patients	39	36
Recent major surgery (no. of patients	62	67
Central venous catheter (no. of patients	46	40
Qualifying thrombotic event (no. of patients)		
DVT alone	235	230
PE, with or without DVT	103	108

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group, DVT deep-vein thrombosis, and PE pulmonary embolism.
† Eight patients were included in the study before the protocol was amended to exclude patients with an ECOG score of 3 or 4.
‡ Antineoplastic treatment included chemotherapy, radiation, and surgery.

Meyer et al (2002)

Baseline Clinical and Biological Characteristics of Study Patients		
Characteristics	Warfarin Sodium Group	Enoxaparin Sodium Group

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	(n = 75)	(n = 71)
Male. No (%)	37 (49.3)	28 (39.4)
Age. Y		
Mean ± SD	66 ± 11	65 ± 13
Range	39-86	25-91
Weight, kg		
Mean ± SD	68 ± 14	70 ± 15
Range	40-100	40-106
Venous thromboembolism, No. (%)		
Isolated DVT	25 (33.3)	19 (26.8)
Isolated PE	11 (14.7)	8 (11.3)
DVT and PE	39 (52.0)	44 (62.0)
Risk Factors, No. (%)		
Immobilisation	20 (26.7)	21 (29.6)
Previous VTE	23 (30.7)	13 (18.7)
Recent surgery	12 (16.0)	18 (25.4)
Varicose Veins	13 (17.3)	11 (15.7)
Congestive heart failure	4 (5.3)	5 (7.0)
BMI >30 kg/m^2, No. (%)	8 (10.7)	8 (11.3)
Blood urea nitrogen, mean ±SD, mg/dl (mmol/L)	17 ± 8 (6.0 ± 3.0)	16 ± 9 (5.6 ± 3.2)
Platelet Count, mean ± SD, x10^3/µl	218 ± 101	225 ± 83
Creatinine, mean ± SD, mg/dl (µmol/L)	0.99 ± 0.26 (87.2 ± 23.1)	0.95 ± 0.26 (84.4 ± 22.9)
Haemoglobin, mean ± SD, g/dl	11.4 ± 2.1	10.9 ± 1.7

Romera et al (2009)

Clinical characteristics of patients with proximal venous thrombosis treated with long-term low-molecular-weight heparin or oral-anticoagulant therapy

Characteristic	All patients		Patients with cancer	
	Acenocoumarol	LMWH	Acenocoumarol	LMWH
	N 122	N 119	N 33	N 36
	No. of patients (%)		No. of patients (%)	
Age (year ± SD)	61.3 ± 16.2	58.9 ± 17.6	64.7 ± 15.2	59.8 ± 15.5
Sex (M, %)	70 (57.4)	64 (53.8%)	20 (60.6)	18 (50)
Risk factors				
Thrombophilia	11 (9%)	11 (9.2%)	4 (12.1)	5 (13.9)
Cancer	33 (27%)	36 (30.3%)		
Bedridden	34 (27.9%)	43 (36.1%)	8 (24.2)	12 (33.3)
Traumatism	14 (11.5%)	18 (15.1%)	0 (0.0)	2 (5.6)
Surgery	8 (6.6%)	11 (9.2%)	3 (9.1)	5 (13.9)
Oral contraception	6 (4.9%)	10 (8.4%)	0 (0.0)	2 (5.6)
Status at entry				
Iliofemoral	22 (18%)	12 (10.1%)	12 (36.4)	4 (11.1)
Femoro-popliteal	72 (59%)	80 (67.2%)	16 (48.5)	28 (77.8)
Popliteal	28 (23%)	27 (22.7%)	5 (15.1)	4 (11.1)
D-dimer (median)	868 (244e13,460)	860	1050 (430e13,460)	1040 (303e9942)
Last D-dimer[a] (median)	253 (100e1678)	240	490 (190e1563)	420 (110e1672)
Last D-dimer <235	54 (45.8%)	53 (49.5%)	7 (21.2%)	8 (25.8%)
Time of evolution				

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<48 h	30 (24.6)	31 (26.1)	12 (36.4)	12 (33.3)
3e7 days	70 (57.4)	66 (55.5)	16 (48.5)	22 (61.1)
>7 days	22 (18)	22 (18.5)	5 (15.1)	2 (5.6)

Cancer DACUS
Baseline Patient Characteristics

	RVT group (n 5 273)	No-RVTgroup (n 5 136)	P value*
Female sex (%)	132 (48.3)	62 (45.5)	0.683
Age, mean 1 SD (years)	57.8 ± 13.9	54.5 ± 14.6	0.054**
One segment DVT, n (%)[a]	78 (28.5)	42 (30.8)	0.065
Prevalence of prothrombin mutation[b]	19/181 (10.4%)	9/89 (10.1%)	n.s.
Prevalence of factor V Leiden[b]	68/194 (35%)	29/91 (31.8%)	n.s.

A18. Priority Question Please clarify which trials were used in the AIC for dabigatran versus warfarin versus placebo described on page 145 that resulted in an RR 0.65 (95% CI: 0.15 to 2.87).

The following trials were used in the AIC of dabigatran versus warfarin (via placebo) for the secondary prevention of recurrent VTE:

Trial ID	Treatment Comparison	Full Reference
DURAC	Warfarin vs placebo	Schulman SG. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med. 1997;336:393-8.
Farraj	Warfarin vs placebo	Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Med J. 2004;25:848-51.
Kearon	Warfarin vs placebo	Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340:901-7.

A19. Please clarify how the subgroup of "Time in INR" presented in Table 59 (pg 162) of the submission has been defined for the purposes of the analysis reported.

In this subgroup, warfarin hazard rates were adjusted to account for trial differences with respect to time in INR 2.0-3.0.

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Clinical effectiveness systematic review

A20. Page 50 of the submission states that the searches for the systematic review of the literature on clinical effectiveness were carried out in two distinct phases. Please clarify the rationale for this.

BI originally decided that UH, LMWH, and fondaparinux should not be included as comparators in the model, therefore the original searches omitted these interventions. Later, BI decided that UH, LMWH, and fondaparinux should be included; therefore the searches were performed for these interventions also.

A21. Warfarin appears to have been omitted as a comparator of interest in some of the literature searches. Please clarify whether warfarin was included as a comparator of interest in the search terms for both acute and secondary prevention. If warfarin was omitted as a term from either search, please clarify the rationale for the omission.

As dabigatran had been compared head-to-head with warfarin / VKA in two randomised trials in the treatment indication, it was considered that other trials investigating warfarin (but not also investigating any of the other listed treatments: dabigatran, rivaroxaban, edoxaban, apixaban, LMWH, UH and fondapariunx) would not add important information to the assessment of comparative effectiveness (principally as these warfarin trials were expected to be older). In the secondary prevention indication, dabigatran had been compared with warfarin and with placebo. It was therefore possible that trials comparing warfarin with placebo might add to the evidence for the effectiveness of dabigatran compared with warfarin or placebo (by adding indirect evidence to the direct head-to-head trial evidence). Therefore these trials were identified in order to assess the feasibility and utility of adding them to the evidence network.

A22. Please provide the citations for the 35 studies included from the systematic review in the "qualitative synthesis"(MS; pg 55 and pg 154).

No.	Full reference
1	Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510.
2	Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342-52.
3	Couturaud F. [Prolongation of oral anticoagulant treatment for eighteen months versus placebo at the decline of a first episode of idiopathic pulmonary embolism treated for six months: a randomised, multicentric, double blind trial. 2006 National PHRC (hospital clinical research programme) "PADIS-EP/Prolongation of anticoagulant treatment for 18 months for a first episode of PE initially treated for 6 months"] [French]. Rev Pneumol Clin. 2008;64:332-6.
4	Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Med J. 2004;25:848-51.
5	Kearon C, Ginsberg JS, Anderson DR, Kovacs MJ, Wells P, Julian JA, et al. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. J Thromb Haemost. 2004;2:743-9.

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6a	Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349:631-9.
7	Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003;139:19-25.
8	Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001;345:165-9.
9	Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340:901-7.
10	Prandoni P, Prins MH, Lensing AWA, Ghirarduzzi A, Ageno W, Imberti D, et al. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. Ann Intern Med. 2009;150:577-85.
11	Schulman SG. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med. 1997;336:393-8.
12	Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012 Apr 5;366(14):1287-97.
13	Schulman S, Kakkar AK, Schellong SM, Goldhaber SZ, Henry E, Mismetti P, et al. A randomized trial of dabigatran versus warfarin in the treatment of acute venous thromboembolism (RE-COVER II). Blood. 2011a Nov 18;118(21):95-6.
14	Schulman S, Eriksson H, Goldhaber SZ, Kakkar A, Kearon C, Mathilde AK, et al. Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism. Presented at the International Society on Thrombosis and Haemostasis; Kyoto, Japan. 25-28 July 2011b. Abstract No. O-TH-033.
15	Schulman S, Baanstra D, Eriksson H, Goldhaber SZ, Kakkar A, Kearon C, et al. Dabigatran versus placebo for extended maintenance therapy of venous thromboembolism. Presented at the International Society on Thrombosis and Haemostasis; Kyoto, Japan. 25-28 July 2011c. Abstract No. O-MO-037.
16	Perez-de-Llano LA, Leiro-Fernandez V, Golpe R, Núñez-Delgado JM, Palacios-Bartolomé A, Méndez-Marote L, et al. Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. Blood Coagul Fibrinolysis. 2010;21(8):744-9.
17	Hull RD, Pineo GF, Brant R, Liang J, Cook R, Solymoss S, et al. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. Am J Med. 2009;122(8):762-9.
18	Romera A, Cairols MA, Vila-Coll R, Martí X, Colomé E, Bonell A, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg. 2009;37(3):349-56.
19	Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. Am J Med. 2007;120(1):72-82.
20	Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119(12):1062-72.
21	Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost. 2006;12(4):389-96.
22	Kucher N, Quiroz R, McKean S, Sasahara AA, Goldhaber SZ. Extended enoxaparin monotherapy for acute symptomatic pulmonary embolism. Vasc Med. 2005;10(4):251-6.
23	Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, Sfiridis P, Nikolaou A, Dimitroulis D, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. Eur J Vasc Endovasc Surg. 2005;29(6):638-50.

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24	Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-53.
25	Kakkar VV, Gebska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thromb Haemost. 2003;89(4):674-80.
26	Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162(15):1729-35.
27	Lopez-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. J Vasc Surg. 2001;33(1):77-90.
28	Veiga F, Escriba A, Maluenda MP, López Rubio M, Margalet I, Lezana A, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. Thromb Haemost. 2000;84(4):559-64.
29	Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. J Vasc Surg. 1999;30(2):283-92.
30	Lopaciuk S, Bielska-Falda H, Noszczyk W, Bielawiec M, Witkiewicz W, Filipecki S, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thromb Haemost. 1999;81(1):26-31.
31	Kirchmaier CM, Wolf H, Schafer H, Ehlers B, Breddin HK. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. Certoparin-Study Group. Int Angiol. 1998;17(3):135-45.
32	Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World J Surg. 1996;20(5):521-6.
33	Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost. 1994;72(2):191-7.
34	Hull R, Delmore T, Carter C, Hirsh J, Genton E, Gent M, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med. 1982;306(4):189-94.
35	Malato A, Siragusa S. The optimal duration of anticoagulant therapy in patients with cancer-related deep vein thrombosis: the advantage of using residual vein thrombosis (the Cancer-Dacus study). J Thromb Haemost. 2011;9:23.

A23. Please indicate which study was excluded "because the results are difficult to interpret" (MS; pg 154) and clarify the reason(s) for exclusion of this study.

The following study was excluded (no data extracted) as the results were not clearly presented: Monreal M, Lafoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost. 1994;71(1):7 11.

Section B: Clarification on cost-effectiveness data

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

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a) all patients who experience a major bleeding event will stop treatment and not restart acute or preventative treatment for venous thromboembolism (VTE) after their bleeding event;

Current treatment guidelines recommend that warfarin should be withheld and reversed during the acute haemorrhage, but the decision to reinitiate therapy is not well-addressed due to the paucity of data.

Most of the guidelines recommend that following a major bleed, the decision about reinstitution of oral anticoagulants should be based on analysis of the individual patient risk of re-bleeding, balanced against risk of recurrent thromboembolic events.

In order to eliminate the uncertainty linked with individual assessment two assumptions withdraw anticoagulant treatment or restart anticoagulant treatment were considered equal for the modelling. Given the fact that in the acute VTE trials (RECOVER pooled) incidence of MBE (3.2% in WFR arm) HR (yes vs no) 1.61 (0.64, 4.00) and MBE + CRBE (13.7% in WFR arm) HR (yes vs no) 2.19 (1.50, 3.19) in patients with history of bleeding were relatively higher compare with incidence of rVTE in patients with history of VTE (2.1 in WFR arm) HR (yes vs no) 1.36 (0.92, 2.01), the preference has been given to the assumption to terminate treatment with anticoagulants after major bleed in the model.

b) neither rivaroxaban nor dabigatran are prescribed at 1st or 2nd VTE recurrence;

Current treatment guidelines do not stratify treatment choice based on history of VTE so that physicians have equal choice of treatment for each individual case of VTE, which is not dependent on the type of anticoagulant used for the treatment of index VTE. Based on the assumption of equal choice, for simplicity in the model it was assumed that all patients will be treated with WFR in case of recurrent VTE.

c) at 1st or 2nd VTE recurrence, patients with active cancer are prescribed low-molecular-weight heparin (LMWH) plus warfarin, rather than LMWH monotherapy;

The model was built for the mixed patient population and patients with active cancer were only a subgroup. The model structure is universal to all type of patients, so that re-treatment with LMWH in unique patient subgroup with active cancer wasn't addressed.

d) at 1st or 2nd VTE recurrence, a patient will receive acute treatment for VTE, but will not receive secondary prevention for future VTE.

According to the NICE guidelines, patients should be offered at least 3 months of treatment with anticoagulants. After 3 months, the decision to continue or not has to be made, so that 6 months may cover both treatment and prevention of recurrent events as it currently defined in clinical practice.

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However, as agreed at the NICE Scoping Meeting, the 'treatment phase' was defined (arbitrarily) as 6 months. The secondary prevention 'phase' was defined as beyond 6 months.

B2 Priority question: Within the model, it is stated that the probability of recurrent VTE for people treated with dabigatran is estimated using data from RECOVER I and II at 6-months plus 30 days post treatment, rather than data at 6-months. Please describe the rationale for choosing the data set including 30 days post treatment.

The primary endpoint of pivotal aVTEt Studies 1160.53 and 1160.46 and pivotal active-controlled sVTEp Study 1160.47 was the composite of recurrent symptomatic VTE and VTE-related deaths (excluding unexplained deaths, i.e., deaths which could not be attributed to a documented cause and for which PE/DVT could not be ruled out). The 30-day follow-up period was scheduled after the planned termination of study drug to observe for potential rebound effects or delayed adverse reactions.

According to the PSAP (or Project Statistical Analysis Plan; see attached document) the efficacy analyses for the aVTEt studies included events that occurred between randomisation and the end of the post-treatment period.

- The end of the post-treatment period for roll-over patients was the day after the last intake of study drug (maximum of last DBG/DBG-matching placebo intake, last warfarin/warfarin-matching placebo intake).

The same censoring rules were applied for subgroups analyses, thus treatment effect was estimated in the same manner.

B3 Priority question: Please describe the rationale for using the combined clinical endpoint of "major or clinically relevant bleeding" to estimate incidence of bleeds within the economic model, rather than analysing "major bleed event" incidence and "clinically relevant non-major bleed event" incidence separately.

The safety endpoint in the acute VTE trials was defined as follow:

1. Incidence of Bleeding Events:

a) Major Bleeding Events (MBE)

b) MBE and Clinically Relevant Bleeding Events (CRBE)

c) Any BE (major, clinically relevant and nuisance bleeds)

So that CRBE were not accessed as individual trial safety endpoint and relative treatment effect wasn't estimated respectively.

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Moreover, in the respective rivaroxaban clinical trials, the safety endpoint was defined as:

"The principal safety outcome is clinically relevant bleeding (i.e., major bleeding and clinically relevant non-major bleeding)."

So, in order to enable a credible indirect comparison vs rivaroxaban, the common safety endpoint was applied.

B4 **Priority question**: In the economic model, the probability of a "major or clinically relevant bleeding" (cell Probs!E18) for people treated with warfarin was estimated to be 8.5% based upon a figure of 217 patients out of the treated set (2554 patients) experiencing either a major bleed or a clinically relevant non-major bleed. The ERG has been unable to verify the 217 figure using the CSRs for RECOVER I and RECOVER II:

- For RECOVER I, treated set, the CSR (page 224 table 12.2.2.1:1) reports 111 people with major or clinically relevant bleeds, or 122 events;
- For RECOVER II, treated set, the CSR (page 170 table 12.2.2.1:1) reports 102 people with major or clinically relevant bleeds, or 120 events.

Please clarify how the figure of 217 people with "major or clinically relevant bleeding events" was estimated with reference to the relevant tables and specific numbers within the CSR.

For the acute VTE treatment studies, 217 patients (TS) out of the warfarin group experienced a major bleed or a clinically relevant non-major bleed (SCS, Table 4.1.1.3). Furthermore, based on project level data, there are 115 RE-COVER I patients (TS) in the warfarin group with MBE or CRBE (SCS, Table 4.1.1.4) and analogue 102 RE-COVER II patients (SCS, Table 4.1.1.5). However, on study level, as outlined in the respective CSRs, 111 RE-COVER I patients (TS) out of the warfarin group experienced a MBE or CRBE and analogue 102 RE-COVER II patients. Hence, on project level, there are four more RE-COVER I patients with MBE or CRBE compared to study level data. This is a result of different applied censoring rules (project vs. study level data).

B5 Please clarify how the following papers were identified and why they were selected:

- Prandoni et al 2007 (probability of recurrent VTE off treatment)

The Prandoni cohort contained highest number of patients being followed up after treatment termination (1,626) along with longest median follow-up 50 months among all identified literature sources in the systematic literature review, so it was selected to derive inputs for the model.

- Pengo et al 2004 (incidence of CTEPH)

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The systematic review was conducted with the broad objective to identify trial-based and observational literature providing evidence on rates of incidence of Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Because of the fact that CTEPH is not a primary study endpoint formal meta-analysis was not performed.

In the Pengo et al. manuscript data from prospective, long-term, follow-up study aimed to assess the incidence of symptomatic CTPH in consecutive patients with an acute episode of pulmonary embolism but without prior venous thromboembolism was presented.

This study provided the highest estimate of CTEPH incidence among all identified in the systematic literature review, thus from the perspective of conservative approach this was the source chosen for use in the model.

- Prandoni et al 1997 (incidence of severe PTS)

Among all studies identified in the systematic literature review, the longest and prospective cohort study was presented in the Prandoni et al publication.

Prandoni et al followed-up consecutive patients with diagnosed, symptomatic DVT and recorded incidence of PTS by severity and reported that the cumulative incidence 2.7% after one year and 8.1% after five years in 528 patients.

- Keogh et al 2007 (CTEPH utility decrement)

We performed a crude review of UK literature and on balance, decided that the Keogh et al publication had relatively robust data, given the QoL from 177 patients were collected with SF-36 and AQoL questionnaires.

B6 In Figure 29 of the submission (page 230) chronic ischemic heart disease is presented as a health state; however, in Table 96, the chronic ischemic heart disease health state is not described. Similarly, in Table 96 a health state of “dyspepsia” is described; however, this health state is not presented in Figure 29. Please confirm which of these health states are modelled in the sensitivity analysis.

Chronic ischaemic heart disease (IHD) is a long-term consequence of both MI and UA affecting 60% (assumed) of MI/UA patients and is associated with a monthly cost of £34 (inflated to 2014 values). Chronic IHD has not been modelled as a separate health state, although Figure 29 is falsely suggesting that.

Dyspepsia, however, is a health state of the model that has erroneously not been presented in Figure 29. MI, UA and dyspepsia apply to sensitivity analyses only.

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B7 The adjustment for warfarin time in therapeutic range described in Section 7.3.1 page 241-242 was calculated using GPRD data. Was a similar analysis completed in which rates of VTE recurrence and major or clinically relevant bleeds were evaluated at different % times in therapeutic range using data from either RECOVER I or II or REMEDY? If so, please provide this analysis.

The adjustment of rates of VTE recurrence and major or clinically relevant bleeds were evaluated at different % times in therapeutic range for warfarin time in therapeutic range based on data from acute VTE studies or REMEDY was not completed, thus CPRD base analysis was used for this purpose.

B8 Results of one-way sensitivity analysis for the full list of parameters contained within the economic model were not presented within the submission.

- If this analysis was completed but not presented within the submission, please provide this analysis.
- If data is not available, please describe, for each analysis, the top ten variables that model results are most sensitive to. Please present total costs, total QALYs, and ICERs for the upper and lower value for each variable.

Table 1, Table 2 and Table 3 present the incremental costs, QALYs and ICERs, respectively, of the 10 variables that the model results are most sensitive to. All results are presented for the following comparisons as per the decision problem:

1. Acute treatment: dabigatran vs. warfarin
2. Acute treatment: dabigatran vs. rivaroxaban
3. Acute treatment: dabigatran vs. LMWH monotherapy (in patients with active cancer)
4. Treatment and secondary prevention: dabigatran vs. warfarin
5. Treatment and secondary prevention: dabigatran vs. rivaroxaban
6. Treatment and secondary prevention: dabigatran vs. LMWH (in patients with active cancer)

Table 1: One-way sensitivity analyses – Incremental discounted costs

No. of Analysis	Top ten variables per analysis	Low value [£]	High value [£]	Difference [£]
1	**Acute treatment: DBG vs Warfarin**			
	Mean LOS, Warfarin (days) PE	128.11	-86.83	214.94
	Mean LOS, Dabigatran (days) PE	-86.3	128.63	214.93
	Cost per day dabigatran 300mg/day £, 220mg/day £	-67.58	109.39	176.97
	Mean LOS, Warfarin (days) Proximal DVT	104.9	-64.22	169.12
	Mean LOS, Dabigatran (days) Proximal DVT	-63.09	106.02	169.11
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	-12.45	67.57	80.02
	Warfarin Incidence Treatment period Major or clinically relevant non-major bleeding	56.02	-14.12	70.14

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	Cost of warfarin monitoring	51.61	-10.44	62.05
	Warfarin Incidence Treatment period Recurrent VTE	47.12	-5.22	52.34
	Duration of acute parenteral treatment (days) Dabigatran Proximal DVT	10.91	31.77	42.68
2	**Acute treatment: DBG vs RVX**			
	Mean LOS, Rivaroxaban (days) PE	86.76	-128.7	215.46
	Mean LOS, Dabigatran (days) PE	-128.18	86.76	214.94
	Rivaroxaban Cost per day £ 20mg and 30 mg	77.11	-119.05	196.16
	Cost per day dabigatran 300mg/day £, 220mg/day £	-109.46	67.52	176.98
	Mean LOS, Rivaroxaban (days) Proximal DVT	64.15	-106.09	170.24
	Mean LOS, Dabigatran (days) Proximal DVT	-104.96	64.15	169.11
	Rivaroxaban Calculated Incidence Treatment period Recurrent VTE	16.41	-69.56	85.97
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	-54.33	25.7	80.03
	Duration of acute parenteral treatment (days) Dabigatran Proximal DVT	-26.88	-12.56	39.44
	CTEPH Cost (£) Monthly cost	-21.88	-36.26	14.38
3	**Acute treatment: DBG vs LMWH monotherapy (in patients with cancer)**			
	LMWH Cost per day £	-1053.93	-1664.47	610.54
	Mean LOS, Dabigatran (days) PE	-1466.4	-1251.47	214.93
	Mean LOS, LMWH (days) PE	-1257.12	-1461.27	204.15
	% Patients LMWH at home, nurse injection (per day after discharge)	-1265.33	-1453.07	187.74
	Cost (£) LMWH at home, nurse injection (per day after discharge)	-1265.33	-1453.07	187.74
	Mean LOS, LMWH (days) Proximal DVT	-1274.08	-1444.32	170.24
	Mean LOS, Dabigatran (days) Proximal DVT	-1442.14	-1274.95	167.19
	Cost per day dabigatran 300mg/day £, 220mg/day £	-1439.77	-1278.63	161.14
	Cost (£) LMWH, administration in clinic (per day after discharge)	-1280.95	-1437.45	156.5
	Cost of other major bleed Units per Patient	-441.97	-395	46.97
4	**Tx then Secondary prevention: DBG vs Warfarin**			
	Cost per day dabigatran 300mg/day £, 220mg/day £	177.03	790.97	613.94
	Planned duration of treatment (months) Dabigatran	216.88	484	267.12
	Mean LOS, Warfarin (days) PE	591.21	376.27	214.94
	Mean LOS, Dabigatran (days) PE	376.79	591.73	214.94
	Mean LOS, Warfarin (days) Proximal DVT	568	398.88	169.12
	Mean LOS, Dabigatran (days) Proximal DVT	401.04	568.26	167.22
	Warfarin Incidence Treatment period Major or clinically relevant non-major bleeding	517.15	450.94	66.21
	Warfarin Incidence Secondary prevention period Major or clinically relevant non-major bleeding	512.17	446	66.17
	Cost of warfarin monitoring	582.41	333.02	249.39
	CTEPH Cost (£) Monthly cost	-22.46	-4.2	18.26
5	**Tx then Secondary prevention: DBG vs RVX**			
	Rivaroxaban Cost per day £ 20mg and 30 mg	116.98	-235.84	352.82
	Cost per day dabigatran 300mg/day £, 220mg/day £	-226.71	107.85	334.56

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	Mean LOS, Rivaroxaban (days) PE	48.3	-167.16	215.46
	Mean LOS, Dabigatran (days) PE	-166.64	48.3	214.94
	Mean LOS, Rivaroxaban (days) Proximal DVT	25.69	-144.55	170.24
	Mean LOS, Dabigatran (days) Proximal DVT	-142.39	24.82	167.21
	Planned duration of treatment (months) Dabigatran	-213.22	-59.44	153.78
	Rivaroxaban Calculated Incidence Treatment period Recurrent VTE	-23.95	-105.55	81.6
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	-90.49	-15.97	74.52
	Duration of acute parenteral treatment (days) Dabigatran Proximal DVT	-65.92	-19.35	46.57
6	**Tx then Secondary prevention: DBG vs LMWH monotherapy (in patients with cancer)**			
	LMWH Cost per day £	-2743.83	-3986.76	1242.93
	% Patients LMWH at home, nurse injection (per day after discharge)	-3166.3	-3564.28	397.98
	Cost (£) LMWH at home, nurse injection (per day after discharge)	-3166.3	-3564.28	397.98
	Cost per day dabigatran 300mg/day £, 220mg/day £	-3532.58	-3198	334.58
	% Patients LMWH, administration in clinic (per day after discharge)	-3199.41	-3531.17	331.76
	Mean LOS, Dabigatran (days) PE	-3472.49	-3257.56	214.93
	Mean LOS, LMWH (days) PE	-3263.37	-3467.21	203.84
	Mean LOS, LMWH (days) Proximal DVT	-3280.17	-3450.41	170.24
	Planned duration of treatment (months) Dabigatran	-1644.3193	-1491.1544	153.1649
	LMWH Calculated Incidence Secondary prevention period Recurrent VTE	-1,452.29	-1,530.01	77.72

Table 2: One-way sensitivity analyses – Incremental discounted QALYs

No. of Analysis	Top ten variables per analysis	Low value	High value	Difference
1	**Acute treatment: DBG vs Warfarin**			
	Utility decrement associated with warfarin	0.0222	0.0690	0.0468
	Warfarin Incidence Treatment period Major or clinically relevant non-major bleeding	0.0178	0.0303	0.0125
	Age of population at model entrance	0.0283	0.0192	0.0091
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	0.0277	0.0190	0.0087
	VTE HR for dabigatran versus warfarin	0.0275	0.0190	0.0085
	Warfarin Incidence Treatment period Recurrent VTE	0.0199	0.0282	0.0083
	Fatal VTE % rate for warfarin	0.0207	0.0278	0.0071
	CRMBE rate for warfarin	0.0208	0.0271	0.0063
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	0.0265	0.0213	0.0052
	Intervention specific % of MBE in CRMBE for warfarin	0.0212	0.0263	0.0051
2	**Acute treatment: DBG vs RVX**			
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	0.0038	-0.0049	0.0087
	VTE HR rivaroxaban versus VKA	-0.0020	0.0032	0.0052

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	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	0.0025	-0.0026	0.0051
	Rivaroxaban Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	-0.0020	0.0025	0.0045
	Fatal VTE % rate for dabigatran	0.0024	-0.0022	0.0046
	Fatal VTE % rate for rivaroxaban	-0.0009	0.0029	0.0038
	Intervention specific %of MBE in CRMBE for rivaroxaban	0.0004	0.0042	0.0038
	Intervention specific %of MBE in CRMBE for dabigatran	0.0047	0.0015	0.0032
	Fatal MBE for dabigatran	0.0018	-0.0007	0.0025
	Intervention specific % of ICH in CRMBE for rivaroxaban	-0.0003	0.0021	0.0024
3	**Acute treatment: DBG vs LMWH monotherapy (in patients with cancer)**			
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	0.0040	-0.0213	0.0253
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	0.0082	-0.0240	0.0322
	LMWH Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	-0.0128	0.0144	0.0272
	CRNMBE rate for dabigatran	-0.0052	-0.0195	0.0143
	CRNMBE rate for LMWH	-0.0170	-0.0077	0.0093
	Treatment effects LMWH vs. VKA Recurrent VTE	-0.0151	-0.0089	0.0082
	Age of population at model entrance	-0.0187	-0.0123	0.0064
	Fatal MBE % dabigatran	-0.0104	-0.0153	0.0049
	Intervention specific % of ICH in CRNMBE for dabigatran	-0.0112	-0.0157	00045
	Fatal VTE % rate for dabigatran	-0.0103	-0.0147	00044
4	**Tx then Secondary prevention: DBG vs Warfarin**			
	Age of the population at the model entrance	0.0629	0.0460	0.0169
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	0.0593	0.0494	0.0099
	Warfarin Incidence Treatment period Major or clinically relevant non-major bleeding	0.0486	0.0617	0.0090
	CRMBE rate for warfarin in secondary prevention	0.0512	0.0591	0.0079
	VTE HR for dabigatran versus warfarin in secondary prevention	0.0558	0.0482	0.0076
	Utility decrement associated with warfarin in secondary prevention	0.0488	0.0558	0.0070
	Disabled from ICH (applied for remaining lifetime on % disabling)	0.0522	0.0581	0.0059
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	0.0577	0.0522	0.0055
	Warfarin Incidence Treatment period Recurrent VTE	0.0507	0.0597	0.0055
	Warfarin Incidence Secondary prevention period Major or clinically relevant non-major bleeding	0.0491	0.0614	0.0123
5	**Tx then Secondary prevention: DBG vs RVX**			
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	0.0057	-0.0035	0.092
	Treatment effects Rivaroxaban vs. VKA Recurrent VTE treatment period	-0.0006	0.0051	0.0057
	Dabigatran Calculated Incidence Treatment period	0.0043	-0.0010	0.0053

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	Major or clinically relevant non-major bleeding			
	Rivaroxaban Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	-0.0003	0.0042	0.0045
	Treatment discontinuation rate of dabigatran	0.0033	0.0006	0.0027
	Treatment discontinuation rate for rivaroxaban	0.0011	0.0028	0.0017
	Age of population at the model entrance	0.0016	0.0023	0.0007
	Intervention specific % of MBE in CRMBE for rivaroxaban	0.0017	0.0022	0.0005
	Intervention specific % of MBE in CRMBE for dabigatran	0.0020	0.0019	0.0001
	Intervention specific % rate of PE in VTE for rivaroxaban	0.0020	0.0019	0.0001
6	**Tx then Secondary prevention: DBG vs LMWH monotherapy (in patients with cancer)**			
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	0.0307	0.0253	0.0054
	LMWH Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	0.0182	0.0483	0.0301
	LMWH Calculated Incidence Secondary prevention period Recurrent VTE	0.0204	0.0428	0.0224
	LMWH Calculated Incidence Secondary prevention period Major or clinically relevant non-major bleeding	0.0194	0.0772	0.0578
	Treatment effects Dabigatran vs. warfarin Recurrent VTE	0.0320	0.0228	0.0092
	CRNMBE HR for dabigatran versus LMWH	0.0009	-0.0081	0.0090
	Age of population at the model entrance	-0.0059	-0.0010	0.0049
	Fatal VTE % rate for LMWH	-0.0035	0.0006	0.0041
	Fatal MBE % for LMWH	-0.0020	-0.0003	0.0023
	Intervention specific % of ICH in CRNMBE for LMWH	-0.0020	0.00001	0.0020

Table 3: One-way sensitivity analyses – ICERs

No. of Analysis	Top ten variables per analysis	Low value [£/QALY]	High value [£/QALY]	Difference [£/QALY]
1	**Acute treatment: DBG vs Warfarin**			
	Mean LOS, Dabigatran (days) PE	-3585.01	5343.30	8928.31
	Mean LOS, Warfarin (days) PE	5,321.57	-3606.72	8927.29
	Cost per day dabigatran 300mg/day £, 220mg/day £	-2807.37	4543.94	7,351.31
	Mean LOS, Warfarin (days) Proximal DVT	4357.39	-2667.58	7,024.97
	Mean LOS, Dabigatran (days) Proximal DVT	-2620.81	4404.15	7024.96
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	-450.03	3550.38	4000.41
	Warfarin Incidence Treatment period Major or clinically relevant non-major bleeding	3141.62	-466.16	3607.78
	Warfarin Calculated Incidence Treatment period Recurrent VTE	2366.73	-185.08	2551.75
	Duration of acute parenteral treatment (days) Dabigatran Proximal DVT	453.18	1319.54	866.36
	Warfarin monitoring costs	2155	-436	2591
2	**Acute treatment: DBG vs RVX**			
	Mean LOS, Rivaroxaban (days) PE	538733.32	-799148.93	1337882.25

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	Mean LOS, Dabigatran (days) PE	-795902.8	538733.32	1334636.12
	Rivaroxaban Cost per day £ 20mg and 30 mg	478,803.80	-739,219.42	1218023.22
	Cost per day dabigatran 300mg/day £ and 220 mg/day	-679,658.61	419,242.99	1098901.6
	Mean LOS, Rivaroxaban (days) Proximal DVT	398346.78	-658762.4	1057109.18
	Mean LOS, Dabigatran (days) Proximal DVT	-651771.49	398346.78	1050118.27
	Disutility MBE (including ICH event, applied in month of the event)	-57723.64	509200.14	566923.78
	Disabled from ICH (applied for remaining lifetime on % disabling)	200513.94	-53762.68	254276.62
	Disutility of clinically relevant non-major bleed (applied in month of the event)	131,809.34	-43,579.10	175388.44
	Planned duration of treatment (months) Rivaroxaban	52,446.84	-112,592.94	165039.78
3	**Acute treatment: DBG vs LMWH monotherapy (in patients with cancer)**			
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	2574077.09	36898.69	2537178.4
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	304635.44	39347.18	265288.26
	LMWH Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	60687.07	-250432.86	311119.93
	LMWH Calculated Incidence Treatment period Recurrent VTE	89004.5	157280.97	68276.47
	LMWH Cost per day £	84877.38	133663.02	48785.64
	Mean LOS, Dabigatran (days) PE	117836.22	100661.99	17174.23
	Mean LOS, LMWH (days) PE	101113.84	117416.57	16302.73
	% Patients LMWH at home, nurse injection (after discharge)	101740.58	116799.88	15059.3
	Mean LOS, LMWH (days) Proximal DVT	102468.55	116071.86	13603.31
	Mean LOS, Dabigatran (days) Proximal DVT	115980.99	102468.55	13512.44
4	**Tx then Secondary prevention: DBG vs Warfarin**			
	Cost per day dabigatran 300mg/day £, 220mg/day £	2734.48	13964.88	11230.4
	Planned duration of treatment (months) Dabigatran	3455.98	8299.69	4843.71
	Mean LOS, Warfarin (days) PE	10,243.04	6,346.86	3896.18
	Mean LOS, Dabigatran (days) PE	6356.33	10252.51	3896.18
	Warfarin Incidence Secondary prevention period Major or clinically relevant non-major bleeding	10081.99	6841.64	3240.35
	Warfarin Incidence Treatment period Major or clinically relevant non-major bleeding	10092.85	6888.78	3204.07
	Mean LOS, Warfarin (days) Proximal DVT	9822.28	6756.66	3065.62
	Mean LOS, Dabigatran (days) Proximal DVT	6777.09	9842.69	3065.6
	Warfarin monitoring costs	10579	6049	4530
	Duration of acute parenteral treatment (days)	-242.13	78.39	320.52

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	Dabigatran PE			
5	**Tx then Secondary prevention: DBG vs RVX**			
	Rivaroxaban Cost per day £ 20mg and 30 mg	57923.53	-130,336.39	188259.92
	Cost per day dabigatran 300mg/day £, 220mg/day £	-125464.09	53060.22	178524.31
	Mean LOS, Rivaroxaban (days) PE	21283.39	-93687.26	114970.65
	Mean LOS, Dabigatran (days) PE	-93408.3	21283.39	114691.69
	Mean LOS, Rivaroxaban (days) Proximal DVT	9219.3	-81623.17	90842.47
	Mean LOS, Dabigatran (days) Proximal DVT	-81022.4	9219.3	90241.7
	Planned duration of treatment (months) Dabigatran	-118264.49	-36201.93	82062.56
	Rivaroxaban Calculated Incidence Treatment period Recurrent VTE	56,539.50	-22,549.56	79089.06
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	-18685.4	52726.65	71412.05
	Dabigatran Calculated Incidence Treatment period Recurrent VTE	-17,812.75	34,193.70	52006.45
6	**Tx then Secondary prevention: DBG vs LMWH monotherapy (in patients with cancer)**			
	LMWH Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	-189693.39	-17158.38	172535.01
	LMWH Calculated Incidence Secondary prevention period Major or clinically relevant non-major bleeding	-171357.81	-46904.07	124453.74
	Years follow-up	-214224.73	-119653.56	94571.17
	LMWH Calculated Incidence Secondary prevention period Recurrent VTE	-225938.37	-148826.28	77112.09
	LMWH Cost per day £	-97611.8	-141695.32	44083.52
	Dabigatran Calculated Incidence Treatment period Major or clinically relevant non-major bleeding	-110469.06	-132604.93	22135.87
	% Patients LMWH at home, nurse injection (per day after discharge)	-112583.16	-126723.97	14140.81
	Cost per day dabigatran 300mg/day £, 220mg/day £	-125587.08	-113720.12	11866.96
	Mean LOS, Dabigatran (days) PE	-81,073.63	-70,171.42	10902.21
	Incidence beyond trial period	-71,187.74	-80,966.46	9778.72

B9 Please run the following scenario analyses and present total costs, total QALYs and ICERs for each relevant comparison:

- LMWH plus warfarin and rivaroxaban are treatment options at 1st or 2nd VTE recurrence;

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- for treatment and secondary prevention analyses, patients experiencing a 1st or 2nd VTE recurrence will receive acute treatment and secondary prevention;
- treatment duration for secondary prevention is set to lifetime for all analyses;
- patients who experience a major bleeding event will be reinstated on acute treatment and/or secondary prevention.

The incremental total costs, incremental total QALYs and ICERs for the requested scenario analyses are presented in the tables below. For full results on each of the scenarios requested please refer to Appendices B9a-f attached.

Table 1 below presents the results of the base case analysis when LMWH plus warfarin is a treatment option at 1st and 2nd VTE recurrence and the results from the scenario when rivaroxaban is the treatment option at 1st and 2nd VTE recurrence. In the newly modelled scenario it was assumed that all patients, if they experience a recurrent VTE event, are initiated with rivaroxaban. The duration of treatment with rivaroxaban was assumed to be 6 months to cover the initial 3 months treatment and a potential extension for an additional 3 months. During these 6 months, respective treatment effects from the pooled EINSTEIN DVT and PE trials (Prinz et al) were applied. It can be seen that in the comparison of LMWH then dabigatran versus LMWH then warfarin, when rivaroxaban is a treatment option at both 1st and 2nd VTE recurrence the impact on ICER is minimal, increasing from £862 to £873.

Table 1 Scenario analysis of rivaroxaban as a treatment option at 1st or 2nd VTE recurrence.

	Incremental cost	Incremental QALY	ICER
LMWH then dabigatran vs. LMWH then warfarin			
Base case scenario LMWH plus warfarin is the treatment option for 1st or 2nd rVTE	£21	0.0239	£862
Newly modelled scenario rivaroxaban is the treatment option for 1st or 2nd rVTE	£21	0.0241	£873

Table 2 presents the results of the base case analysis and the results of the scenario analysis when the re-treatment period, after a 1st or 2nd VTE recurrence, is extended to 24 months (in order to include acute retreatment and secondary prevention). Extending the retreatment period to 24 months has a small effect on the ICER, increasing it from £8,319 in the base case, to £8,785 in the scenario analysis. The change in the ICER is primarily driven by an increase in re-treatment costs of warfarin (see Appendix B9b).

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Table 2 Scenario analysis of the treatment and secondary prevention analysis where patients experiencing a 1st or 2nd VTE recurrence receive acute treatment and secondary prevention

Scenario	Incremental cost	Incremental QALY	ICER
LMWH then dabigatran vs. LMWH then warfarin			
Base case	£458	0.0551	£8,319
Scenario	£474	0.0539	£8,785

The base case results and results from the scenario analyses, where the treatment duration for secondary prevention is extended to lifetime, are shown in Table 3. For the comparison of LMWH then dabigatran versus LMWH then warfarin, extending the secondary prevention treatment duration to lifetime decreases the ICER, from £8,319 in the base case, to £6,942. Dabigatran remains dominant in this scenario analysis for the comparison of LMWH then dabigatran versus rivaroxaban and versus LMWH monotherapy in patients with active cancer.

Table 3 Scenario analysis of treatment duration for secondary prevention set to lifetime for all analyses

Scenario	Incremental cost	Incremental QALY	ICER
LMWH then dabigatran vs. warfarin			
Base case	£458	0.0551	£8,319
Scenario	£1,822	0.2624	£6,942
LMWH then dabigatran vs. rivaroxaban			
Base case	-£67	0.0020	Dabigatran is dominant
Scenario	-£6	0.0451	Dabigatran is dominant
LMWH then dabigatran vs. LMWH monotherapy (in patients with active cancer)			
Base case	-£3,340	0.0197	Dabigatran is dominant
Scenario	-£30,559	0.2687	Dabigatran is dominant

In order to test the effect of the scenario where patients who experience a major bleeding event (MBE) are reinstated on acute treatment and/or secondary prevention, it is assumed that patients who experience a MBE do not discontinue treatment for any period of time. When patients continue treatment after a MBE, there is an insignificant impact on the ICER from £962 in the base case to £1,492 in the scenario analysis.

Table 4 Scenario analysis of patients who experience a major bleeding event not discontinuing acute treatment and/or secondary prevention

Scenario	Incremental cost	Incremental QALY	ICER
LMWH then dabigatran vs. warfarin			
Base case	£21	0.0239	£862
Scenario	£33	0.0221	£1,492

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B10 Please provide the references for the studies identified and included from the systematic review of the economic evidence.

Study	Reference
Bayer plc (2011) (Manufacturer submission to NICE)	NICE STA Rivaroxaban in the treatment of deep vein thrombosis and prevention of recurrent venous thromboembolic events, Bayer plc (2011)
Braidy (2011)	Braidy N, Bui K, Bajorek B. Evaluating the impact of new anticoagulants in the hospital setting. Pharmacy Practice 9(1):January-March.
Kourlaba (2012) (Abstract)	Economic evaluation of rivaroxaban in stroke prevention for patients with atrial fibrillation in Greece, *Cost Effectiveness and Resource Allocation* 2014, 12:5
Marchetti (2001)	Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med 2001; 111(2):130-139
Seaman (2012) (Abstract) (note: superseded by Seaman (2013))	Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: A U.S. perspective, Thrombosis Research 132 (2013) 647–651.
Bookhart (2013) (Abstract)	Treatment of pulmonary embolism treatment with rivaroxaban and LMWH-VKA: Length of stay and economic implications in the emergency department setting, Annals of Emergency Medicine 62 (4)
McLeod (2013) (Abstract)	Cost-effectiveness of rivaroxaban for the treatment of pulmonary embolism and secondary prevention of venous thromboembolism-a UK perspective, Journal of Thrombosis and Haemostasis 11, p90
Parali (2013) (Abstract)	The cost-effectiveness of rivaroxaban compared to enoxaparin plus adjusted-dose warfarin for the treatment of deep venous thrombosis (DVT) in turkey, Value in Health 16 (3)
Wolowacz (2013) (Conference poster presentation)	Cost-effectiveness of dabigatran etexilate for the secondary prevention of recurrent deep vein thrombosis and pulmonary embolism in the United Kingdom, Value in Health 16 (7)
Coleman (2014)	Cost-Effectiveness Analysis of Extended Duration Anticoagulation with Rivaroxaban to Prevent Recurrent Venous Thromboembolism, Thrombosis Research 133 (2014) 743–749
Lefebvre (2014)	Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism, Journal of medical economics 17 (1):52-64

B11 With reference to the systematic review of cost-effectiveness evidence, please describe the rationale for including only economic evaluations which assessed at least one of the following therapies: dabigatran, rivaroxaban, edoxaban or apixaban.

At the time that this systematic review was designed, BI had identified these as the interventions of interest in the economic model.

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B12 Please describe the rationale for estimating the cost of clinically relevant non-major bleeds that require hospitalisation using a weighted average of the following reference costs: MA22Z Lower Genital Tract Minor Procedures - Category 1, MA23Z Lower Genital Tract Minor Procedures - Category 2, MA25Z Upper Genital Tract Minor Procedures - Category 1, MA26Z Upper Genital Tract Minor Procedures - Category 2.

The condition listed in the trial definition of clinically relevant non-major bleed that is most likely to incur additional cost is spontaneous rectal bleed. The HRG code for Endoscopic or Intermediate Large Intestine Procedures 19 years and over [FB03A] was originally selected for the unit cost (National Reference Costs 2006-2007). This code was no longer available in the 2010-2011 NHS Reference Costs and the nearest codes did not seem appropriate as the length of stay and overall cost differed from FB03A. The set of codes were therefore selected on the basis that type of care expected, length of stay and cost were expected to be more similar to that for Endoscopic or Intermediate Large Intestine Procedures 19 years and over [FB03A].

Section C: Textual clarifications and additional points

C1 Some discrepancies have been identified between outcomes reported within the submission compared with those reported in the model; these are listed in the tables below.

Please review Tables 1 to 4 below to confirm whether the submission or the model values are correct. If both values are correct, please explain the reason for the difference.

Please update the economic model and final results, if appropriate, should any of the discrepancies be in error.

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Table 1. Acute treatment of DVT and PE; dabigatran versus rivaroxaban

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model	Correct value	Reason for error/difference	Updated final results
Summary of resources consumed, LMWH plus dabigatran	Total drug costs	£408	Table 134, page 351	£487	'Results!E12'	£487	Editing error	Not needed, results are as presented in submission
	Investigational treatment, drug	£323		£354	'Results!E13'	£354		
	Re-treatment with warfarin, drug	£8		£17	'Results!E15'	£17		
	Re-treatment with warfarin, acute parenteral drug	£31		£70	'Results!E16'	£70		
	Total monitoring (administration) costs	£244		£520	'Results!E17'	£520		
	Investigational treatment, admin	£22		£24	'Results!E18'	£24		
	Re-treatment with warfarin, admin	£210		£476	'Results!E19'	£476		
	Re-treatment with warfarin, acute parenteral admin	£5		£12	'Results!E20'	£12		
Summary of resources consumed, rivaroxaban	Total drug costs	£1,260	Table 134, page 351	£488	'Results!F12'	£480	Costs!G49 and Costs!J49 need to be manually set to 0 to reflect the base case analysis specified in the submission.	Not needed, results are as presented in submission
	Investigational treatment, drug	£1,222		£393	'Results!F13'	£393		
	Re-treatment with warfarin, drug	£7		£17	'Results!F15'	£17		
	Re-treatment with warfarin,	£31		£70	'Results!F16'	£70		

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Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model	Correct value	Reason for error/difference	Updated final results
	acute parenteral drug							
	Total monitoring (administration) costs	£911		£515	'Results!F17'	£513		
	Investigational treatment, admin	£700		£25	'Results!F18'	£25		
	Re-treatment with warfarin, admin	£206		£476	'Results!F19'	£476		
	Re-treatment with warfarin, acute parenteral admin	£5		£12	'Results!F20'	£12		
Total costs, rivaroxaban, deterministic results	Total costs	£7,523	Table 16, page 26 and Table 145, page 356	£7,532	'Results!F39'	£7,523	Costs!G49 and Costs!J49 need to be manually set to 0 to reflect the base case analysis specified in the submission.	Not needed, results are as presented in submission

Table 2. Acute treatment of DVT and PE, dabigatran versus LMWH in the subgroup of patients with active cancer

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model	Correct value	Reason for error/difference	Updated final results
Summary of resources consumed, dabigatran	Total drug costs	£372	Table 135, page 352	£408	'Results!E12'	£408	Error on our part as we presented these values for a 6-month time horizon in the submission, were the	Not needed as correct results are presented in the submission
	Re-treatment with warfarin, drug	£1		£8	'Results!E15'	£8		
	Re-treatment with warfarin,	£2		£31	'Results!E16'	£31		

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	acute parenteral drug						model should have been set to a lifetime (60 years) time horizon to reflect the base case as described in the submission.	
	Total monitoring (administration) costs	£45		£244	'Results!E17'	£244		
	Investigational treatment, admin	£22		£22	'Results!E18'	£22		
	Re-treatment with warfarin, admin	£15		£210	'Results!E19'	£210		
	Re-treatment with warfarin, acute parenteral admin	£0		£5	'Results!E20'	£5		
Summary of resources consumed, LMWH	Total drug costs	£1,224	Table 135, page 352	£1,260	'Results!F12'	£1,260	Error on our part as we presented these values for a 6-month time horizon in the submission, were the model should have been set to a lifetime (60 years) time horizon to reflect the base case as described in the submission.	Not needed as correct results are presented in the submission
	Re-treatment with warfarin, drug	£0		£7	'Results!F15'	£7		
	Re-treatment with warfarin, acute parenteral drug	£2		£31	'Results!F16'	£31		
	Total monitoring (administration) costs	£709		£911	'Results!F17'	£911		
	Investigational treatment, admin	£700		£700	'Results!F18'	£700		
	Re-treatment with warfarin, admin	£9		£206	'Results!F19'	£206		
	Re-treatment with warfarin, acute parenteral admin	£0		£5	'Results!F20'	£5		

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Table 3. Acute treatment and secondary prevention of DVT / PE, dabigatran versus rivaroxaban

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model	Correct value	Reason for error/difference	Updated final results
Summary of resources consumed, rivaroxaban	Total drug costs	£793	Table 143, page 354	£801	'Results!F12'	£793	Costs!G49 and Costs!J49 need to be manually set to 0 to reflect the base case analysis specified in the submission.	Not needed, results are as presented in submission
	Total monitoring costs	£508		£510	'Results!F17'	£508		
Total costs, deterministic results, rivaroxaban	Total costs	£7,852	Table 17, page 27 and Table 146, page 356	£7,862	'Results!F39'	£7,852	Costs!G49 and Costs!J49 need to be manually set to 0 to reflect the base case analysis specified in the submission.	Not needed, results are as presented in submission

Table 4. Acute treatment and secondary prevention of DVT and PE, dabigatran versus LMWH in the subgroup of patients with cancer

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model	Correct value	Reason for error/difference	Updated final results
Incremental life years gained, LMWH	Life years	Two values presented: 0.0119 0.0090	Table 126, page 348; Table 17, page 27; Table 146, page 356	0.0090	'Results!M28'	0.0090	Error on our part as we presented these values for the equipoise patient subgroup, when the model should have been set to the cancer subgroup to reflect the base case as described in the submission.	Not needed, results are as presented in submission
Incremental QALYs, LMWH	QALYs	Two values presented: 0.0197 0.0282	Table 126, page 348; Table 17, page 27; Table 146, page 356; Table 151, page 368	0.0197	'Results!M29'	0.0197		

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C2 The CTEPH utility decrement described within the submission (0.12, page 302) does not match with the value for CTEPH decrement in the model (0.10, 'Utilities'!F75). Please confirm whether the 0.10 or 0.12 value is correct.

The 0.12 value is the correct one (0.10 was a prior assumption). 'Input data'!H1237 may be amended accordingly.

C3 For the probability of recurrent VTE used within the economic model for the warfarin arm of RECOVER I and II, cell 'Probs'!N17 states that the value is based upon the intent to treat (ITT) dataset; however, the sample size appears to be that of the treated set. Please confirm which dataset has been used.

Probs'!N17 wrongly states that the value is based upon the ITT dataset. In fact, the parameter values in line 17 stem from the treated set formed of all randomised subjects who had received at least one dose of active study medication (during the study period plus an additional 30-day follow-up).

C4 Please confirm which databases were searched for the cost-effectiveness literature review. Page 219 of the submission states "MEDLINE, MEDLINE In-Process, Embase, Econ-Lit, BIOSIS and the Cochrane Library including the NHSEED", compared with page 453 Section 8.17.1 which states "Medline, Embase, Medline (R) In-Process, EconLIT, NHS EED".

Databases searched were MEDLINE and MEDLINE In-Process, EMBASE, EconLit, BIOSIS and the Cochrane Library (including the National Health Service's Economic Evaluation Database (NHS EED), the Health Technology Assessment database, and the Database of Abstracts of Reviews of Effects (DARE)). EconLit was only searched in the original systematic review whereas DARE was searched in the update only. The original search strategy was slightly amended during the update since DARE is much more UK-centric than EconLit, which is a US database. It has been found that information of relevance to the NHS is more likely to be found using DARE.

C5 Please clarify the potential discrepancy around comparison of data for rivaroxaban and dabigatran in the acute treatment of venous thromboembolic events (VTEs). A statement in Section 6.7.2 (pg 147) suggests that rivaroxaban was evaluated in only the secondary prevention of VTE, but data on use of rivaroxaban in acute treatment of VTE are presented and discussed.

This is an error on our part, and the statement "for secondary prevention only" in Section 6.7.2 (pg147) should be removed. To clarify, the comparison for dabigatran and rivaroxaban in the submission has been evaluated for both the acute treatment and secondary prevention of VTE.

C6 Within the economic model, the calculation within cell NHSRC 2013!T332 subtracts Unit costs!N429 from a weighted average reference cost; however, there is no value in

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Unit costs!N429. Please confirm whether the intention of this calculation was to subtract 'Unit costs'!N135 from NHSRC 2013!T332 (to mimic the calculation for DVT).

The weighted average cost of inpatient stay for both DVT and PE was intended to be adjusted to remove drug costs. As the ERG (BMJ Group) correctly points out, 'Unit costs'!N135 should have been substracted from 'NHSRC 2013'!T332. This is a modelling error.

C7 In the economic model, the cost reported for parenteral treatment for UH Regimen 1 and 2 are £21.58 and £7.05 respectively (Unit costsN102:103 and Unit costsN125:126). These correspond to a daily cost of £4.32 and £1.41 respectively. In the submission, Table 115, the daily costs are reported to be £4.67 and £1.76. Please confirm whether the submission or model costs are correct.

The daily costs for parenteral treatment for UFH are £4.32 and £1.41, respectively. I.e. the model costs are correct, whereas Table 115 wrongly reports the drug costs per day of Regimen 1 and 2 of UFH.